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Teaching Course 5

Refractory status epilepticus: What to do and how dangerous is it to the brain? (Level 2)

Is convulsive or non-convulsive SE a risk factor for cognitive dysfunction?

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Is convulsive or nonconvulsive status epilepticus a risk factor for cognitive dysfunction?

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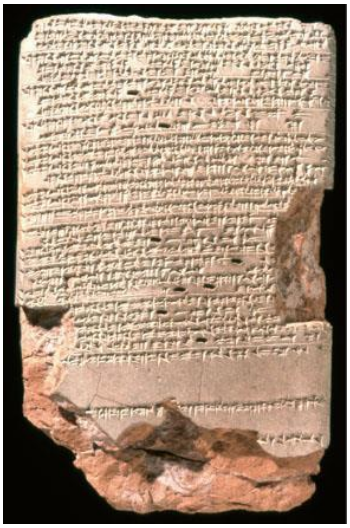
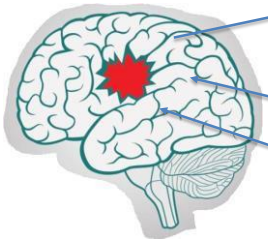
Conflict of Interest

In relation to this presentation and manuscript:

❑ the Author has no conflict of interest in relation to this manuscript.

Babylonean cuneiform text of the Sakkiku (c. 1050 BC)





Additional factors

- Type of brain lesion
- SE class, duration and refractoriness
- Age
- Comorbidity

Cognition in patients with epilepsy

- Difficult to study
- Baseline function usually unknown

- Cognitive function a main issue for people with epilepsy

Fisher RS, Epilepsy Res, 2000

Cognition in patients with epilepsy

- Memory- and learning difficulties
- Poor attention and concentration
- Problems planning
- Language deficits

William Reed Business Media LTD 2019

- Worse after many GTC-seizures
- Partly before seizure debut

Elger, 2004, Lancet Neurol.

Studies on cognitive dysfunction after SE

- Small and retrospective
- Mostly in children
- Rarely neuropsychological evaluations
- Extrapolations from MRI studies (humans) and animal experiments

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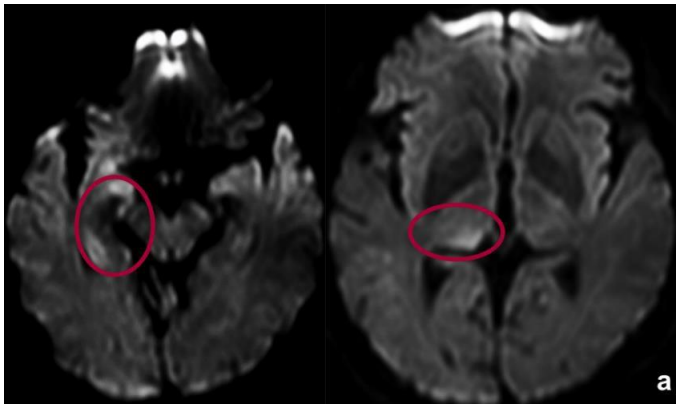
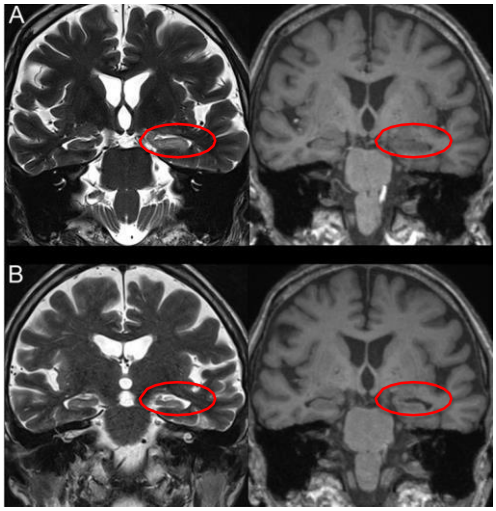
Meldrum, 1970s and 80s

Brain alterations peri-ictally

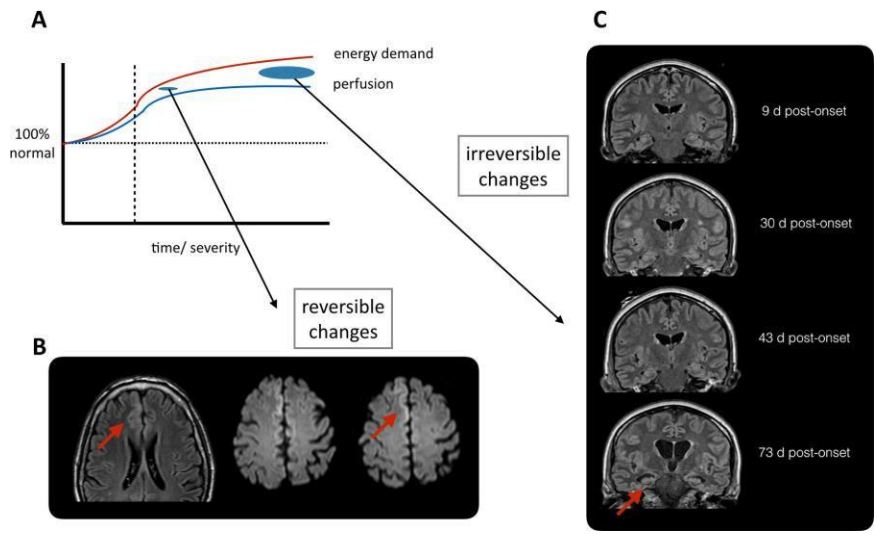


PERI-Ictal alterations:
DWI signal hyperintensity in the pulvinar of thalamus (right) and in the hippocampus (right)

Giovannini G. et al, Epilepsia, 2018

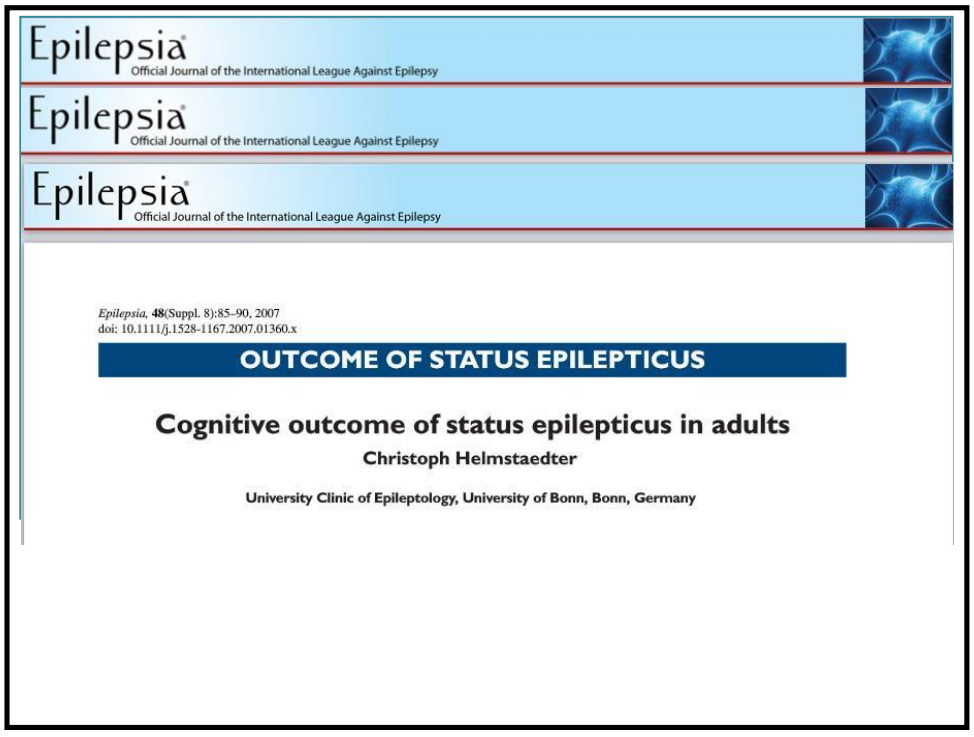


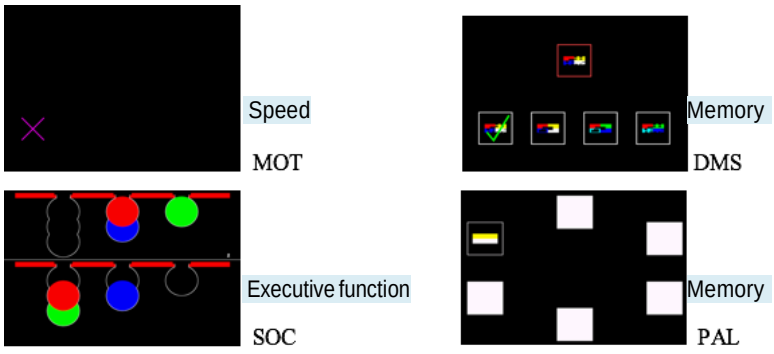
Fujisao, Front. Neurol., 2017



Meletti et al, Epilepsia, 2017

Is the cognitive dysfunction we find a direct consequence of SE?

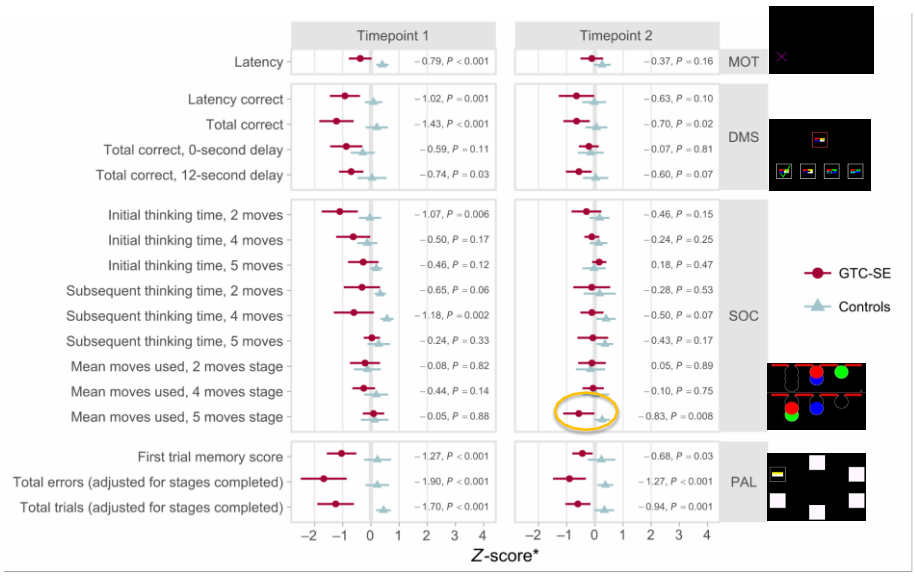




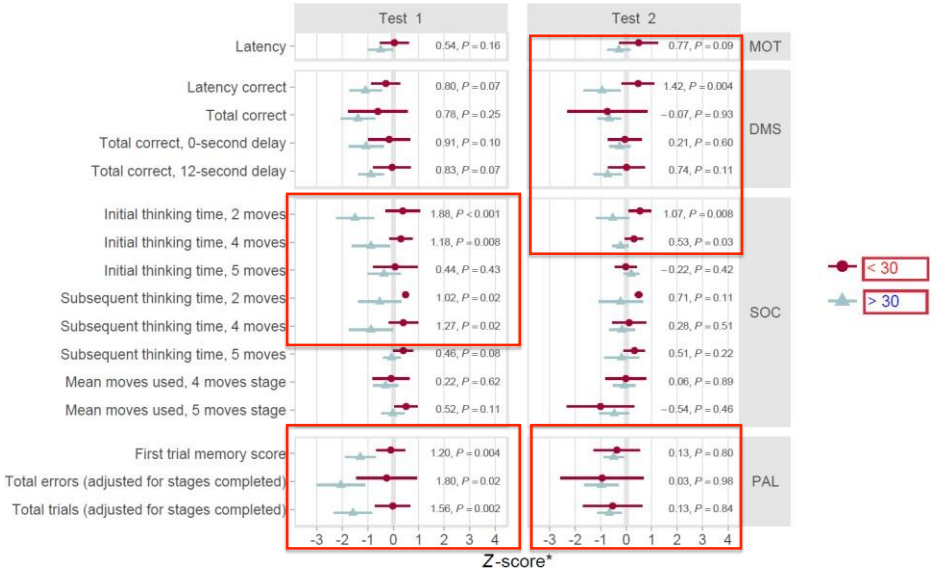
Power et.al, Acta Neurl. Scand., 2017

Cognition after GTC-SE

Time 1(postictally, patients = 33)
Time 2 (after 1 year, patients = 27)



Patients with SE < 30 min performed better than patients with SE > 30 min



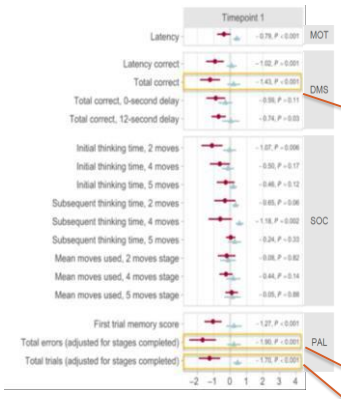
Covariates

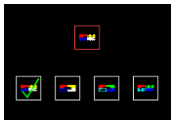
National Adult Reading Test (NART) a surrogate for lacking baseline IQ?

1.	poncho	26.	bouquet
2.	safe	27.	freelancer
3.	seede	28.	gaullist
4.	beige	29.	gips
5.	trikot	30.	guineaner
6.	adagio	31.	mauritier
7.	sioux	32.	rouge
8.	stoiker	33.	protegé
9.	suite	34.	sweater
10.	teak	35.	tertiær
11.	venetianer	36.	tweed
12.	yacht	37.	utrangere
13.	bijouteri	38.	denguefeber
14.	bordeaux	39.	disagio
15.	clairvoyance	40.	falkoner
16.	collage	41.	pirquet
17.	engros	42.	plaisir
18.	geip	43.	xylofon
19.	regime	44.	deja vu
20.	depot	45.	bidet
21.	jeep	46.	enquete
22.	arrangement	47.	curacao
23.	ljome	48.	hors d'œuvre
24.	boccia	49.	bag
25.	machiavellisk	50.	gentleman

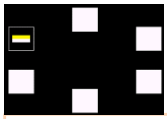
Symptomatic SE with brain lesions

Memory tests significant after covariate adjustments (Timepoint 1)





DMS total correct
adjusted diff. -0.90, P 0.05

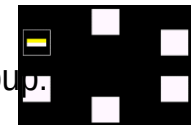


PAL total trials
adjusted diff. -1.03, P 0.02

PAL total errors
adjusted diff. -1.20, P 0.05

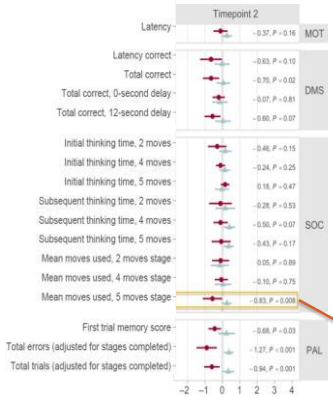
Memory tests after 1 year with covariate adjustments

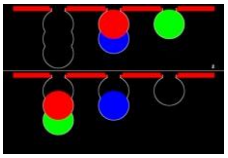
- Not significantly poorer for CSE
- With NCSE also included in the SE group.



PAL total errors, mean diff. -1.10 (P = 0.029) and trials, mean diff. -0.92 (P = 0.016)

Executive dysfunction after 1 year significant after adjustments



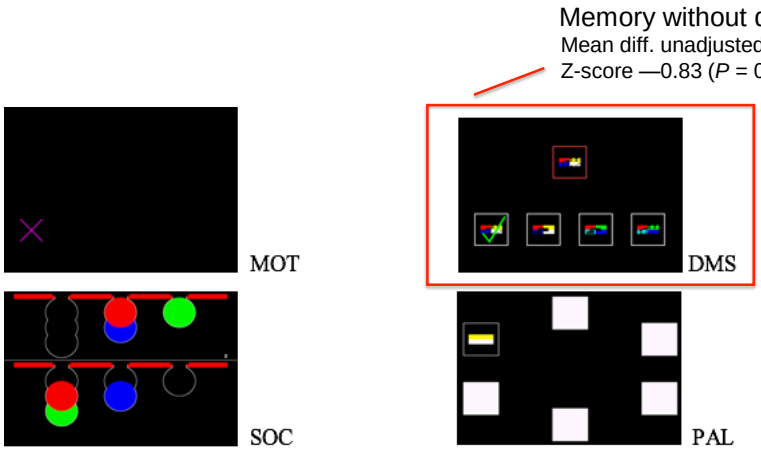


SOC 5 moves task
adjusted diff. −0.94, *P* 0.02

Cognitive consequences of focal SE

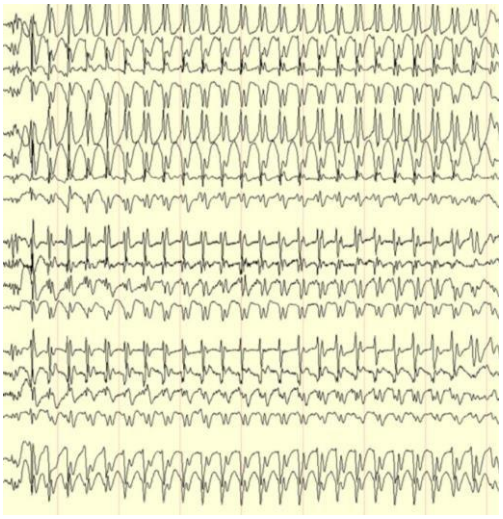
- Less clear
  - prognostic factors matter more than for CSE
    - comorbidity, focus
  - Transient cognitive dysfunction common
- Focal acute symptomatic SE (to stroke f.x.) synergistically worsen damage

Poorer performance after focal SE than after GTC-SE



Power et. al, Epilepsy Res., 2018

Cognitive prognosis after absence SE seems excellent



https://www.epilepsydiagnosis.org

Thomas P (Epilepsia 2007), Walker MC (Int Rev Neurobiol. 2007),
Kavuk I (Eur J Med Res. 2005)

Rating of impairment in patients after SE (GTC and focal)

	0-25	6	24
	26-40	9	36
	41-67	9	36
	>67	1	4

Impairment classification based on GNDS (general neuropsychological deficit summary)
(Reitan & Wolfson, 1993)

Gramstad et.al, in submission, 2019

Impairment rating in subgroups

- Brain lesions: poorer GNDS
  - Means/SD 44,3/17,6 versus 29,6/13,3 p = .027
- SE > 30 min: poorer GNDS
  - Means/SD 41,4/16,0 versus 21,7/10,3 p = .010

Gramstad et.al, in submission, 2019

Conclusions

- Cognitive dysfunction common after SE
  - Large memory problems that improve, but partially continue
  - Possibly development of executive dysfunction
- Not all explained by pre-SE dysfunctions
- NCSE not better than CSE, but more related to underlying conditions? (synergism)
- Duration is a robust negative predictor for cognitive dysfunction

Table 2. Axis 1: Classification of status epilepticus (SE)

(A) With prominent motor symptoms
A.1 Convulsive SE (CSE, synonym: tonic–clonic SE)
A.1.a. Generalized convulsive
A.1.b. Focal onset evolving into bilateral convulsive SE
A.1.c. Unknown whether focal or generalized
A.2 Myoclonic SE (prominent epileptic myoclonic jerks)
A.2.a. With coma
A.2.b. Without coma
A.3 Focal motor
A.3.a. Repeated focal motor seizures (Jacksonian)
A.3.b. Epilepsia partialis continua (EPC)
A.3.c. Adversive status
A.3.d. Oculoclonic status
A.3.e. Ictal paresis (i.e., focal inhibitory SE)
A.4 Tonic status
A.5 Hyperkinetic SE
(B) Without prominent motor symptoms (i.e., nonconvulsive SE, NCSE)
B.1 NCSE with coma (including so-called "subtle" SE)
B.2 NCSE without coma
B.2.a. Generalized
B.2.a.a Typical absence status
B.2.a.b Atypical absence status
B.2.a.c Myoclonic absence status
B.2.b. Focal
B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms)
B.2.b.b Aphasic status
B.2.b.c With impaired consciousness
B.2.c Unknown whether focal or generalized
B.2.c.a Autonomic SE

- 5.3 Cognitive outcome and functional outcome
- Cognitive outcomes are usually evaluated based on clinical judgment or measured using a wide variety of neuropsychological tests. The underlying etiology is the main factor associated with long-term cognitive outcome in children, with symptomatic SE or progressive encephalopathy contributing to increased risk. Other factors are young age at the time of SE and neuroimaging abnormalities. Also, seizure burden in uncontrolled epilepsy, rather than SE, is more frequently associated with poor cognitive outcome
- The impact of SE on cognitive outcome is debatable. Animal models show that prolonged seizures result in neuronal loss and brain connectivity changes. A clinical study showed that children with SE had worse long-term cognitive outcome than healthy controls, with nonfebrile SE associated with worse cognitive impairments than febrile SE.37 In contrast, large studies showed no difference in cognitive outcome when comparing children with and without SE, although controls in this study were children with epilepsy.33, 34 Most adult studies focus on functional rather than cognitive outcomes using standardized scales like the modified Rankin Score and the Glasgow Outcome Scale, with functional deficits seen in 21-61% and these could be more severe in RSE or SRSE (67%).
- Functional outcomes in children are mostly based on clinical impression, yielding a wide spectrum of functional impairment after SE from 0% to 79% and this range may also be related to different definitions and assessment of impairment, and often lack of good baseline information. The evaluation of long-term cognitive outcomes is further complicated by evolution over time in some cases, and in particular outcomes in children are often not static as development progresses. In a pediatric study, impaired performance at discharge persisted at 1 year,37 whereas in another series deficits disappeared or improved over time.15, 22, 46 Predictors of poor functional outcome include etiology (nonfebrile SE, acute symptomatic SE, progressive encephalopathy)17, 26, 28, 36, 37 and SE duration17, 26, 27, 45 (Table 1).

Prognose fokal status

- Mest avhengig av årsak
- Status synergistisk med årsak (encephalitt, slag etc) - forverrer prognosen
- Forbigående funn av økt signalintensitet i T2 og diffusjonsforstyrrelser ved MR
- Forbigående forstyrrelse av kognitiv funksjon og affekt

Thomas RH (Epilepsia 2007), Walker MC (Int Rev Neurobiol. 2007), Kavuk I (Eur J Med Res. 2005), Kaplan PW (Epileptic Disord. 2000)