Royal Veterinary College
University of London

Epilepsy

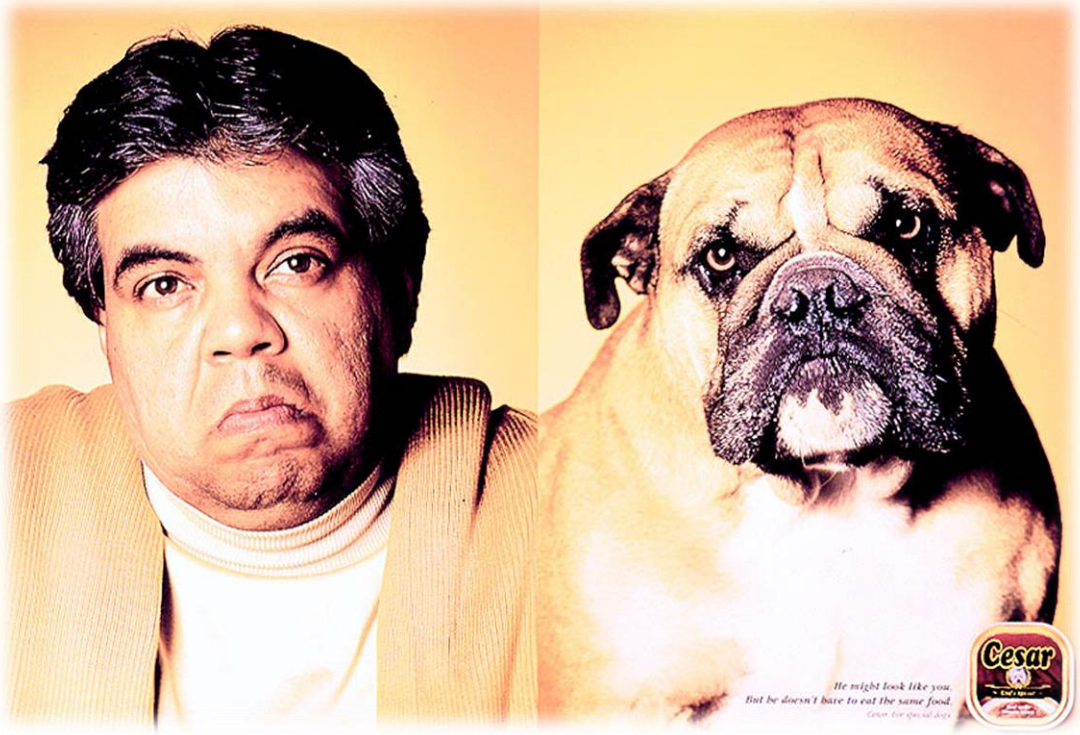
Holger A. Volk DVM, DipECVN, PhD, FHEA, MRCVS
Head of Department CSS & Professor of Veterinary Neurology & Neurosurgery
Royal Veterinary College

Inspire to Innovate, Innovate to Inspire






Similarities



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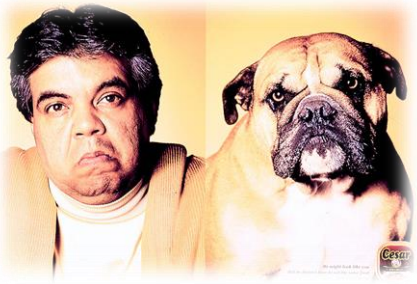
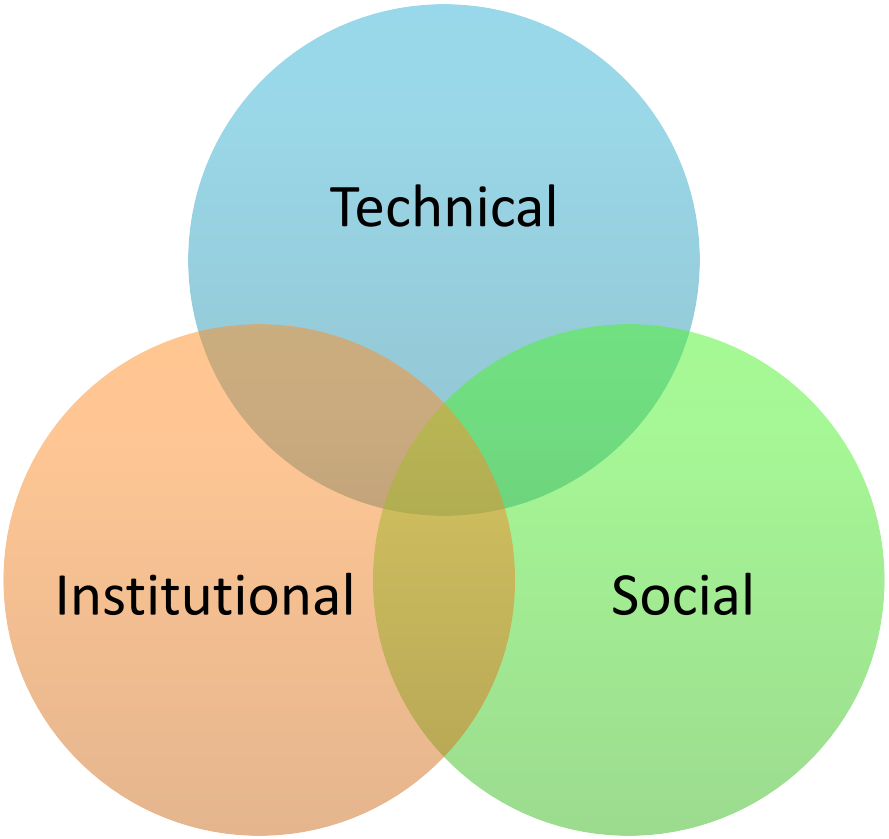
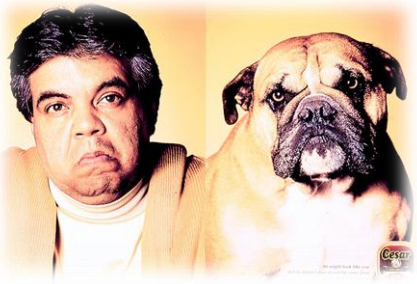
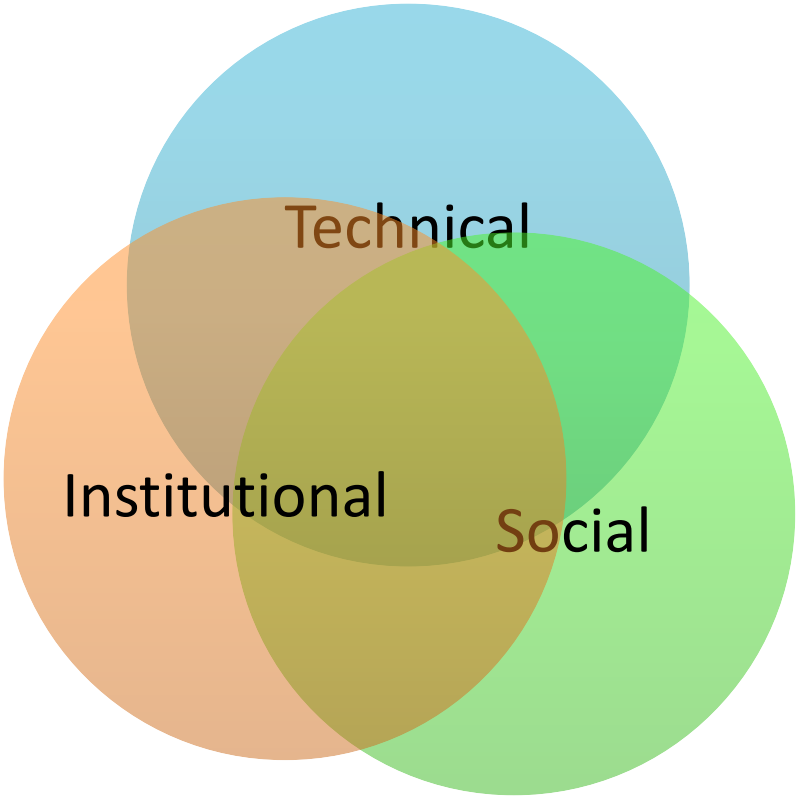
OneHealth





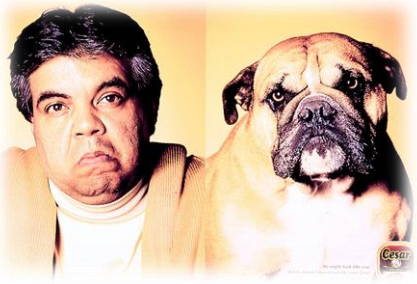
OneHealth





OneHealth

1+1=3 Synergy



Unpredictable & Uncontrollable

Impact

Dogs with epilepsy (poorly controlled, high seizure frequency) -> increased risk of[1-4]

- premature death
- behaviour changes
- reduced quality of life (QoL).

Seizures not only affect QoL for affected dogs, but also for owner[3-4].

1. Berendt M, Gredal H, Ersbøll AK, et al. JVIM 2007.
2. Shihab N, Bowen J, Volk HA. Epilepsy Behav 2011.
3. Chang Y, Mellor DJ, Anderson TJ. JSAP 2006.
4. Wessmann A, Volk HA, Parkin T, et al. JVIM.

Paper

Quality-of-life aspects in idiopathic epilepsy in dogs

A. Wessmann, H. A. Volk, R. M. A. Packer, M. Ortega, T. J. Anderson

Veterinary Record (2016) doi: 10.1136/vr.103355

- **Carer-perceived dog's QoL impacted by**
  - High seizure frequency
  - Receiving 3rd antiepileptic drugs
- **Owner's QoL impacted by**
  - Sedation level
  - Ataxia level

  Reductions in perceived canine QoL scores associated with reductions in carer QoL, and vice versa

Physiology & Behavior 177 (2017) 27–33

Contents lists available at ScienceDirect

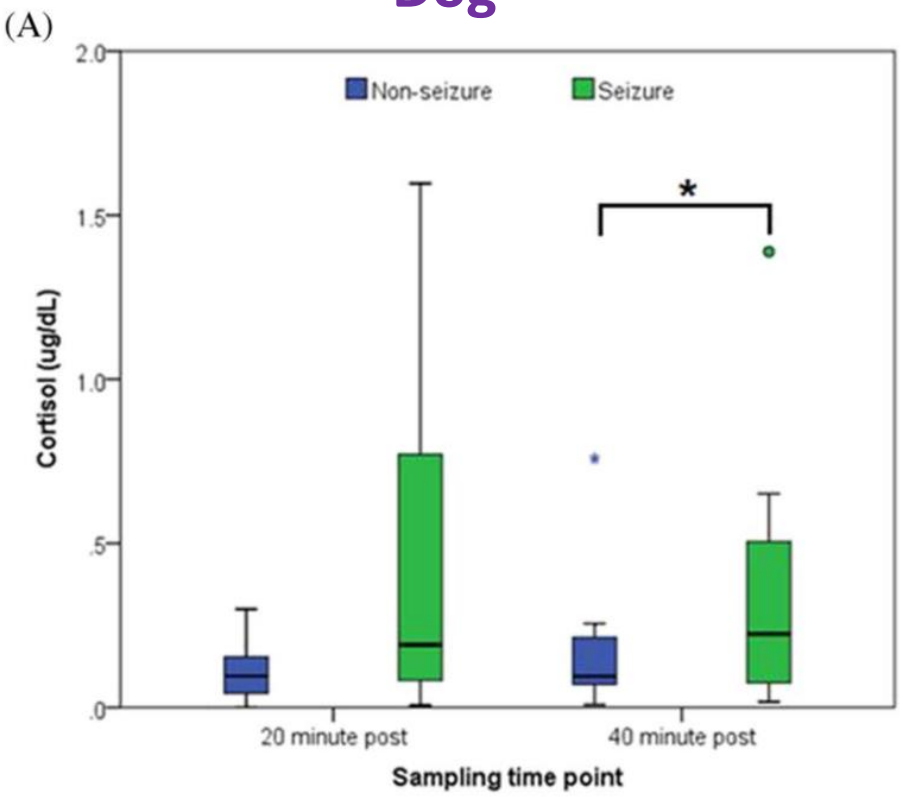
Physiology & Behavior

journal homepage: www.elsevier.com/locate/physbeh

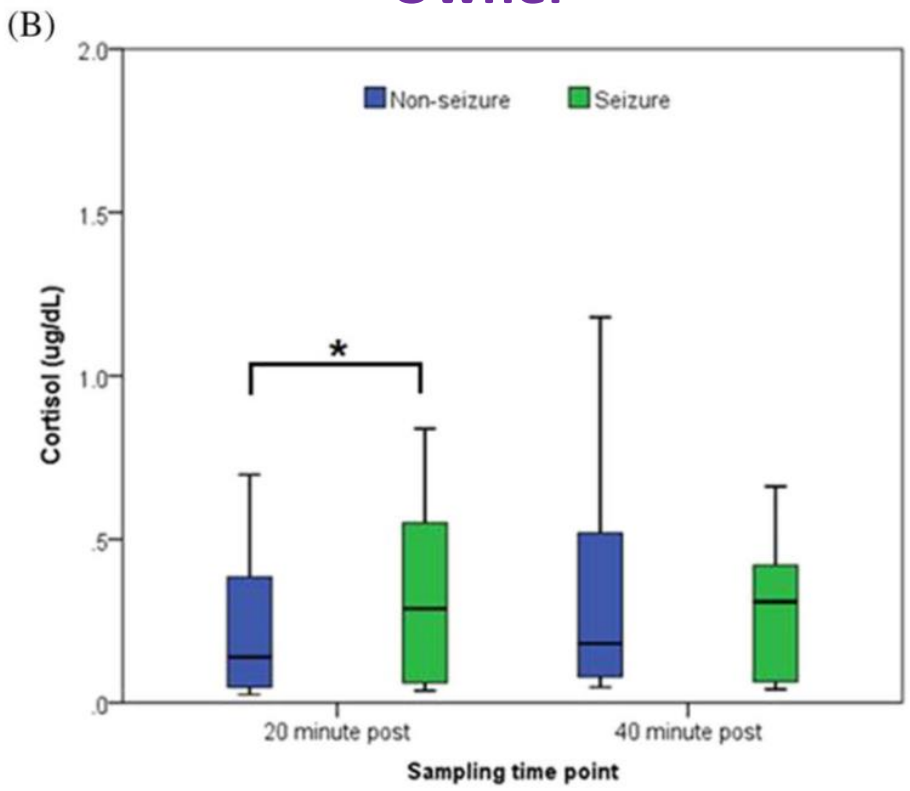
Physiological reactivity to spontaneously occurring seizure activity in dogs with epilepsy and their carers

R.M.A. Packer[a,*], H.A. Volk[a], R.C. Fowkes[b]

Dog



Owner



Evaluation of the Impacts of Epilepsy in Dogs on Their Caregivers

Julie A. Nettifee, BS, RVT, VTS (Neurology), Karen R. Munana, DVM, MS, DACVIM (Neurology), Emily H. Griffith, PhD

JAAHA | 53:3 **May/Jun 2017**

- QoL significantly associated with
  - Seizure type (cluster)
  - Seizure frequency
  - Side-effects
  - No additional medication

- QoL not associated with the number of antiepileptic medications or average monthly cost of treatment

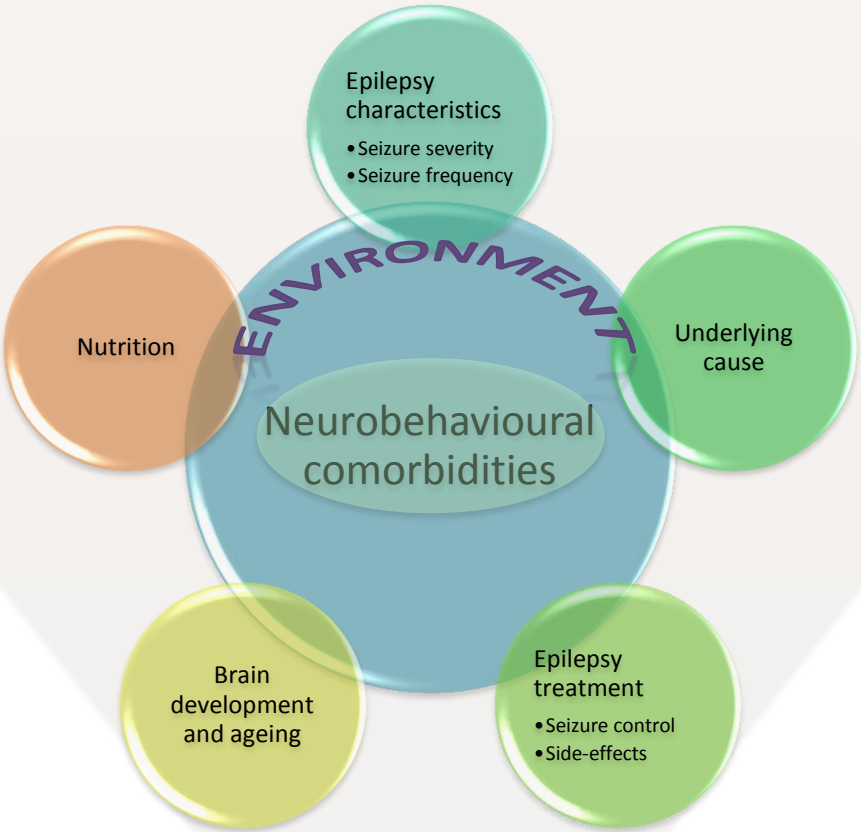
Evaluation of the Impacts of Epilepsy in Dogs on Their Caregivers

Julie A. Nettifee, BS, RVT, VTS (Neurology), Karen R. Munana, DVM, MS, DACVIM (Neurology), Emily H. Griffith, PhD

JAAHA | 53:3 **May/Jun 2017**

- Median expenditure for antiepileptic medication was $51–75.
  - Cost not associated with quality of life score.
- Support
  - 80% reported receiving veterinary support
    - veterinarian (reported by 89% of owners),
    - online educational materials (26%),
    - veterinary technician (24%),
    - printed educational materials (10%),
    - and client-to-client interactions (8%).
  - 68% online support groups for owners of pets with epilepsy

- Regular contact with and easy access to veterinarian important in reducing anxiety associated with their dog's epilepsy. (Berendt et al. 2007)

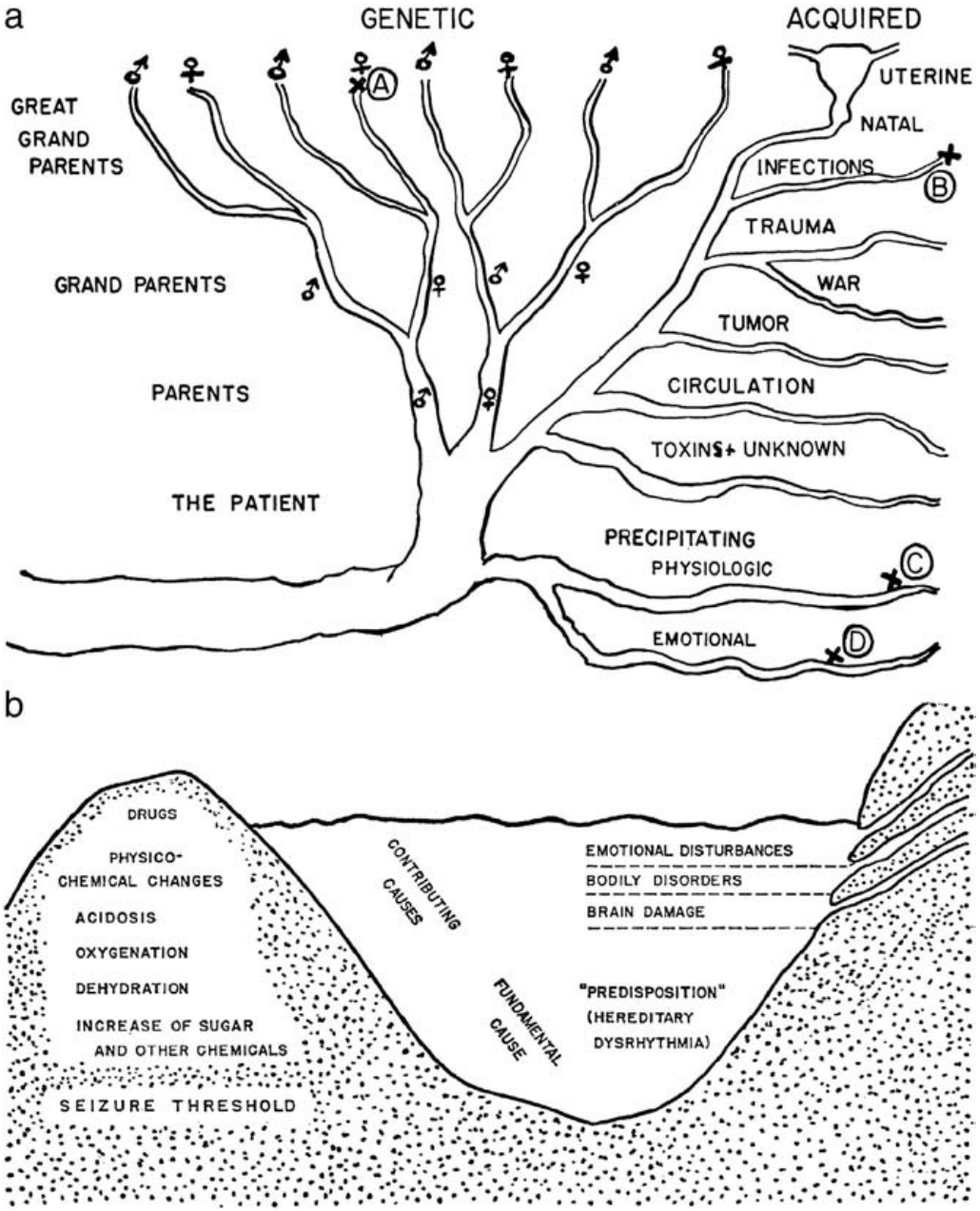


Quality of life

RVC

Idiopathic epilepsy ≠ One disease

RVC



Lennox WG, Lennox M. Epilepsy and related disorders. Boston: Little Brown; 1960.

Berendt *et al. BMC Veterinary Research* (2015) 11:182
DOI 10.1186/s12917-015-0461-2

BMC Veterinary Research

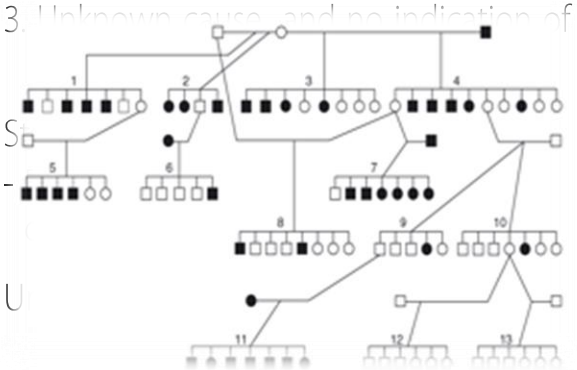
Early terminology	Terminology currently in use	Suggested veterinary terminology 2015
Primary Epilepsy - Epilepsy where no structural cerebral pathology is suspected	Idiopathic Epilepsy - Epilepsy where no structural cerebral pathology is suspected. A genetic component may be involved	Idiopathic Epilepsy 1. Proven genetic background
Secondary or Acquired epilepsy - Epilepsy caused by identified cerebral pathology	Symptomatic Epilepsy - Epilepsy caused by identified cerebral pathology	
Cryptogenic - Meaning hidden	Probably or possibly symptomatic epilepsy - A suspected symptomatic cause, which however remains obscure	

Belgian shepherd
Late onset epilepsy (mean 3.3 years) with focal onset seizures
ADAM23 gene
Famula & Oberbauer 1997, Berendt et al 2009, Seppäla et al 2012

Berendt *et al. BMC Veterinary Research* (2015) 11:182
DOI 10.1186/s12917-015-0461-2

BMC
Veterinary Research

Early terminology	Terminology currently in use	Suggested veterinary terminology 2015
Primary Epilepsy - Epilepsy where no structural cerebral pathology is suspected	Idiopathic Epilepsy - Epilepsy where no structural cerebral pathology is suspected. A genetic component may be involved	Idiopathic Epilepsy 1. Proven genetic background 2. Suspected genetic background 3. Unknown cause, and no indication of
Secondary or Acquired epilepsy - Epilepsy caused by identified cerebral pathology	Symptomatic Epilepsy - Epilepsy caused by identified cerebral pathology	S -
Cryptogenic - Meaning hidden	Probably or possibly symptomatic epilepsy - A suspected symptomatic cause, which however remains obscure	U



Koskinen *et al. BMC Genetics* (2017) 18:8
DOI 10.1186/s12863-017-0478-6

BMC Genetics

RESEARCH ARTICLE Open Access

ADAM23 is a common risk gene for canine idiopathic epilepsy

Lotta L. E. Koskinen[1,2,3], Eija H. Seppälä[1,2,3], Jutta Weissl[4], Tarja S. Jokinen[5], Ranno Viitmaa[5], Reetta L. Hänninen[1,2,3], Pascale Quignon[6,7], Andrea Fischer[4], Catherine André[6,7] and Hannes Lohi[1,2,3*]

Abstract

Background: Idiopathic or genetic adult-onset epilepsy is a common neurological disorder in domestic dogs. Genetic association has been reported only with *ADAM23* on CFA 37 in few breeds. To identify novel epilepsy genes, we performed genome-wide association (GWA) analyses in four new breeds, and investigated the association of the previously reported *ADAM23* haplotype with the epilepsy phenotype in eight breeds.

Results: GWA analysis did not reveal new epilepsy loci. *ADAM23* association ($p < 0.05$) was identified in five breeds. Combined analysis of all eight breeds showed significant association ($p = 4.6e^{-6}$, OR 1.9).

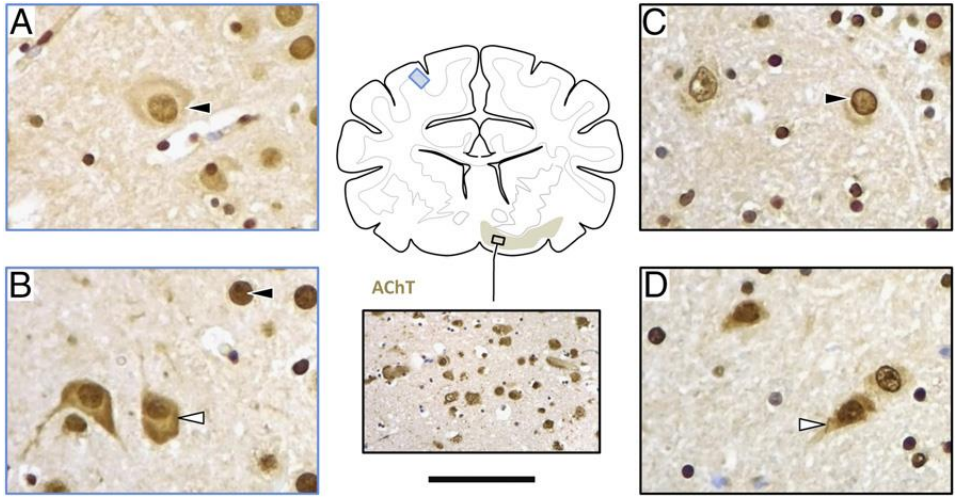
Conclusions: Our results further support the role of *ADAM23* in multiple breeds as a common risk gene for epilepsy with low penetrance. The lack of findings in the GWA analyses points towards inefficient capture of genetic variation by the current SNP arrays, causal variant(s) with low penetrance and possible phenocopies. Future work will include studies on ADAM23 function and expression in canine neurons, as well as whole-genome sequencing in order to identify additional IE genes.

Keywords: Dog, *Canis familiaris*, Epilepsy, Idiopathic epilepsy, *ADAM23*, GWA, Association

Generalized myoclonic epilepsy with photosensitivity in juvenile dogs caused by a defective DIRAS family GTPase 1

Franziska Wielaender[a,1], Riika Sarviaho[b,c,d,1], Fiona James[e], Marjo K. Hytönen[b,c,d], Miguel A. Cortez[f,g], Gerhard Kluger[h,i], Lotta L. E. Koskinen[b,c,d], Meharji Arumilli[b,c,d], Marion Kornberg[j], Andrea Bathen-Noethen[k], Andrea Tipold[l], Kai Rentmeister[m], Sofie F. M. Bhatti[n], Velia Hülsmeyer[a], Irene C. Boettcher[o], Carina Tästensen[o], Thomas Flegel[o], Elisabeth Dietschi[p], Tosso Leeb[p], Kaspar Matiasek[q], Andrea Fischer[a,2,3], and Hannes Lohi[b,c,d,2,3]

PNAS | March 7, 2017 | vol. 114 | no. 10 | 2669–2674



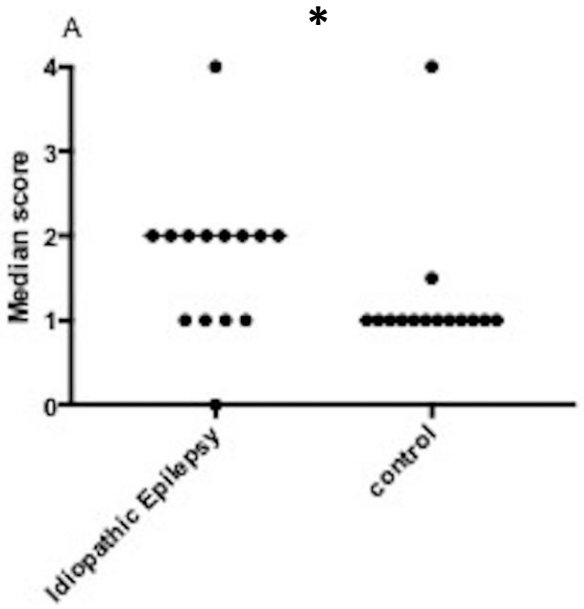
What next in canine epilepsy research?

What next in canine epilepsy research?

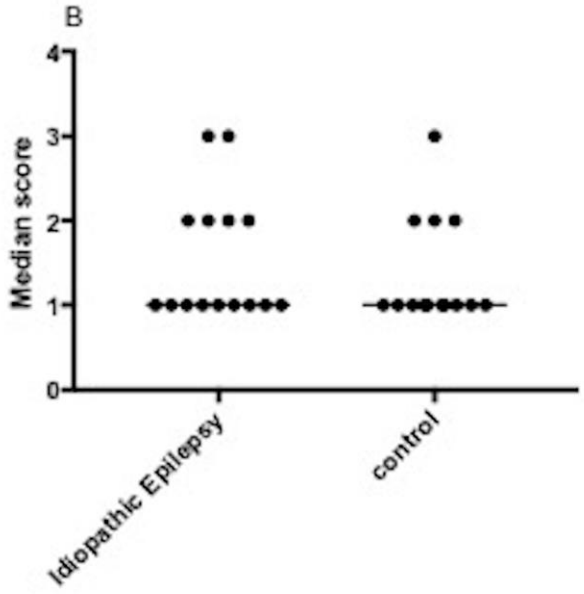
Research Area	Primary care *vs.* Specialist vets			Owner *vs.* Primary care			Owner *vs.* Specialist vets		
	X^2	p	Who rated higher?	X^2	p	Who rated higher?	X^2	p	Who rated higher?
Existing AEDs	1.2	0.876		14.3	0.006	Owner	5.7	0.128	
New AEDs	11.8	0.019	Specialist	17.6	0.001	Owner	4.1	0.395	
Vet education	6.2	0.186		37.6	<0.001	Owner	2.7	0.432	
Side effects of AEDs	2.4	0.692		24.1	<0.001	Owner	10.8	0.028	Owner
Genetic aetiology	13.8	0.008	Specialist	22.8	<0.001	Owner	2.6	0.465	
Non genetic aetiology	5.4	0.247		13.8	<0.008	Owner	0.7	0.871	
Non AED management	3.8	0.430		32.3	<0.001	Owner	5.9	0.205	
Seizure detection	15.6	0.004	Specialist	25.5	<0.001	Owner	2.8	0.596	
Diagnosing epilepsy	2.1	0.709		15.4	0.004	Owner	1.6	0.650	
Lifespan	4.1	0.393		24.3	<0.001	Owner	7.9	0.097	
Seizure classification	8.4	0.079		3.6	0.456		11.3	0.023	Specialist
Prognosis	2.7	0.609		0.6	0.965		3.7	0.442	
Co-morbidities	4.6	0.329		11.1	0.025	Owner	6.9	0.143	
Anxiety	1.8	0.880		23.5	<0.001	Owner	10.7	0.030	Owner
Hyperactivity	6.6	0.161		31.8	<0.001	Owner	6.2	0.186	
Attention	8.9	0.064		29.1	<0.001	Owner	5.8	0.211	
Physical capabilities	3.6	0.463		18.4	0.001	Owner	12.1	0.016	Owner
Social interactions	5.8	0.213		18.2	0.001	Owner	6.2	0.182	

Assessment of cognitive impairments in canine idiopathic epilepsy

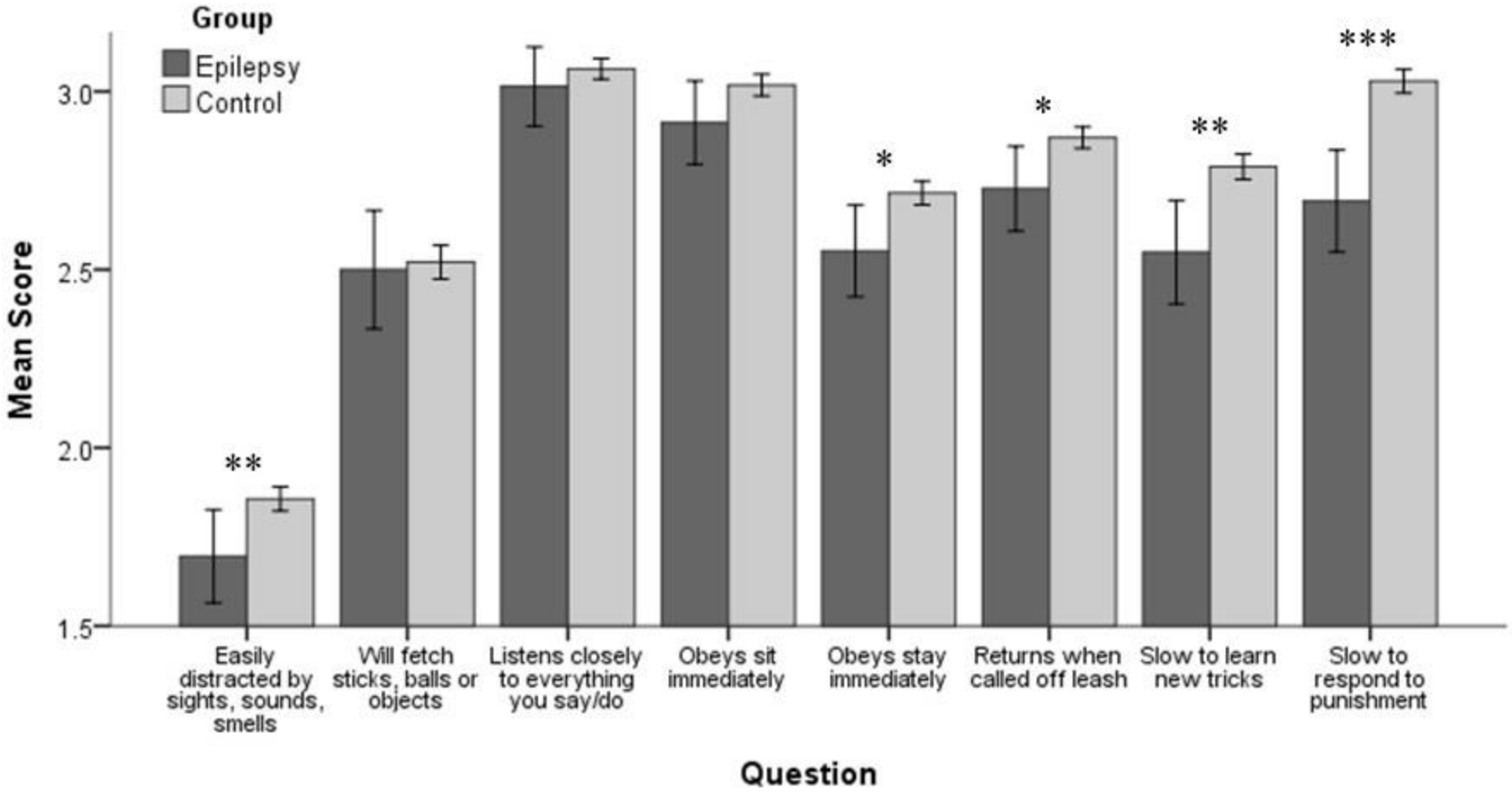
Spatial Working Memory



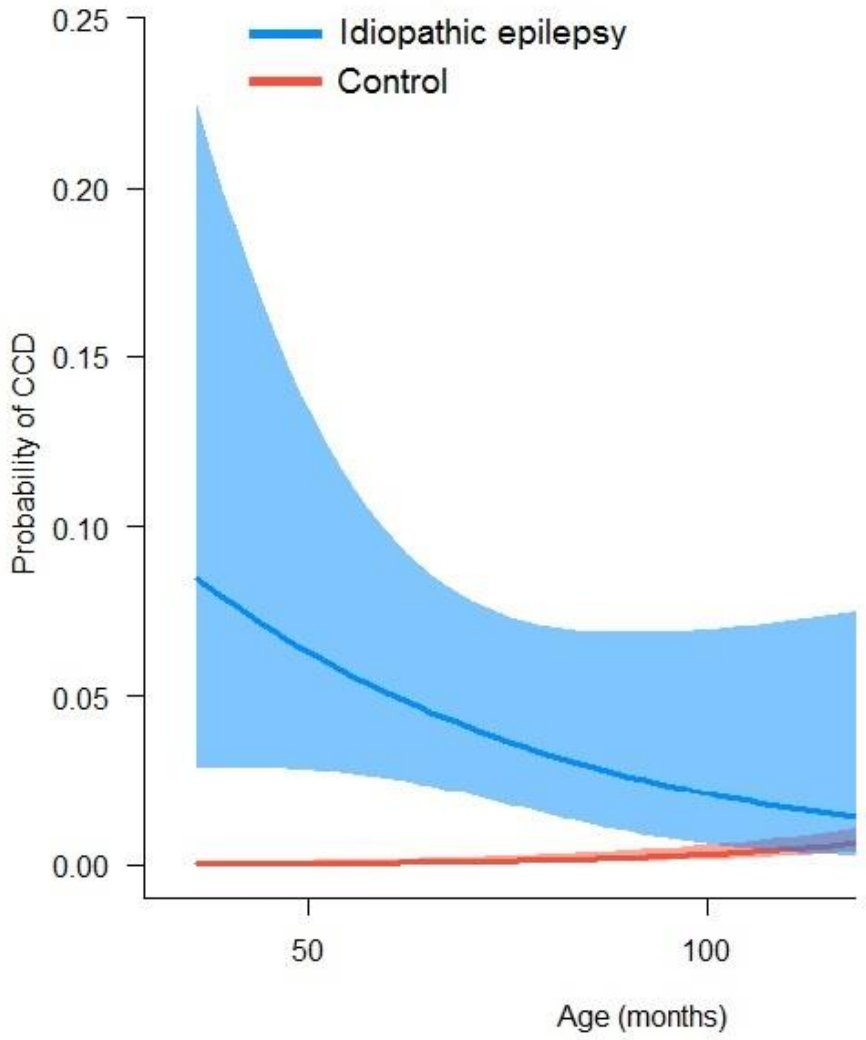
Problem Solving Abilities



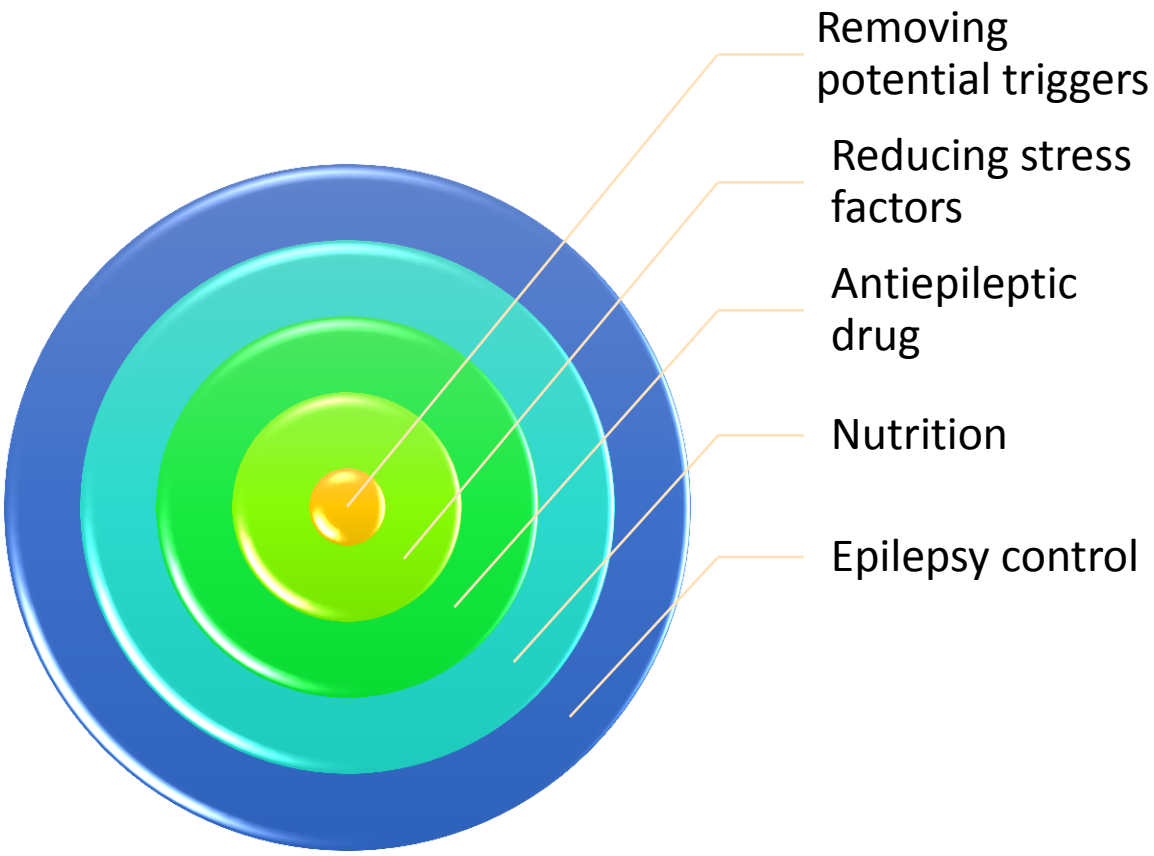
Trainability is effected by epilepsy



Cognitive Dysfunction (CCDR)



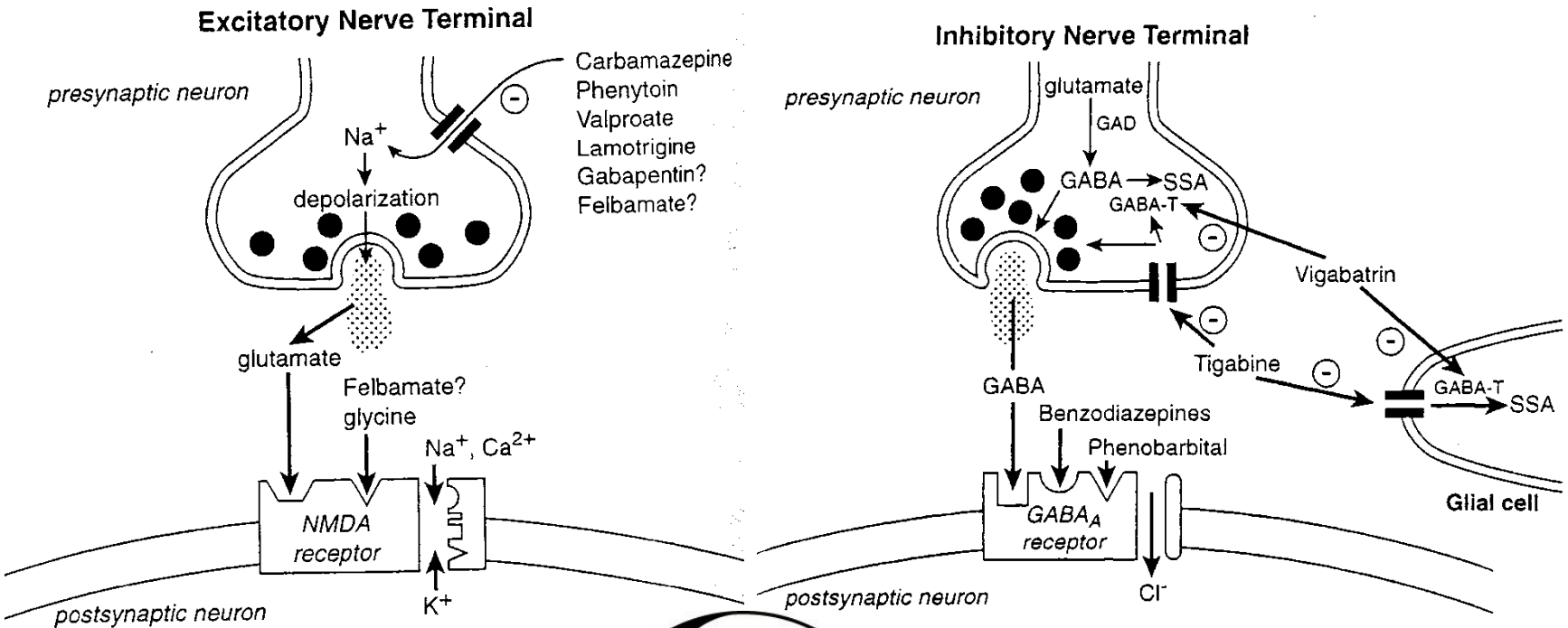
A holistic approach….

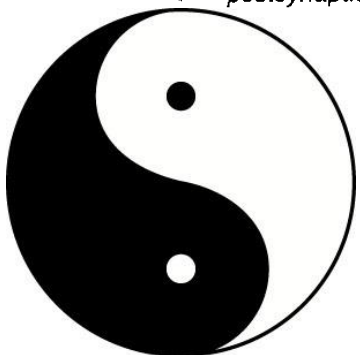


Have you ever cooked spaghetti?

RVC

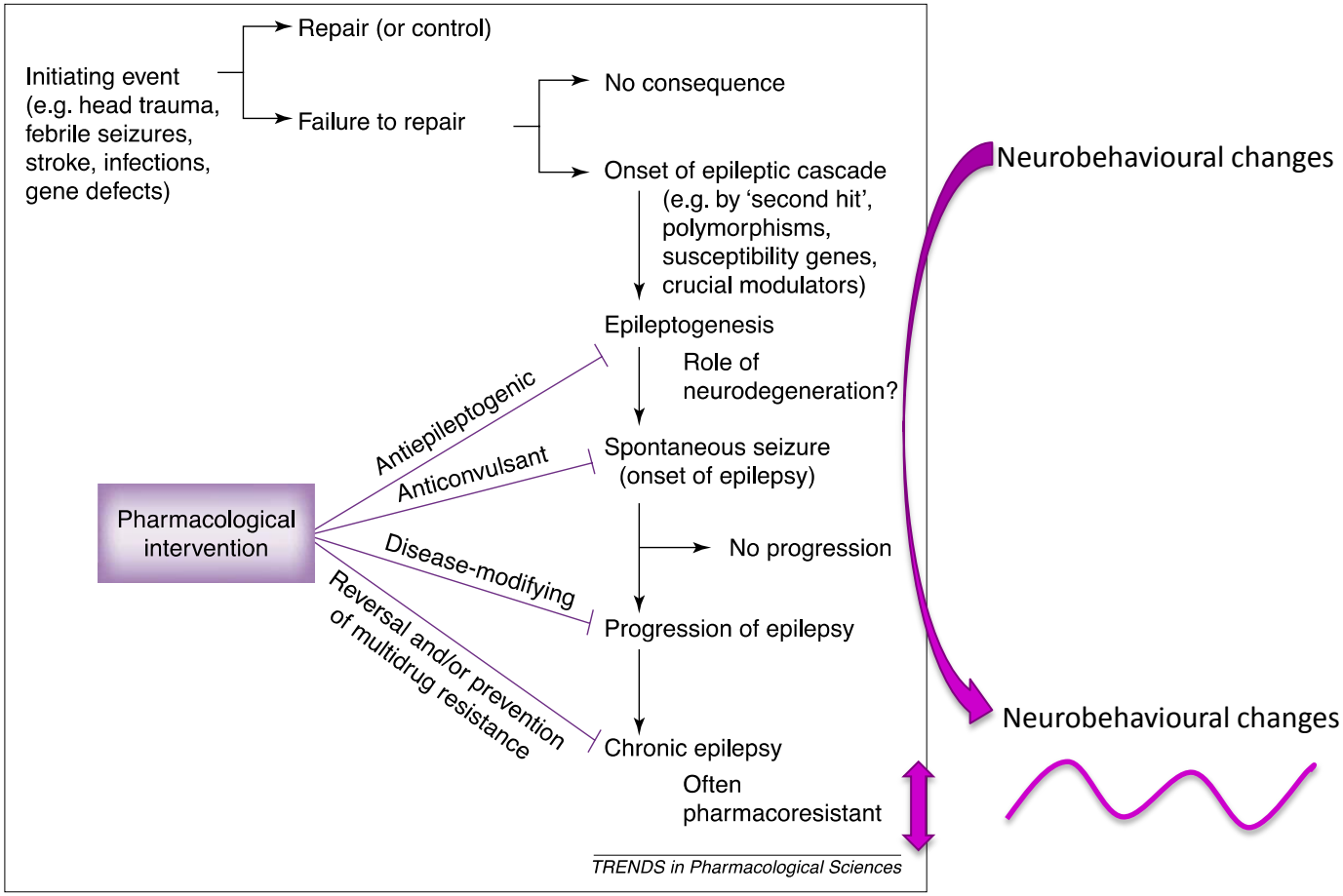
Therapy – Mode of action





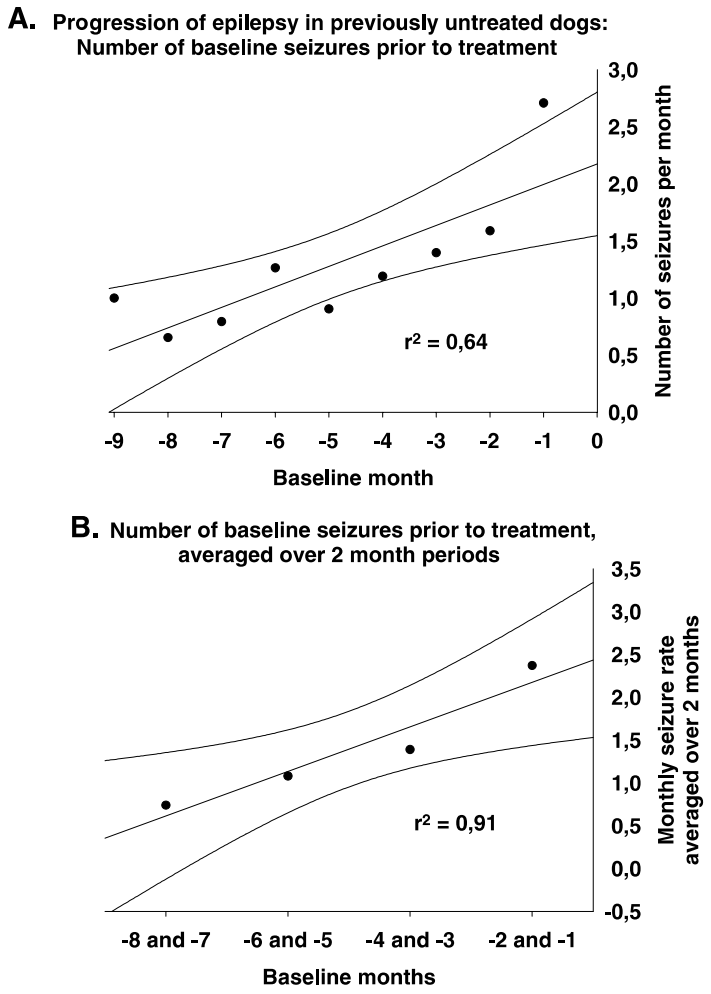
RVC

What do we treat?



Löscher, Trends in Pharmacological Sciences, 2002

Seizure begs another seizure?

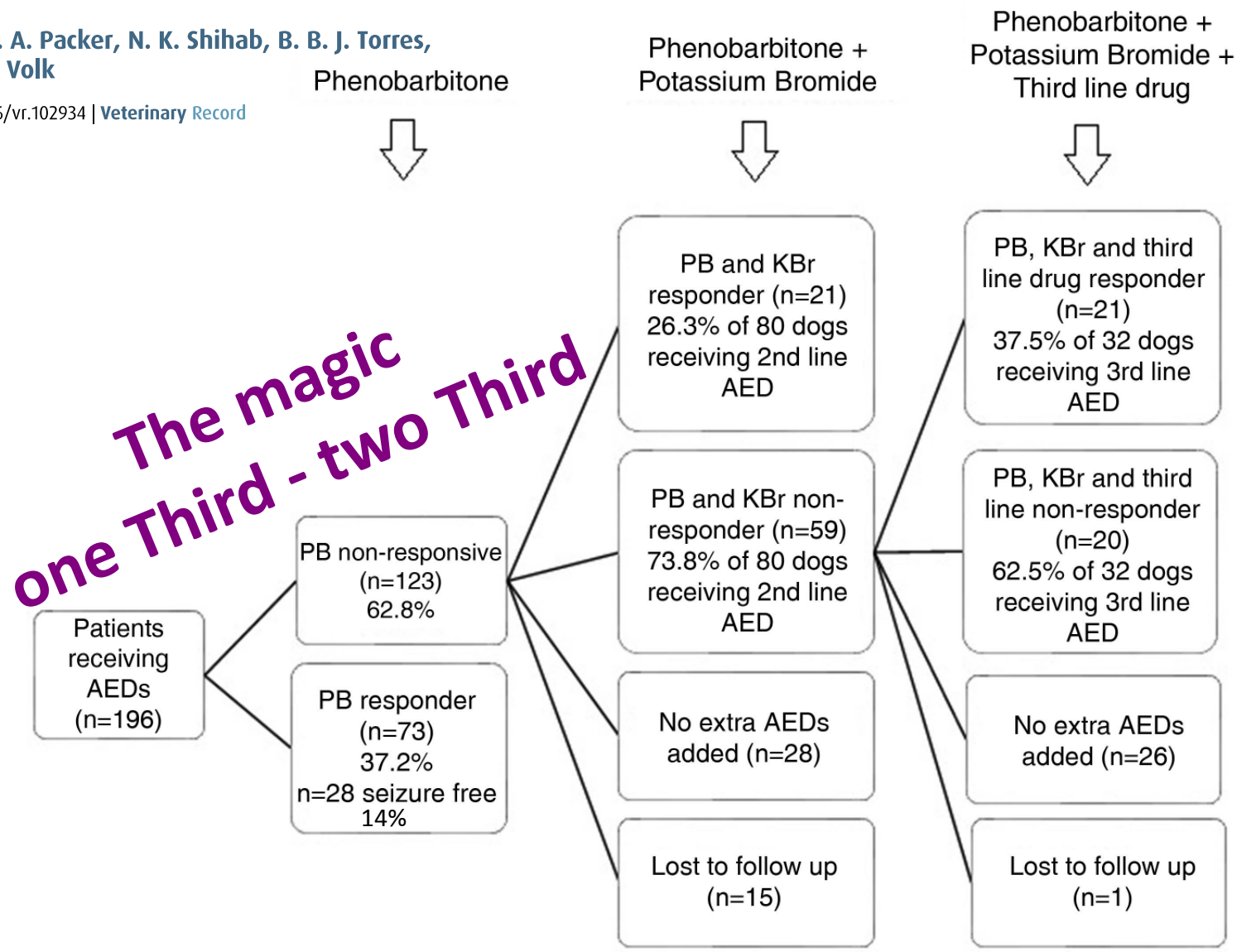


Löscher et al., 2004

Responses to successive anti-epileptic drugs in canine idiopathic epilepsy

R. M. A. Packer, N. K. Shihab, B. B. J. Torres, H. A. Volk

10.1136/vr.102934 | Veterinary Record



Fredsø et al. BMC Veterinary Research (2017) 13:54
DOI 10.1186/s12917-017-0966-y

BMC Veterinary Research

RESEARCH ARTICLE Open Access

A prospective observational longitudinal study of new-onset seizures and newly diagnosed epilepsy in dogs

N. Fredsø[1*], N. Toft[2], A. Sabers[3] and M. Berendt[1]

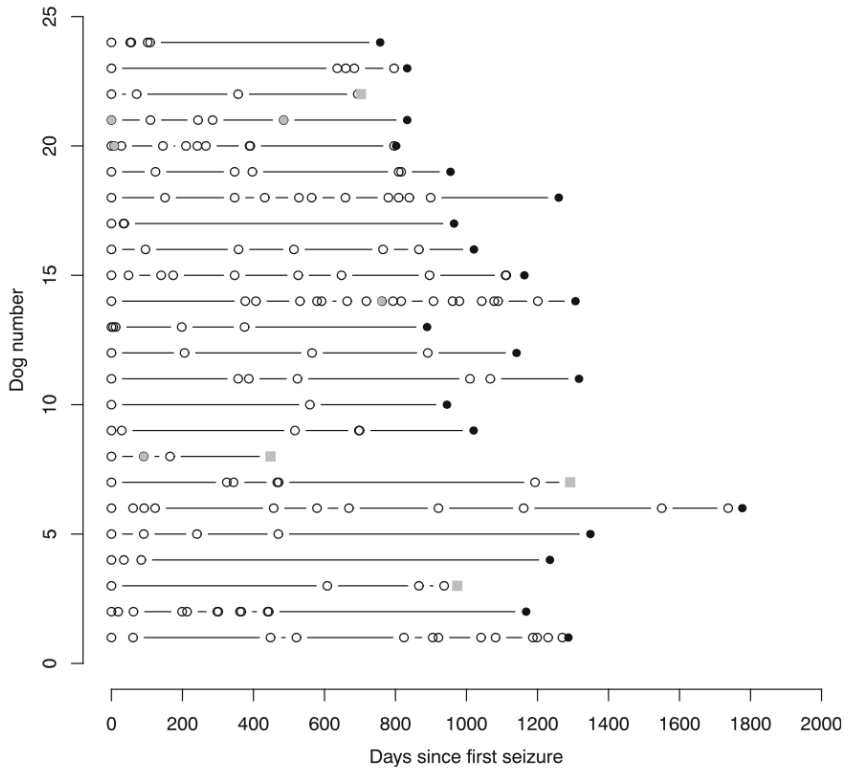


Fig. 2 Seizure recurrence in 24 untreated dogs with idiopathic epilepsy. Open circles = seizure. *Black* circles = end of study. *Gray* circles = cluster seizure. *Gray* squares = Death/euthanasia

Drug-resistant epilepsy

Environment?

Diet?

Impact of

genetic Factors (epistatic, epigenetic)

disease-associated factors

drug-induced factors

Seizure density

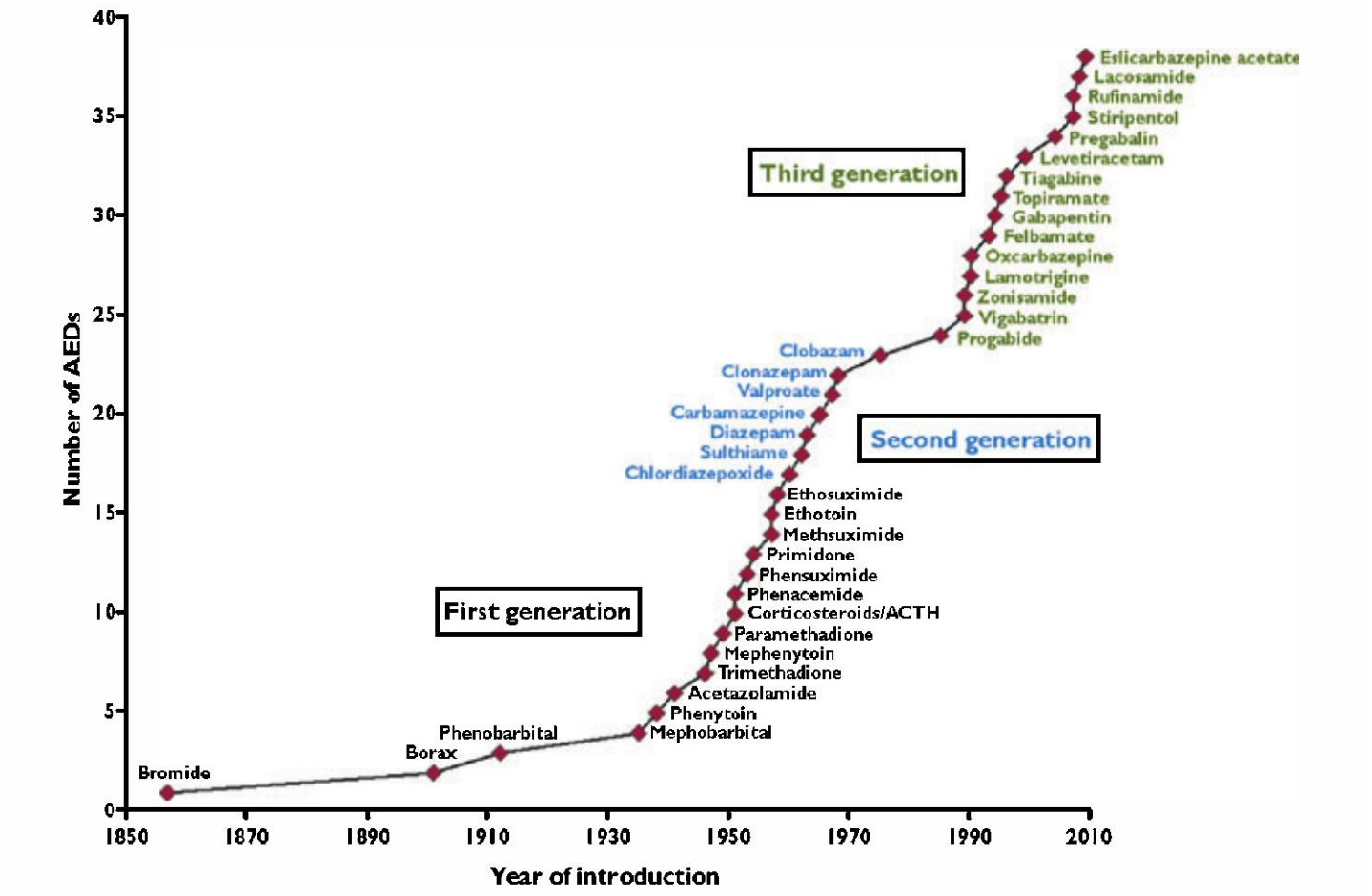
? Changes in drug targets

? Changes in local brain uptake of anticonvulsant drugs

Is there a magic wand?

RVC

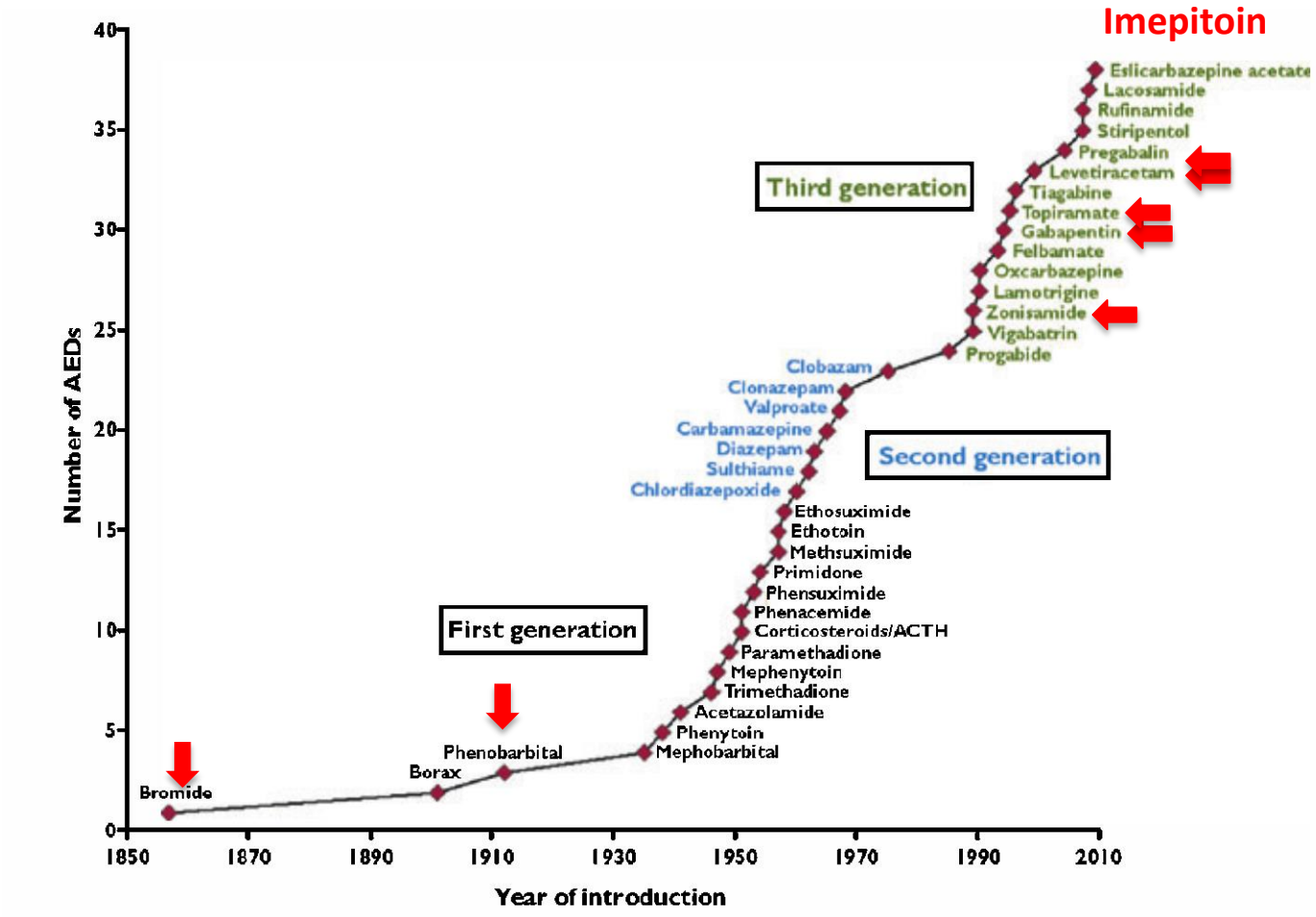
Chronology of human AED market



Loscher and Schmidt 2011

RVC

Dog



Loscher and Schmidt 2011

RVC

Education prior to treatment

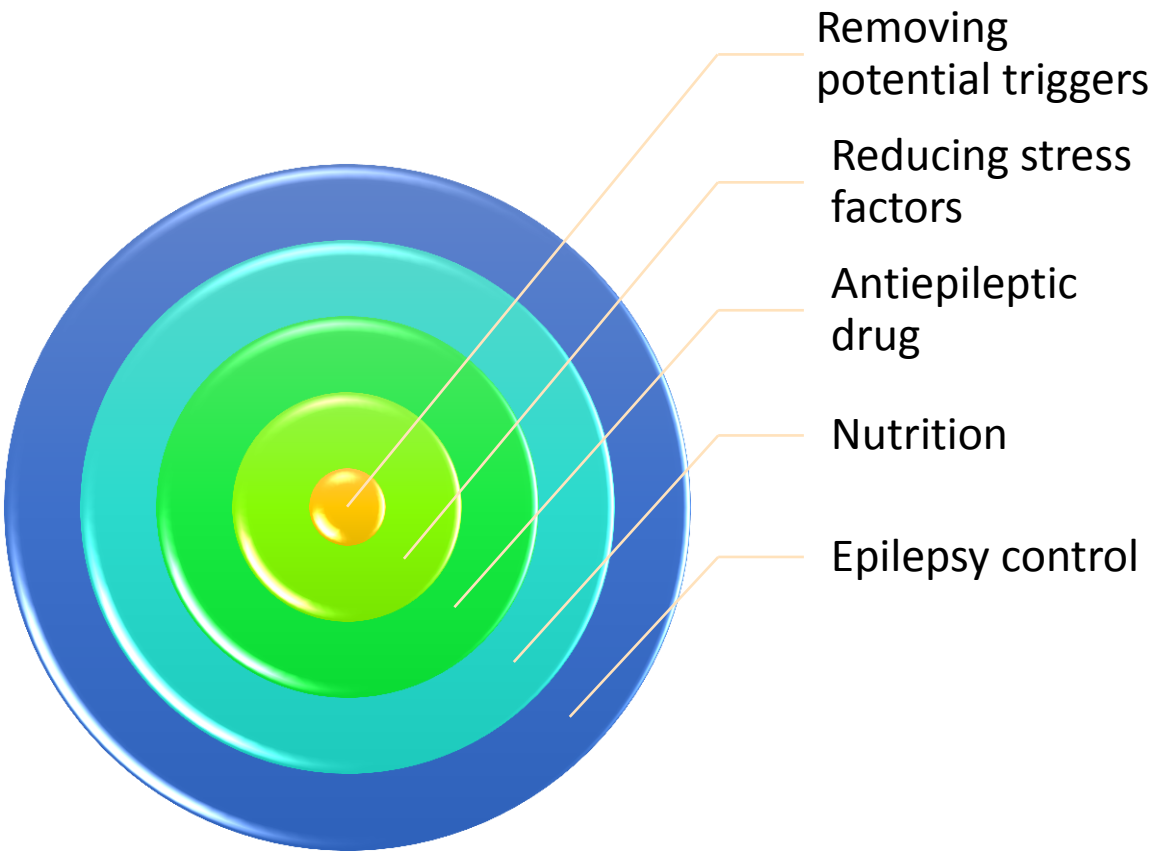
Life-time commitment - “your dog may always have a seizure”

Chart for seizure frequency

Side effects

http://www.rvc.ac.uk/news-and-events/press-office/rvc-creates-a-dog-epilepsy-smart-phone-app-to-help-manage-mans-best-friend-s-fits

A holistic approach….



What is the role of diets?

RVC

Diets

- General dietary considerations
- Specialised nutrition
  - Hypoallergenic diet
  - Omega-3 fatty acid supplementation
  - Ketogenic diet (KD)

British Journal of Nutrition, page 1 of 10
doi:10.1017/S000711451500313X

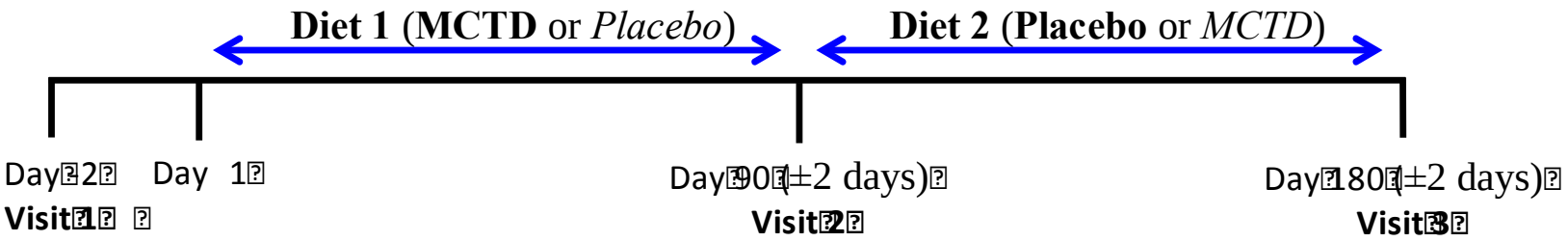
A randomised trial of a medium-chain TAG diet as treatment for dogs with idiopathic epilepsy

Tsz Hong Law[1,2], Emma S. S. Davies[1], Yuanlong Pan[3], Brian Zanghi[3], Elizabeth Want[2] and Holger A. Volk[1]*

[1]Department of Clinical Science and Services, Royal Veterinary College, Hatfield AL9 7TA, UK
[2]Section of Computational and Systems Medicine, Imperial College, London SW7 2AZ, UK
[3]Nestlé Purina Research, St Louis, MO 63164, USA

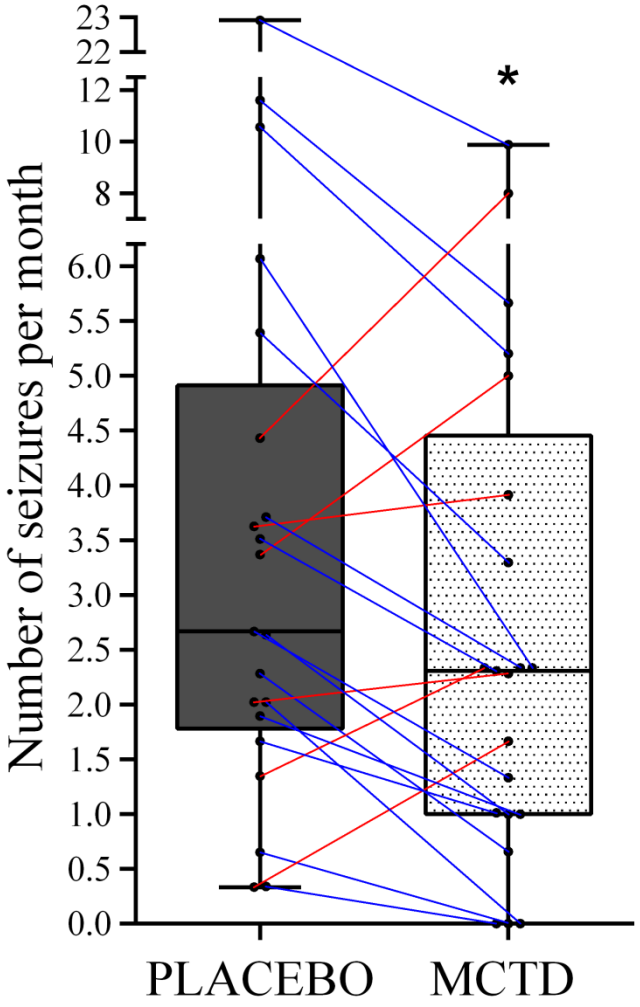
(Submitted 20 April 2015 – Final revision received 16 July 2015 – Accepted 21 July 2015)

Medium chain triglycerides diet (MCTD) study design



- 6-month prospective, randomised, double-blinded, placebo controlled crossover dietary trial
- Idiopathic epilepsy
- ≥1 Antiepileptic drug (AED) chronically treated (steady state)
- ≥3 seizures in last 3 months

Seizure **frequency** per month



Seizure frequency	Placebo	Test
Minimum	0.33	0.00
Median	2.67	2.31
Maximum	22.92	9.89

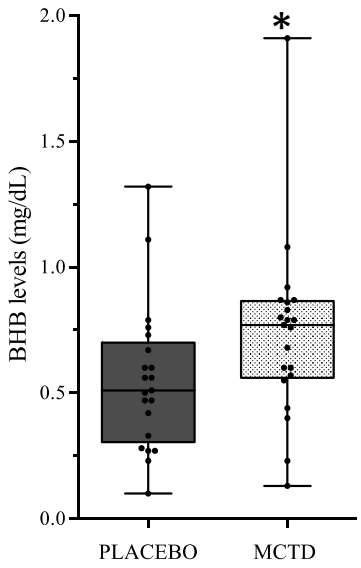
Wilcoxon's matched pairs signed rank test

P=0.0195 (2-sided)

3 become seizure free
7 responders (>50% reduction in seizures)
5 reduction in seizures
6 no response

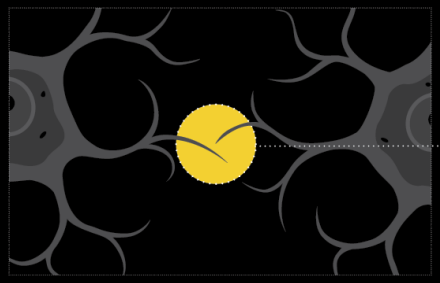
Results

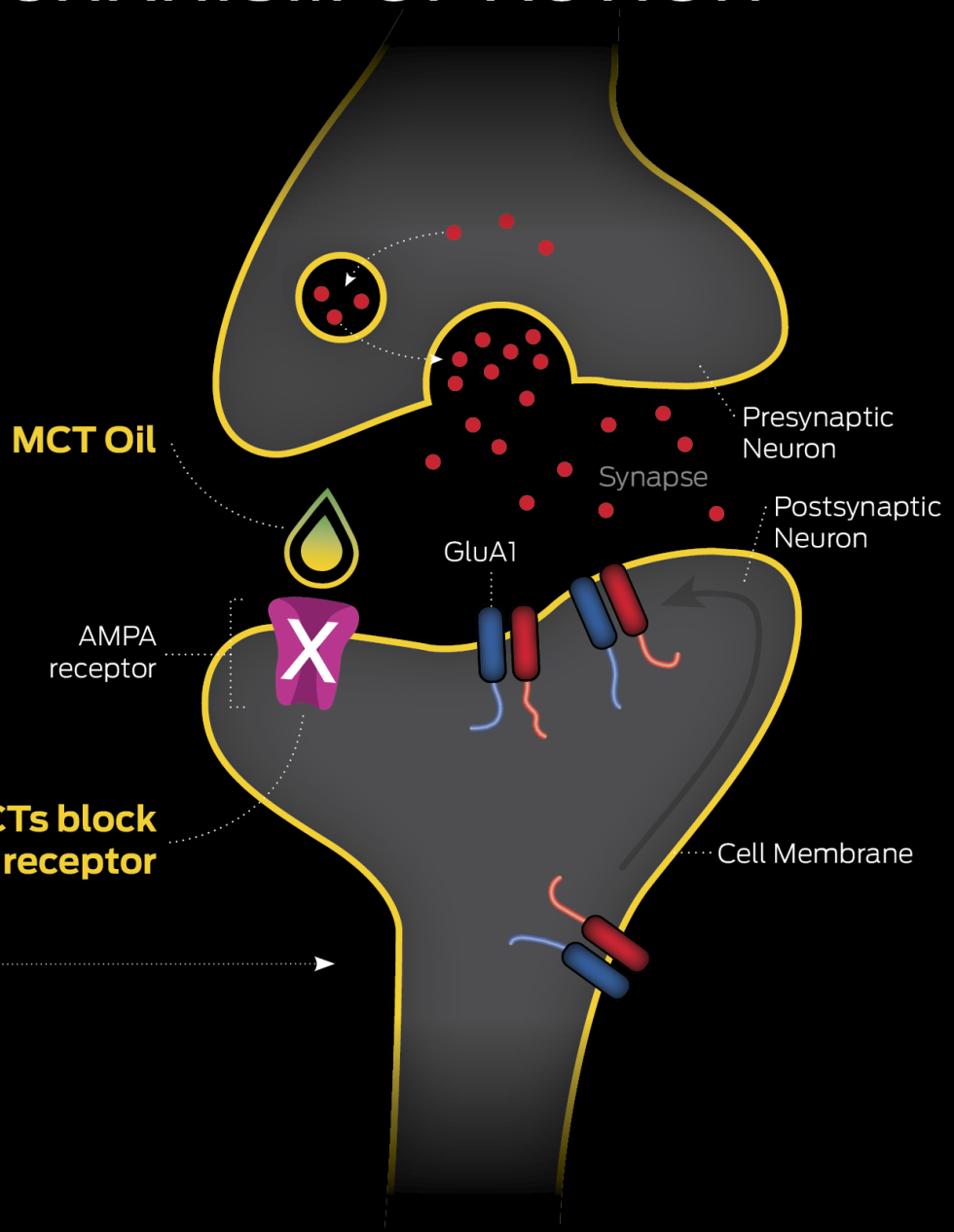
- No significant change between both diets in:
  - Phenobarbital serum levels (26.50µg/ml, 23.50-34.00µg/ml v. 32.50µg/ml, 25.00-36.75µg/ml, p=0.4233)
  - Potassium bromide serum levels (1.23mg/ml, 1.09-1.89mg/ml v. 1.29mg/ml, 1.02-1.61mg/ml, p=0.4037)
  - Weight (29.79, ±15.16kg v. 29.61, ±15.51kg, p=0.2997)
- There was a significant increase in blood level hydroxybutyrate (BHB) on MCTD



A NOVEL MECHANISM OF ACTION

- Typical antiepileptic drugs (phenobarbital and potassium bromide) are GABAergic enhancing inhibitory neurotransmission
- Experts believe MCTs (C10:0 – decanoic acid) may have direct anti-seizure effects via blockage of AMPA receptors inhibiting excitatory neurotransmission; enhancing typical antiepileptic therapy[10]





Review

Epilepsy beyond seizures: a review of the impact of epilepsy and its comorbidities on health-related quality of life in dogs

Rowena M. A. Packer, Holger A. Volk

Veterinary Record (2015), 306-315 doi: 10.1136/vr.103360

Royal Veterinary College
University of London

Thank you


Holger Volk


Patrick Kenny
Head of Service


Steven De Decker


Joe Fenn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