



Qualität für Menschen

# Von DEE bis Cannabis

Peter Borusiak



# Lebensphasen bei schwer verlaufenden kindlichen Epilepsien

Wandel der klinisch dominierenden Probleme im Verlauf

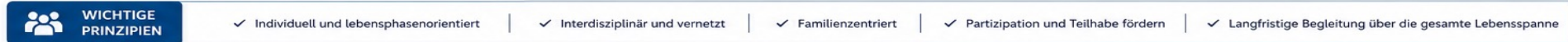
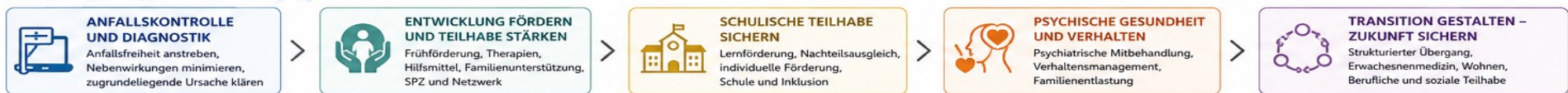
Die Problemlast verschiebt sich im Verlauf: von den Anfällen hin zu Entwicklungs-, Verhaltens- und Teilhabeaspekten



Wandernder klinischer Schwerpunkt



Ziele und Schwerpunkte der Versorgung



**i** Bei schwer verlaufenden kindlichen Epilepsien (insbesondere Entwicklungs- und epileptische Enzephalopathien) verschiebt sich die Bedeutung der Symptome im Verlauf. Während zu Beginn die Anfälle im Vordergrund stehen, werden später neurokognitive, psychiatrische und soziale Folgen bedeutsamer als die Epilepsie selbst. Die epileptische Aktivität kann die Hirnentwicklung zusätzlich beeinträchtigen. Viele Syndrome zeigen eine altersabhängige klinische Evolution.

Quellen (Auswahl):

- Specchio N. et al. *Nature Reviews Disease Primers*. 2024;10:89.
- Wirrell EC. et al. *Epilepsia*. 2022.
- Stafstrom CE. et al. *Epilepsy Behav*. 2021.
- Kwan P., Arzimanoglou A., Berg AT. *Epileptic Disord*. 2010.

## Mein Plan

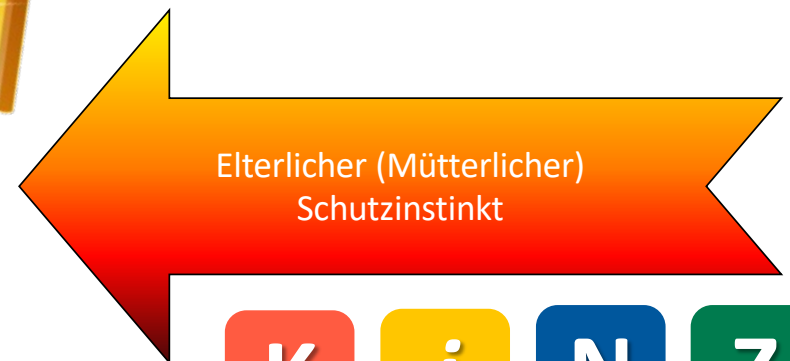
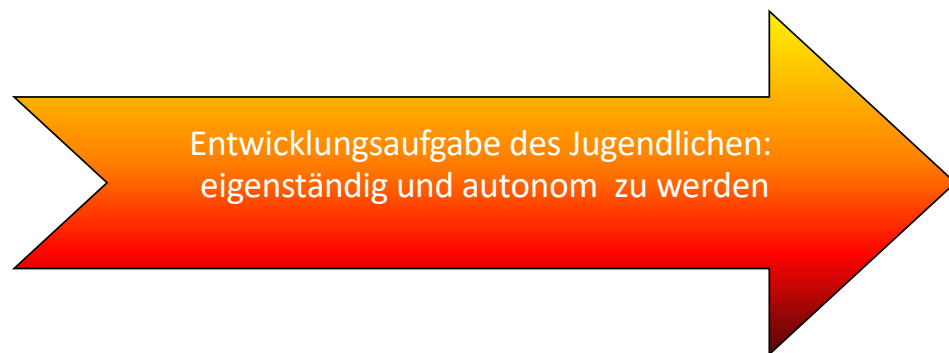
- Wer darf eigentlich was? Fokus: Jugendliche
- Stimmt die erste Grafik eigentlich – Ergebnisse einer Elternbefragung

## Ihr Plan?

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- 
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# Themen

- Alkohol, Cannabis und sonst so
- Disco
- Schwimmen, Baden
- „Adhärenz“

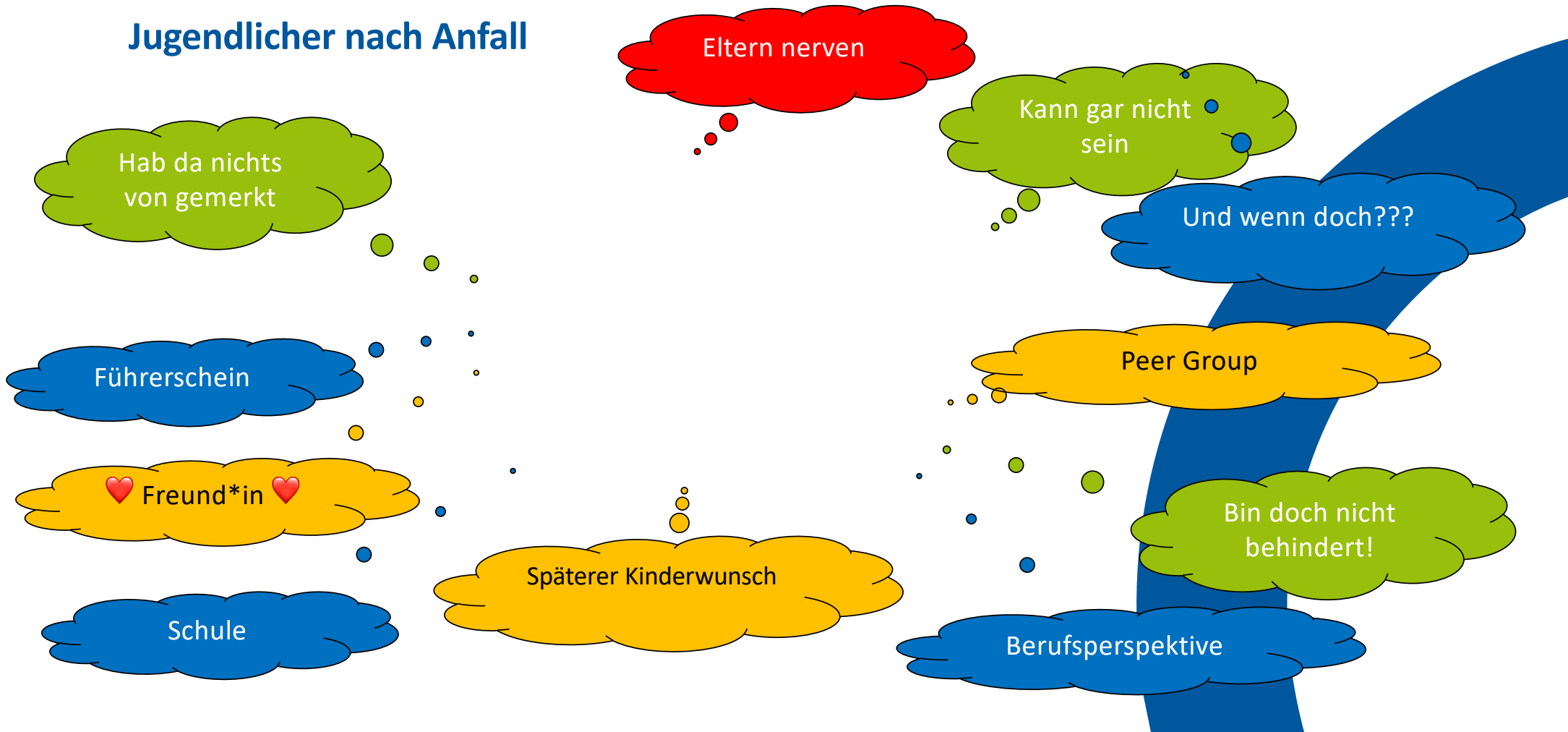


# Was ist eigentlich los?

- Häufigkeit pubertärer Konflikte in den verschiedenen sozialen Untergruppen ähnlich
- Je größer die Lücke zwischen Ansichten von Eltern und Heranwachsenden über die Reife (und Übernahme von Verantwortung) ist, umso mehr Streit
- Die meisten Streitigkeiten sind eher leicht – grundsätzliche Werte stimmen weitgehend überein
- Entwicklung formal-operationalen Denkens
  - ✓Ableitung logischer Regeln durch innere Reflektion (es muss nicht immer alles ausprobiert werden)
  - ✓Abstraktes Denken

Jugendliche erwerben formale Operationen – und wenden sie an – das führt zum streitbaren Teenager, der seinen Standpunkt vertritt (und endlos diskutiert) – dadurch lernen die Jugendlichen die Werte ihrer Eltern besser kennen (und übernehmen sie nicht selten)

**Jugendlicher nach Anfall**



# Verbote und Gebote

## bloß kein:

- Fernsehen, Disco
- Zocken
- Stress, Toben
- Schulsport
- Schwimmen, Baden
- Radfahren, Klettern
- Reizklima, Sonne
- Impfen
- Fliegen

## immer schön:

- Tabletten regelmäßig
- Tabletten pünktlich
- früh zu Bett
- viel schlafen
- Helm tragen
- unter Aufsicht
- Anfälle verheimlichen

# Alkohol

- Doppelblindstudie (Höppner et al.; Epilepsia 1983)
- 1 – 3 Gläser Vodka/Orangensaft – Orangensaft pur
- Kein Unterschied in der Anfallshäufigkeit für
  - Komplex fokale Anfälle
  - Grand mal
- Kein Einfluss auf Serumkonzentrationen von CBZ, PB, PHT
- Evtl. leichte Erhöhung von VPA
- Kein Einfluss auf spike-Dichte im EEG

# Kaffee

*Seizure* 2004; 13: 284–285  
doi:10.1016/S1059-1311(03)00079-7

CASE REPORT

## Heavy coffee drinking and epilepsy


LEONARDO BONILHA & LI M. LI

N=1, 40 J. ♂, 2 ½ | Kaffee

# Brause

Epilepsy & Behavior 23 (2012) 384–385

Contents lists available at [SciVerse ScienceDirect](#)



**Epilepsy & Behavior**

journal homepage: [www.elsevier.com/locate/yebeh](http://www.elsevier.com/locate/yebeh)

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Case Report

## Single tonic–clonic seizure after energy drink abuse

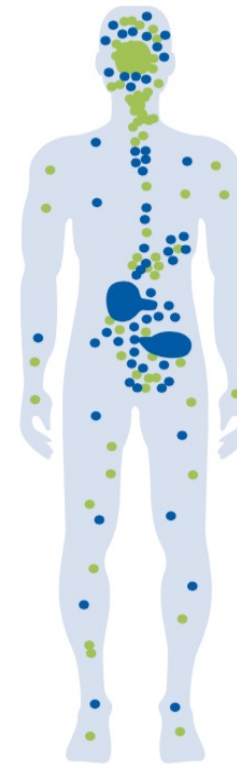
Rocco S. Calabrò\*, Domenico Italiano, Giuseppe Gervasi, Placido Bramanti

*IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy*

- N=1, 20 J. ♂, 5-6 Dosen Red Bull/d
- Coffein & Taurin
- Nicht wirklich überzeugend durch RB ausgelöst
  
- 13,97 Mrd. Dosen wurden 2025 verkauft

# Endocannabinoidsystem

- Cannabinoid-Rezeptoren
  - Metabotrop, G-Protein-gekoppelt
  - CB1 neuronal, CB2 Immunsystem
- Endocannabinoidsystem aktiviert bei exzessiver neuronaler Aktivität
  - Bioregulation bei Inflammation, Gedächtnis, Stimmung,...
  - Überaktivierung: Sucht, Diabetes, Lebererkrankungen
- Cannabinoide sind die einzigen Medikamente, die an den CB-Rezeptoren andocken



**CB1**  
VORKOMMEN

- ▶ Zentrales Nervensystem
- ▶ Peripheres Nervensystem
- ▶ Gastrointestinaltrakt
- ▶ Reproduktionsorgane
- ▶ Gefäßwände
- ▶ Fettzellen
- ▶ Hepatozyten
- ▶ u.a.

**CB2**  
VORKOMMEN

- ▶ Immunsystem
- ▶ Mikroglia
- ▶ Zentrales Nervensystem
- ▶ Hämatopoetische Zellen
- ▶ u.a.

Szarflarski & Bebin, Epil Behav 2014

# Cannabinoide

- Marihuana (Rauch, Öl, Tinktur, ...) > 100 Phytocannabinoide
  - Pharmakologisch am meisten untersucht und wichtigsten Tetrahydrocannabinol und Cannabidiol ( $\Delta^9$ -THC und CBD)

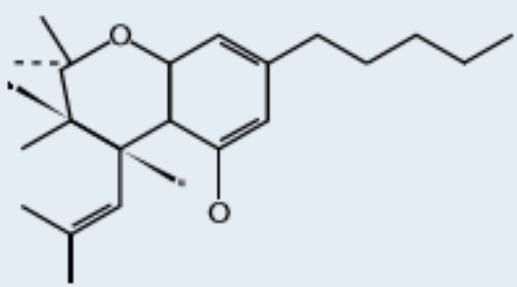
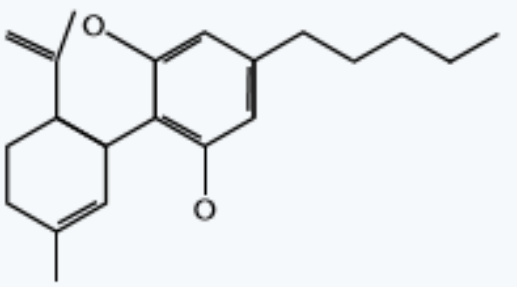
Cannabinoid	Structure	Central Nervous System Targets	Actions
$\Delta^9$ -Tetrahydrocannabinol		CB <sub>1</sub> R CB <sub>2</sub> R (microglia) TRPA1 TRPV2 TRPM8 $\alpha_3$ GlyR 5-HT <sub>1A</sub> R PPAR- $\gamma$ GPR18 GPR55	Partial agonist Partial agonist Agonist Agonist Antagonist Enhancer Antagonist Activator Agonist Agonist
Cannabidiol		CB <sub>1</sub> R CB <sub>2</sub> R (microglia) GPR55 TPA1 TRPV1-3 TRPV4 TRPM8 5-HT <sub>1A</sub> R 5-HT <sub>2A</sub> R $\alpha_3$ GlyR PPAR- $\gamma$ Ca <sub>v</sub> 3 ion channel Adenosine reuptake	Antagonist Antagonist Antagonist Agonist Agonist Agonist Antagonist Enhancer Antagonist Enhancer Activator Inhibitor Inhibitor
Cannabidivarin		TRPA1 TRPM8 TRPV4 TRPV1-3 DAGL- $\alpha$	Agonist Antagonist Agonist Agonist Inhibitor

**Figure 1. Selected Pharmacologic Features of Cannabinoids Showing Antiseizure Effects in Preclinical Models.**  
 The exact targets that mediate the antiseizure effects of cannabinoids are unknown. Several cannabinoids are known to bind to multiple targets in the central nervous system and exert effects at nanomolar or low micromolar concentrations. These targets include transient receptor potential cation channel, subfamily V, members 1, 2, and 3 (TRPV1-3), glycine receptor  $\alpha$  ( $\alpha_3$ GlyR), peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ), calcium-gated ion channel (Ca<sub>v</sub>3 ion channel), and diacylglycerol lipase  $\alpha$  (DAGL- $\alpha$ ). There are conflicting results from multiple studies on the effects of  $\Delta^9$ -tetrahydrocannabinol on G-protein-coupled receptor (GPR) 55. CB<sub>1</sub>R and CB<sub>2</sub>R denote cannabinoid receptor types 1 and 2, 5-HT the serotonin receptors 5-hydroxytryptophan type 1A and 3A, TRPA transient receptor potential cation channel, subfamily A, and TRPM transient receptor potential cation channel, subfamily M. Adapted from Cascio and Pertwee<sup>9</sup> and Pertwee and Cascio.<sup>10</sup>

Friedman & Devinski NEJM 2015

# Cannabinoide

Friedman & Devinski NEJM 2015

Cannabinoid	Structure	Central Nervous System Targets	Actions
$\Delta^9$ -Tetrahydrocannabinol		<ul style="list-style-type: none"> <li>CB<sub>1</sub>R</li> <li>CB<sub>2</sub>R (microglia)</li> <li>TRPA1</li> <li>TRPV2</li> <li>TRPM8</li> <li><math>\alpha_1\beta</math> GlyR</li> <li>5-HT<sub>3A</sub>R</li> <li>PPAR-<math>\gamma</math></li> <li>GPR18</li> <li>GPR55</li> </ul>	<ul style="list-style-type: none"> <li>Partial agonist</li> <li>Partial agonist</li> <li>Agonist</li> <li>Agonist</li> <li>Antagonist</li> <li>Enhancer</li> <li>Antagonist</li> <li>Activator</li> <li>Agonist</li> <li>Agonist</li> </ul>
Cannabidiol		<ul style="list-style-type: none"> <li>CB<sub>1</sub>R</li> <li>CB<sub>2</sub>R (microglia)</li> <li>GPR55</li> <li>TPRA1</li> <li>TRPV1-3</li> <li>TRPV4</li> <li>TRPM8</li> <li>5-HT<sub>1A</sub>R</li> <li>5-HT<sub>3A</sub>R</li> <li><math>\alpha_3</math>GlyR</li> <li>PPAR-<math>\gamma</math></li> </ul>	<ul style="list-style-type: none"> <li>Antagonist</li> <li>Antagonist</li> <li>Antagonist</li> <li>Agonist</li> <li>Agonist</li> <li>Agonist</li> <li>Antagonist</li> <li>Enhancer</li> <li>Antagonist</li> <li>Enhancer</li> <li>Activator</li> </ul>

# Ein wenig Pharmakologie

- Je nach Zusammensetzung der Cannabinoide haben einzelne Komponenten ggf. unterschiedliche (oder unterschiedlich starke) Effekte
- z.B. erhöht CBD erwünschte Effekte von  $\Delta$ 9-THC (Analgesie, Antiemese, Antiinflammation) und reduziert unerwünschte psychotrope Effekte
- Abusus bei höherer CBD: $\Delta$ 9-THC-Ratio macht weniger Psychose und höhere Tolerabilität

## Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products

Ryan Vandrey, PhD<sup>1</sup>; Jeffrey C. Raber, PhD<sup>2</sup>; Mark E. Raber<sup>2</sup>; [et al](#)

» [Author Affiliations](#) | [Article Information](#)

JAMA. 2015;313(24):2491-2493. doi:10.1001/jama.2015.6613

## Results

Of 75 products purchased (47 different brands), 17% were accurately labeled, 23% were underlabeled, and 60% were overlabeled with respect to THC content (**Table 1**). The

# Baden

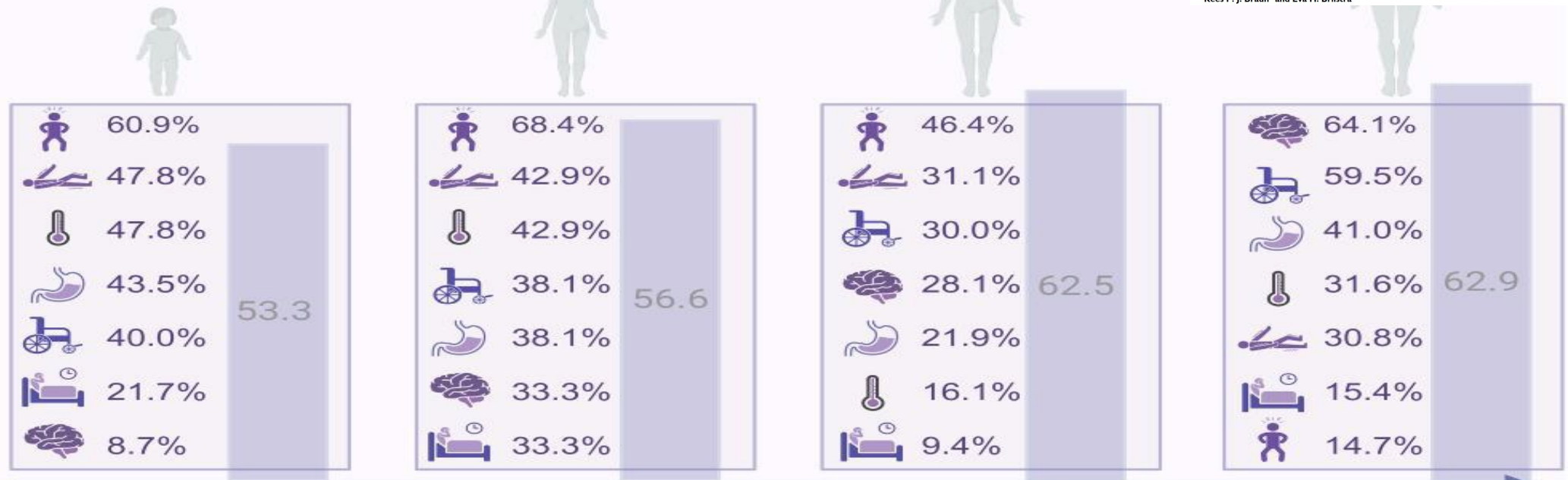
- Ansonsten gesunde Kinder mit Epilepsie haben kein erhöhtes Mortalitätsrisiko, aber
- Risiko für (tödliche) Unfälle in Zusammenhang mit Wasser deutlich erhöht
- Raten zwischen 4,4-fach und 23-fach erhöht
- Todesfälle fast alle unbeaufsichtigt

# Evolution of Dravet syndrome

HRQoL

## Quality of life in SCN1A-related seizure disorders across the lifespan

©Crista A. Minderhoud,<sup>1</sup> Amber Postma,<sup>2</sup> Floor E. Jansen,<sup>1</sup> Janneke R. Zinkstok,<sup>2,3,4</sup> Judith S. Verhoeven,<sup>5</sup> Bianca Berghuis,<sup>6</sup> Wim M. Otte,<sup>1</sup> Marian J. Jongmans,<sup>7,8</sup> Kees P. J. Braun<sup>1</sup> and Eva H. Brilstra<sup>9</sup>



Toddler

Child

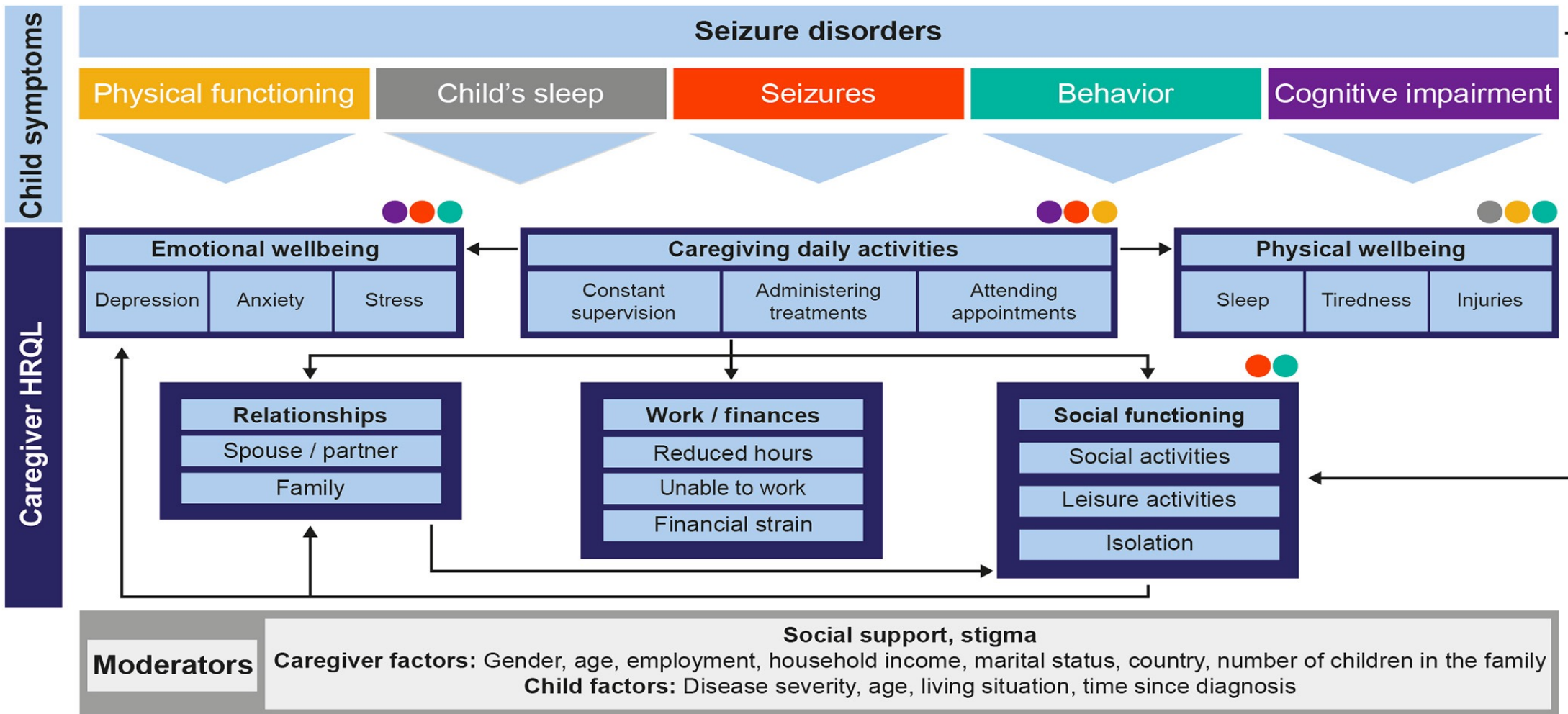
Teen

Adult

- Behavioral problems in the clinical range
- Daily seizures
- Sleeping problems, a composite sleep index >4

- ≤3 ≤weekly symptoms of dysautonomia
- Uses a wheelchair on 500 meters

- ≤3 ≤weekly gastrointestinal and eating problems
- Severe intellectual disability



**Fig. 3.** Conceptual model to represent the impact on caregiver HRQL of caring for a child with a DEE. The colored boxes at the top show the main areas of symptoms or functioning that impact caregiver HRQL (physical functioning, child's sleep, seizures, behavior, and cognitive impairment). Not all symptoms are present in all disorders. The blue boxes show areas of caregiver impact with arrows indicating the direction of impact. The areas most directly impacted by the child's symptoms are shown in the second row of boxes (emotional wellbeing, daily activities, and physical wellbeing), with the more distal areas of impact (relationships, work/finances, and social functioning) shown in the third row. The colored circles indicate which corresponding symptom or functional problem impacts that domain of caregiver HRQL or burden. The gray box outlines some factors that may moderate (positively or negatively) the extent to which caregiver HRQL is impacted. For example, in some studies, caregivers report that there is a stigma surrounding seizures which means they find it difficult to get support from others, whereas caregivers also report the positive impact of having social support. DEE, developmental epileptic encephalopathy; HRQL, health-related quality of life.

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<sup>c</sup> Department of Pedagogical and Educational Sciences, Faculty of Social and Behavioral Sciences, Utrecht University, The Netherlands  
<sup>d</sup> Department of Neurology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands  
<sup>e</sup> Department of Genetics, University Medical Center Utrecht, The Netherlands  
<sup>f</sup> Department of Psychiatry, Radboud University Medical Center, Nijmegen, The Netherlands  
<sup>g</sup> Karolink Child- and Adolescent Psychiatry Nijmegen, The Netherlands

Present in age group	
3-13	14-22

Aggression or anger	++++	++
Anxiety		+
Concentration difficulties	+	
Compulsive and repetitive habits	+	++
Dangerous behavior	++++	++
Information processing	+	+
Intense focus on details		+
Impulsivity	+++	+



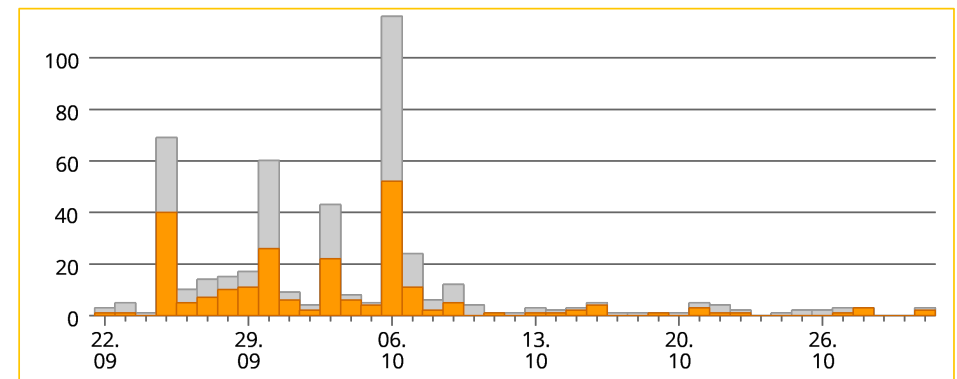
# Dravet – Erhebung bei 20 Müttern

**Table 2**  
 Illustration of sorts of behavior mentioned by these parents.

Behavior code	Quote
Aggression or anger	'I used to tell her that if she did something naughty, she had to sit on the bench in the hall. Her sister was sitting on the sofa and she walked over, hit her hard, and said to me 'I'll go sit on the bench then.' 'She has had a lot of medication and I recognize the aggressive behavior although not deliberate aggression. But yes, she throws her plate on the ground out of frustration and also other aggressive behavior: hitting, pinching or biting.'
Anxiety	'He lives, in our opinion, with a lot of anxiety. He constantly seeks reassurance. And he asks a lot of questions. All the questions irritate those around him. And the need for constant reassurance irritates people too. And he is aware of this irritation.'
Concentration difficulties	'He is so quickly distracted that in school he is not able to learn or even listen.'
Compulsive and repetitive habits	'He used to be more easygoing [...] But the rigidity has become predominant in the last 5 or 6 years. His compulsive behavior combined with the rigidity makes it very difficult.' 'He is like: 'Can I ask something?', 'Can I ask something?'. But it's not a discussion, and this repetitive behavior takes hours. [...] It drives me crazy, but I can't stop it either.'
Dangerous behavior	'It's not just the seizures, which come on so unexpectedly, and whether you can save her teeth. [...] I always say, you can never be more than an arm's length away so you can intervene in case she is about to do something dangerous. She always wants to run.' 'Yes, he's impulsive. When you turn around, he's walking around with a pair of scissors he just found, or he's sitting on top of the cat's scratching tower. He doesn't see danger anywhere.'
Information processing	'The slow processing of information is very difficult. We often just say 'stop'. We must be very clear.'
Intense focus on details	'He'll say something like, 'oh last year when we saw Grandma and Grandpa he was wearing that red jacket.' His memory is really very good.'
Impulsivity	'The impulsivity is still there. I can't go to the supermarket with her because she fills the shopping cart and doesn't take no for an answer.' 'Just as the others mentioned, she's entirely uninhibited, which causes her to be reckless. She just doesn't see any danger, so safety is a really important factor for us. We've tried 100.000 times to tell her how to look before crossing the road. But if she sees something she likes across the road, she crosses without looking.'

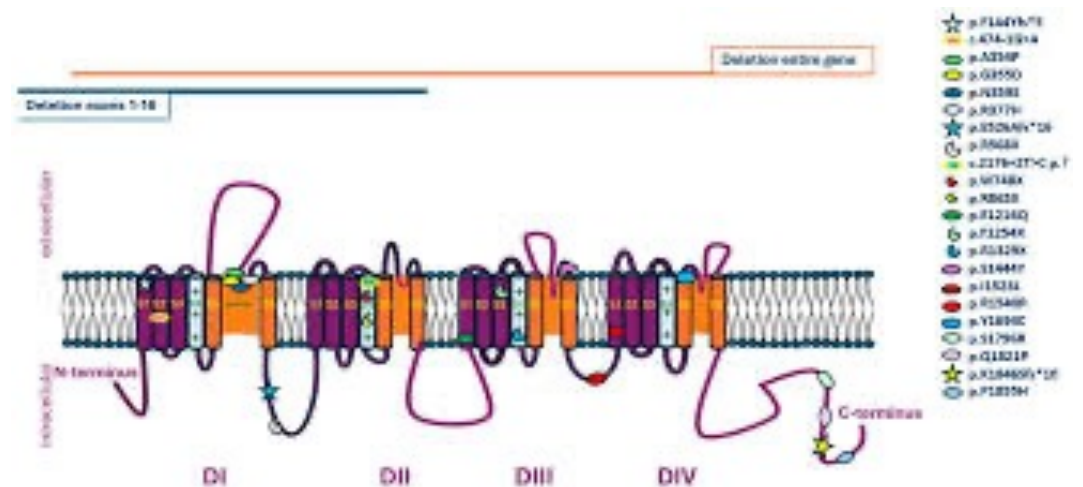
# Ergebnisse einer Umfrage

- 467 Fragebögen begonnen, 232 abgeschlossen
- Auswertbar n = 224
- Unter 18 Jahre n = 187
- Dravet n = 40
  
- Alter 11 Mo – 29 Jahre ( $12,0 \pm 6,3$  J.)
- U18:  $9,9 \pm 4,3$  J.



# Ursachen

- Dravet / SCN1A (n = 40)
- SCN2A (n = 6)
- Dup15q (n = 7)
- Glut-1-Defekt (n = 4)
- CDKL5 (n = 4)



# Ursachen

- Hirnfehlbildung Lissenzephalie
- Lennox-Gastaut
- Chromosomen Deletion (inkl LIS1)
- Cacna 1b biallel verändert
- KCNQ2
- Mikrodeletion 15q26.1 (unter anderem CHD2-Gen betroffen)
- Ringchromosom 20
- Deletion in der Chromosomenregion 21q22.13-q22.2
- CHD2
- GNA-11, Hypocalzämie
- Tuberöse Sklerose Komplex
- prrt2
- 15q11.2 Deletionssyndrom
- SLC6A1
- Radio Tartaglia Syndrom
- Rett-Syndrom
- De novo missense Variante atp6v1b2
- Neonatale Epilepsie
- DEPDC5-Gen
- Scn8a
- Deletion scn1a scn2a scn3a scn9a
- ReNu4-2
- 2q13 microdeletation
- 6Q26/27 Deletion Syndrom, Deformation der Hypocampi
- KBG Syndrom
- KCNQ5
- Mutation im KCNT1-Gen
- SETD1B
- KCNQ2



	All	N=224	All < 18 Years	N=187	Non-Dravet	N=184	Dravet	N=40
1	Epilepsy/Seizures	2,93	Epilepsy/Seizures	2,90	Epilepsy/Seizures	2,97	Epilepsy/Seizures	2,75
2	Cognitive Development	4,88	Cognitive Development	5,02	Sleep	4,97	Cognitive Development	4,03
3	Sleep	5,21	Sleep	5,16	Cognitive Development	5,07	Externalizing behavior problems	5,38
4	Externalizing behavior problems	6,45	Externalizing behavior problems	6,21	Externalizing behavior problems	6,68	Communication	5,83
5	Communication	6,59	Communication	6,47	Internalizing behavior problems	6,71	Sleep	6,35
6	Internalizing behavior problems	7,03	Internalizing behavior problems	6,99	Communication	6,76	Pain	7,98
7	Nutrition	7,83	Additional health problems	7,95	Additional health problems	7,73	Motor skills (mobility)	8,08
8	Additional health problems	7,84	Nutrition	7,99	Nutrition	7,76	Nutrition	8,15
9	Pain	8,40	Motor skills (mobility)	8,46	Pain	8,49	Screaming/Crying	8,23
10	Motor skills (mobility)	8,46	Pain	8,47	Motor skills (mobility)	8,55	Additional health problems	8,38
11	Screaming/Crying	9,04	Screaming/Crying	8,87	Fine motor skills	9,02	Internalizing behavior problems	8,48
12	Fine motor skills	9,05	Fine motor skills	9,03	Screaming/Crying	9,22	Fine motor skills	9,23
13	Self-harming behavior	9,94	Self-harming behavior	9,96	Self-harming behavior	9,96	Self-harming behavior	9,85
14	Visual disturbances	11,33	Visual disturbances	11,52	Visual disturbances	11,12	Visual disturbances	12,33

# Statistik - Keine Unterschiede

- Alleinerziehende vs. Nicht alleinerziehende (n = 33 und 190)
- U18 vs. Ü18

Mann-Whitney-U-Tests für alle 14 Rangvariablen. Keine signifikanten Unterschiede für 13 der 14 Variablen (alle  $p > .05$ ). Für die Variable „externalisierende Verhaltensauffälligkeiten“ ergab sich ein signifikanter Unterschied ( $U = 2686.50$ ,  $Z = -2.15$ ,  $p = .031$ ). Allerdings nach Bonferroni-Korrektur nicht mehr signifikant

- Verschiedene Altersgruppen

Für keine der 14 untersuchten Symptomprioritäten ergaben sich signifikante Unterschiede zwischen den fünf Altersgruppen (AG1-AG5)



Kinderneurologisches Zentrum Bonn

# Diskussion

- Warum stehen die Anfälle in allen Altersgruppen so weit oben?
- Warum sind Ziele vielleicht wichtiger als die Lebensqualität?