

# Effects of hypoglycemia on brain

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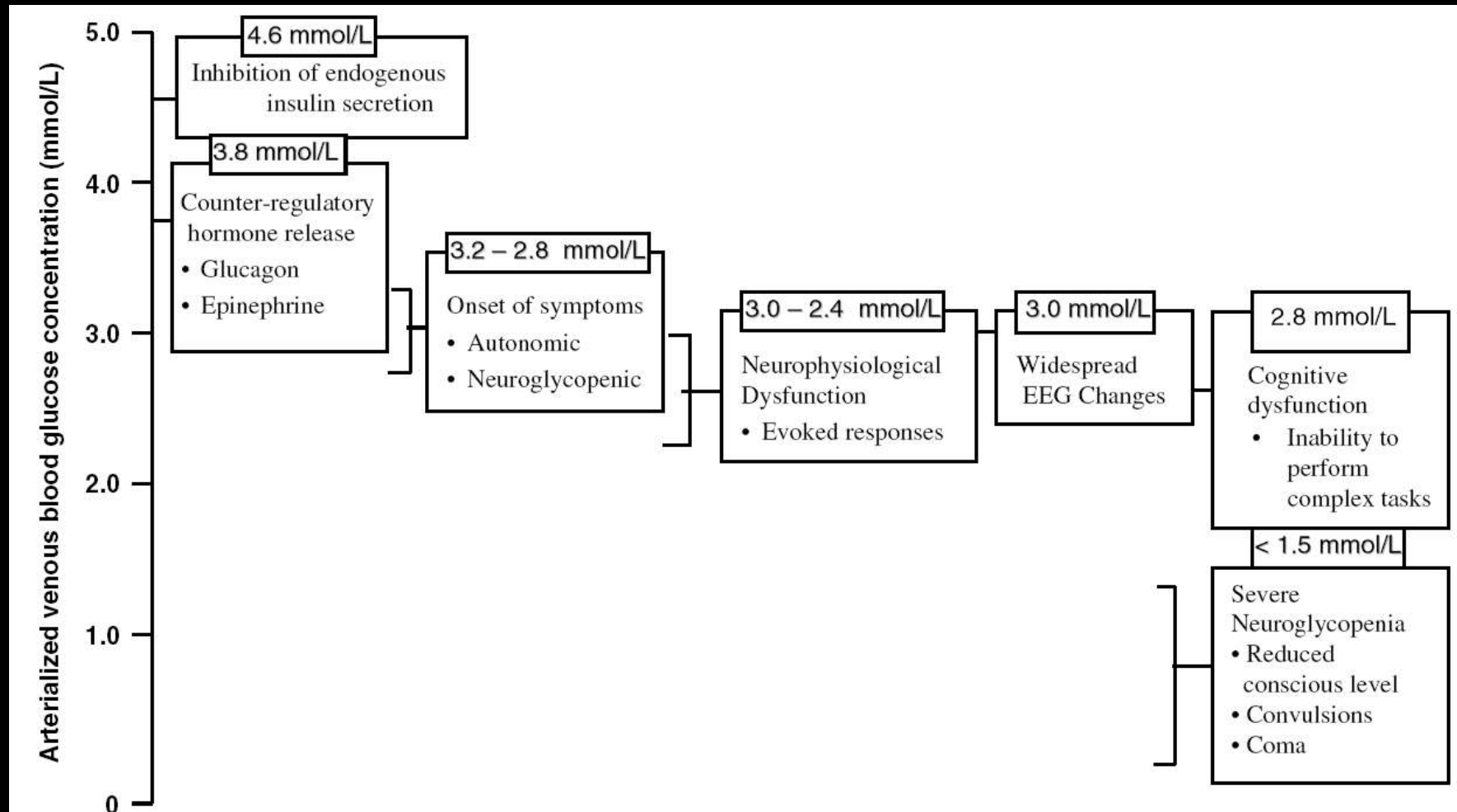
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# Glucose and brain

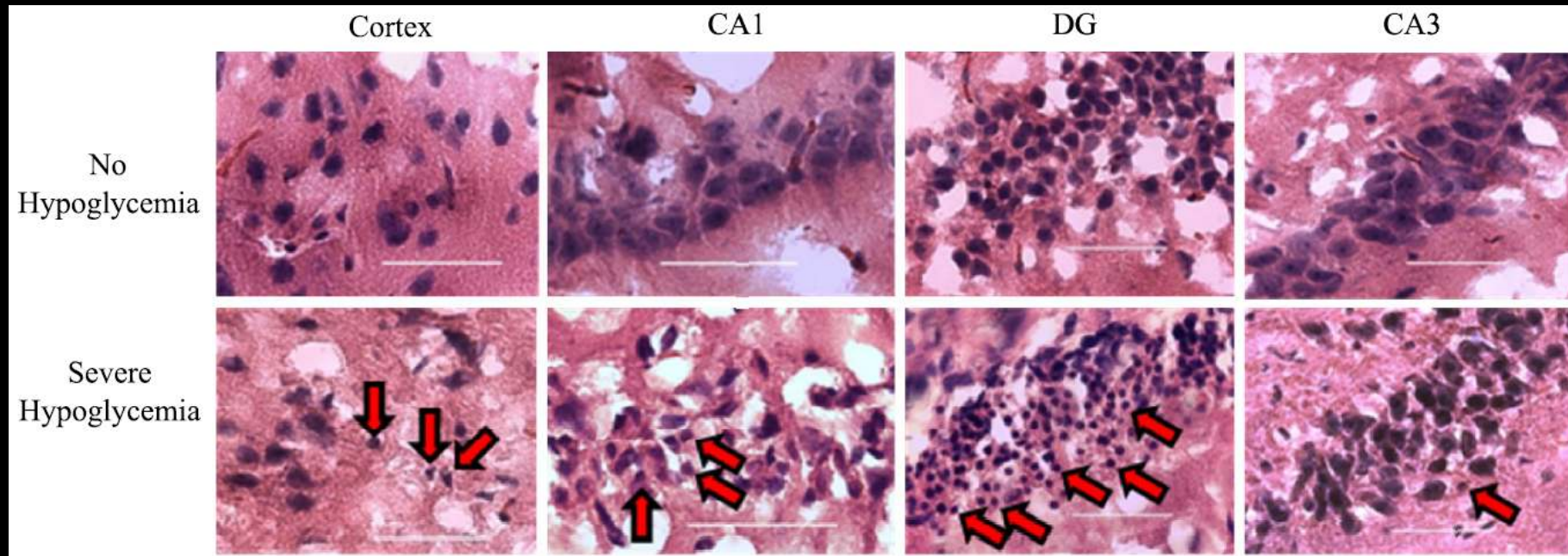
- The brain is dependent on glucose as its principal fuel
- Interruption of glucose supply by systemic hypoglycemia leads to dysfunction of neurons and glia
- Hypoglycemia can produce virtually all neurologic symptoms and signs
  - Acute: focal neurologic deficits, seizure, confusion, stupor, coma, death
  - Chronic and repetitive: cognitive impairment
- Hypoglycemia can mimic various neurological disorders
  - Stroke, epilepsy, encephalitis, encephalopathy
  - Psychiatric diseases, dementia

# Hierarchy of responses to hypoglycemia



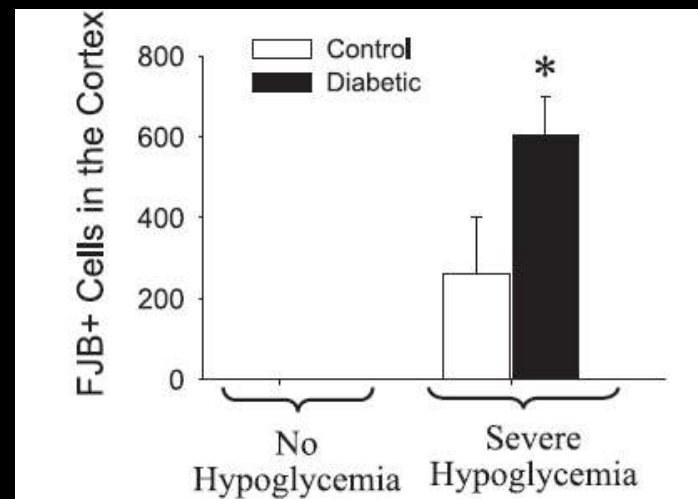
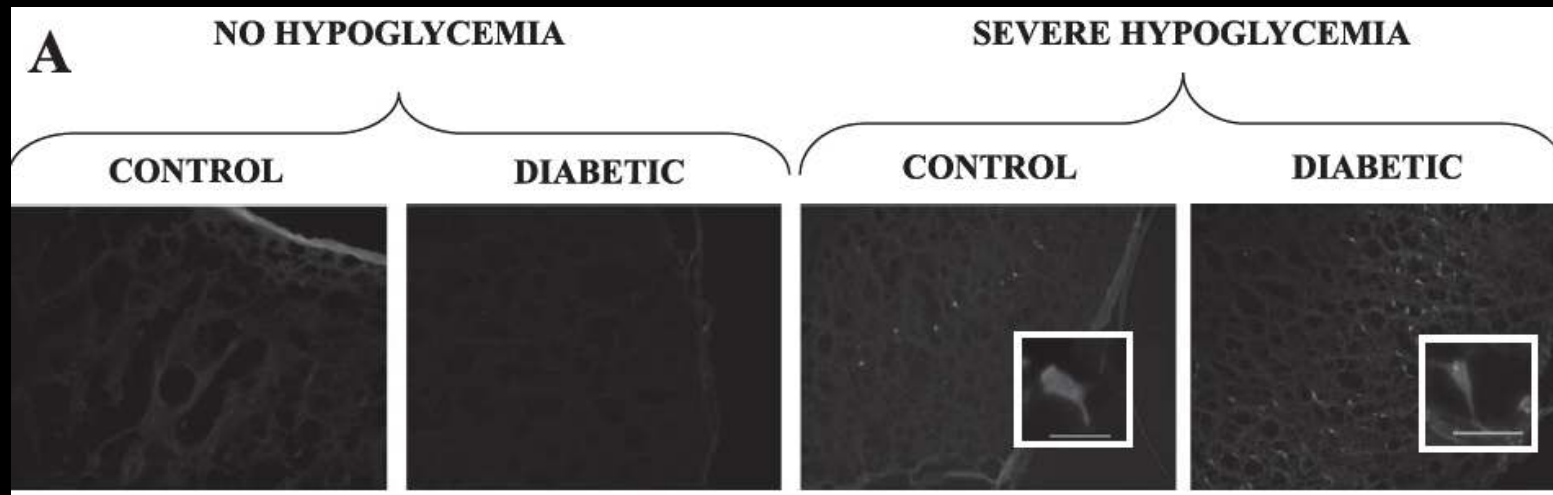
# Selective vulnerability

- Selective vulnerability of brain damage to severe hypoglycemia



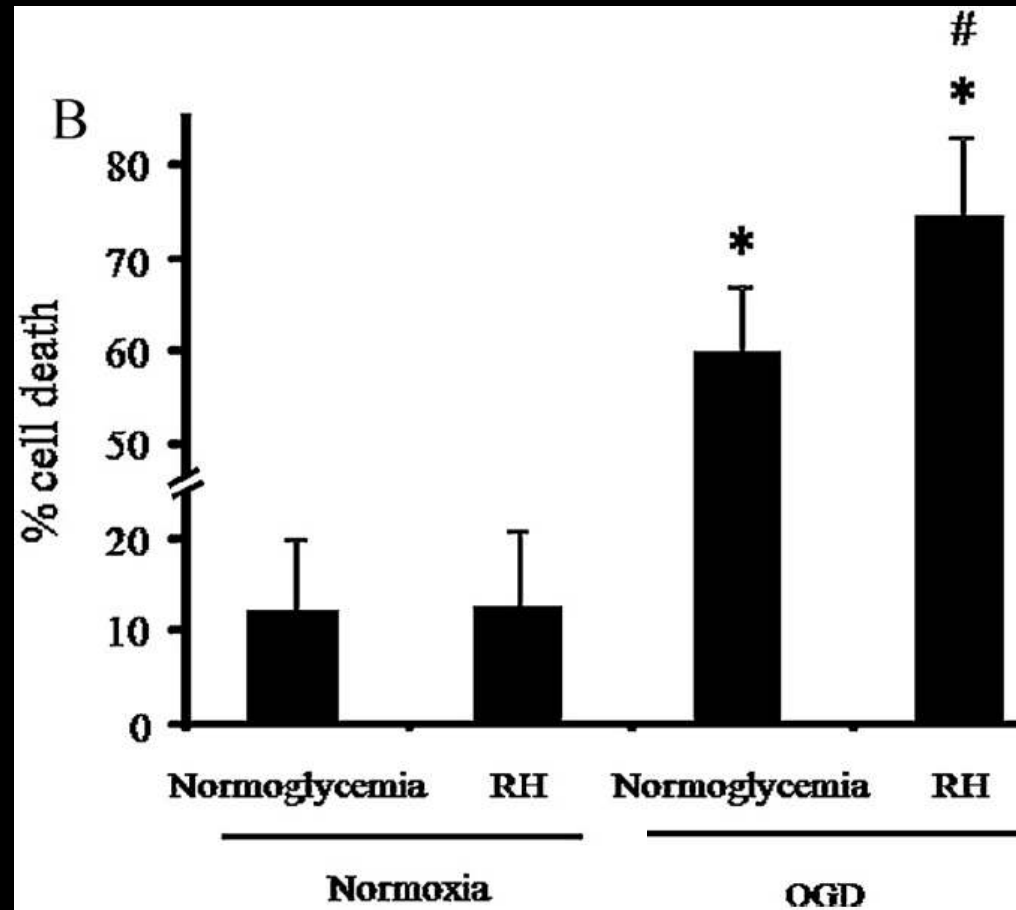
# Brain damage to hypoglycemia

- Diabetes increases brain damage caused by severe hypoglycemia



# Impact of recurrent hypoglycemia on brain ischemia

- Recurrent hypoglycemia increases oxygen glucose deprivation-induced hippocampal cell damage



# EEG in hypoglycemic encephalopathy

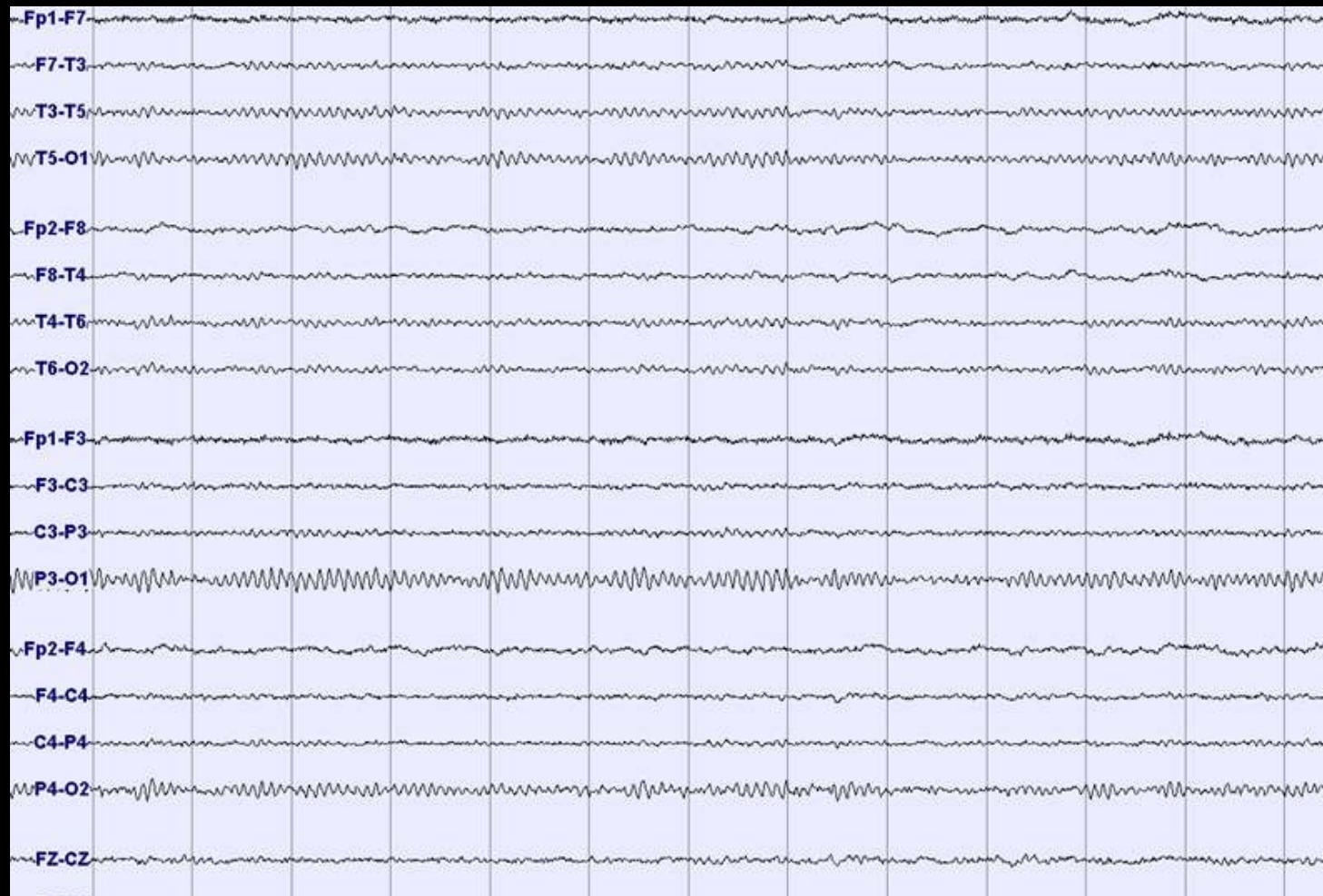
- Role of EEG (electroencephalogram) in hypoglycemia
  - Determination of the presence of brain damage
  - Assessment of degree of hypoglycemic brain damage
  - Prognostication following hypoglycemic brain damage

Stages of Hypoglycemia		
Clinical	EEG	Blood glucose (mM)
Normal	Normal	>3.5
Anxiety (adrenergic discharge)	↑ amplitude, ↓ frequency (θ, δ waves)	2–3.5
Stupor	δ waves	1–2
Coma, cushioning response (↑BP)	Flat	<1.36



# EEG in hypoglycemic encephalopathy

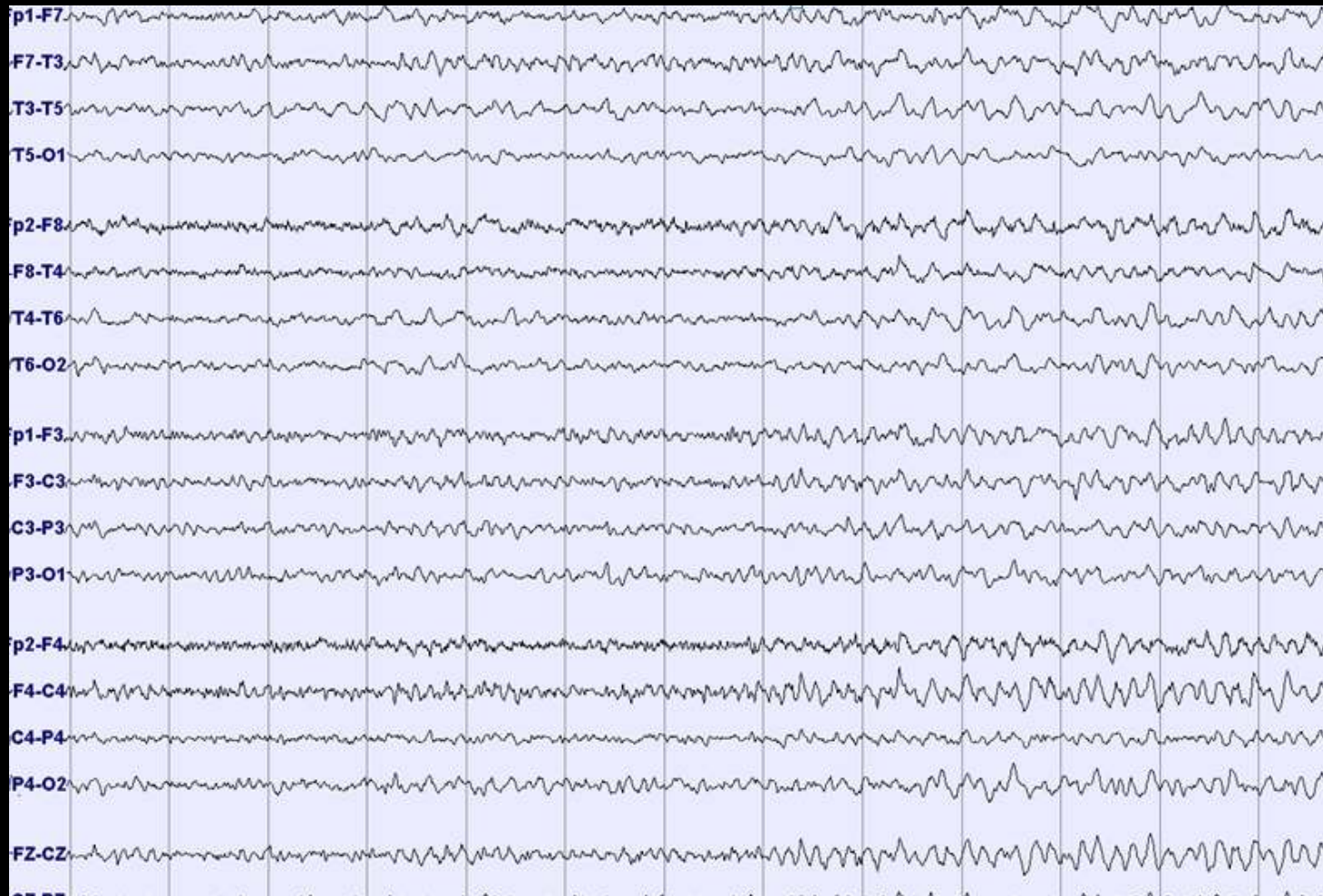
- Normal EEG





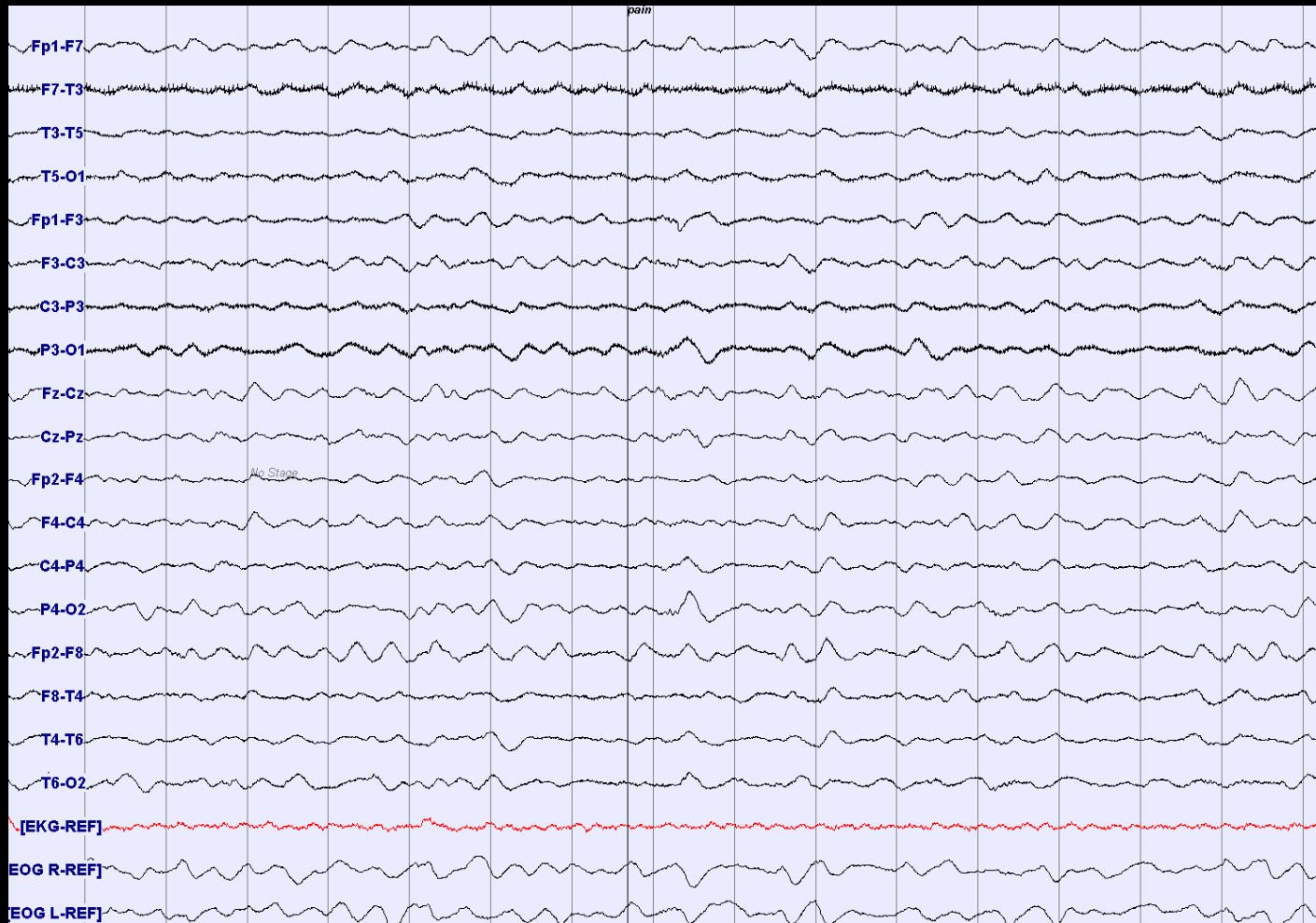
# EEG in hypoglycemic encephalopathy

- A case of mild hypoglycemia presenting with mild confusion and disorientation (45 mg/dl)



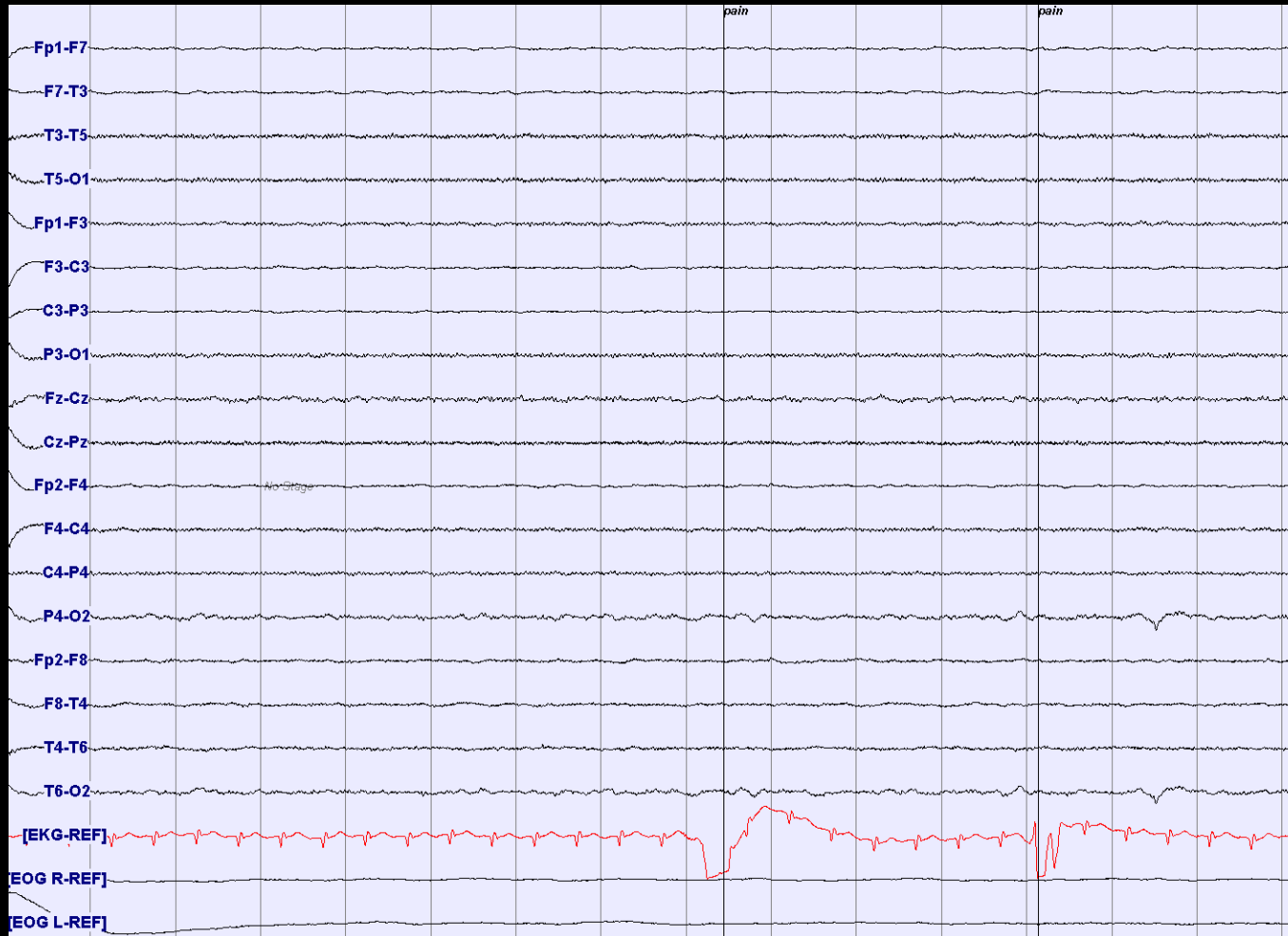
# EEG in hypoglycemic encephalopathy

- A case of profound hypoglycemia (26 mg/dl) presenting with lethargy and stupor



# EEG in hypoglycemic encephalopathy

- A case of prolonged and profound hypoglycemia (19 mg/dl) presenting with deep coma





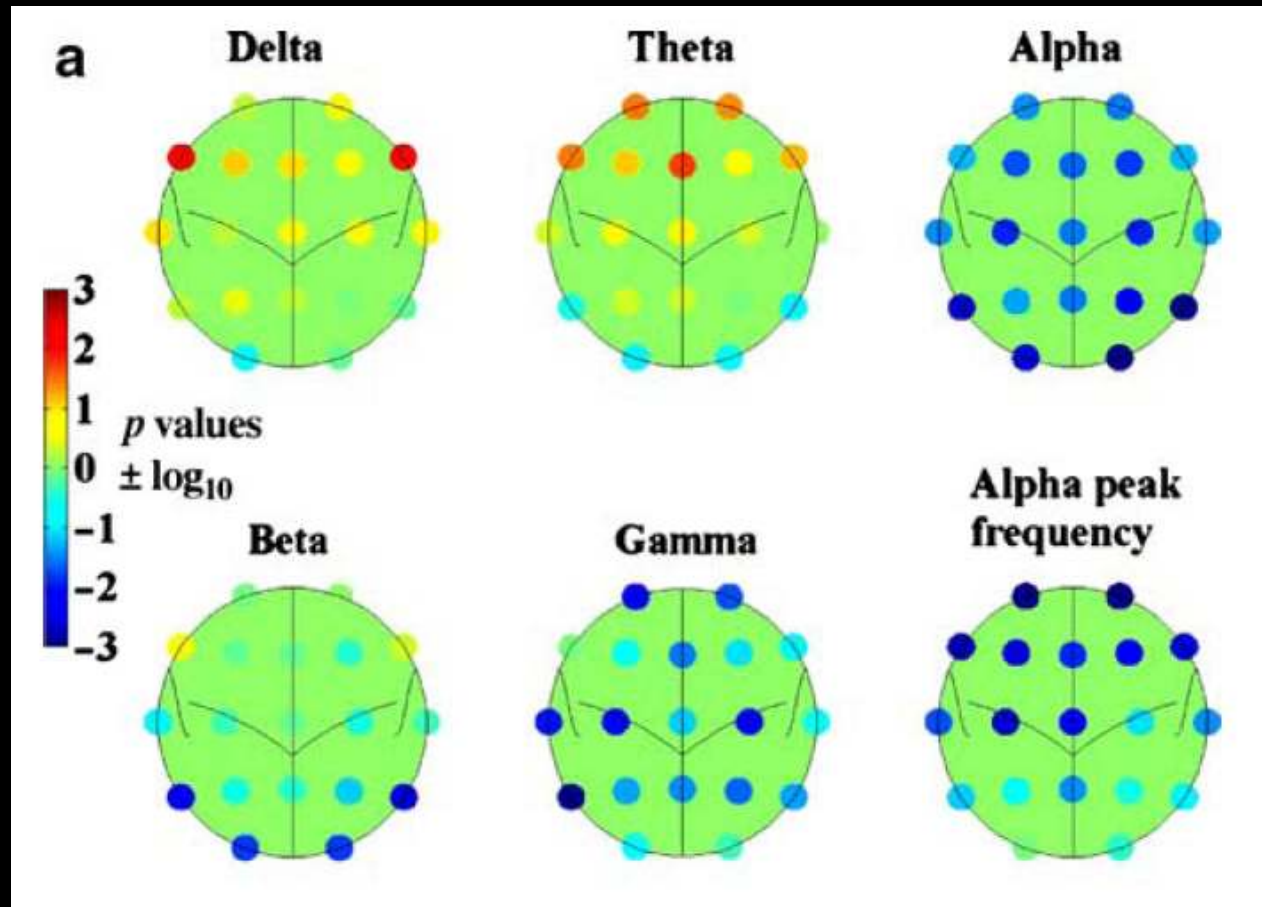
# EEG in hypoglycemic encephalopathy

- A case of profound hypoglycemia (27 mg/dl) presenting with drowsiness and unresponsiveness



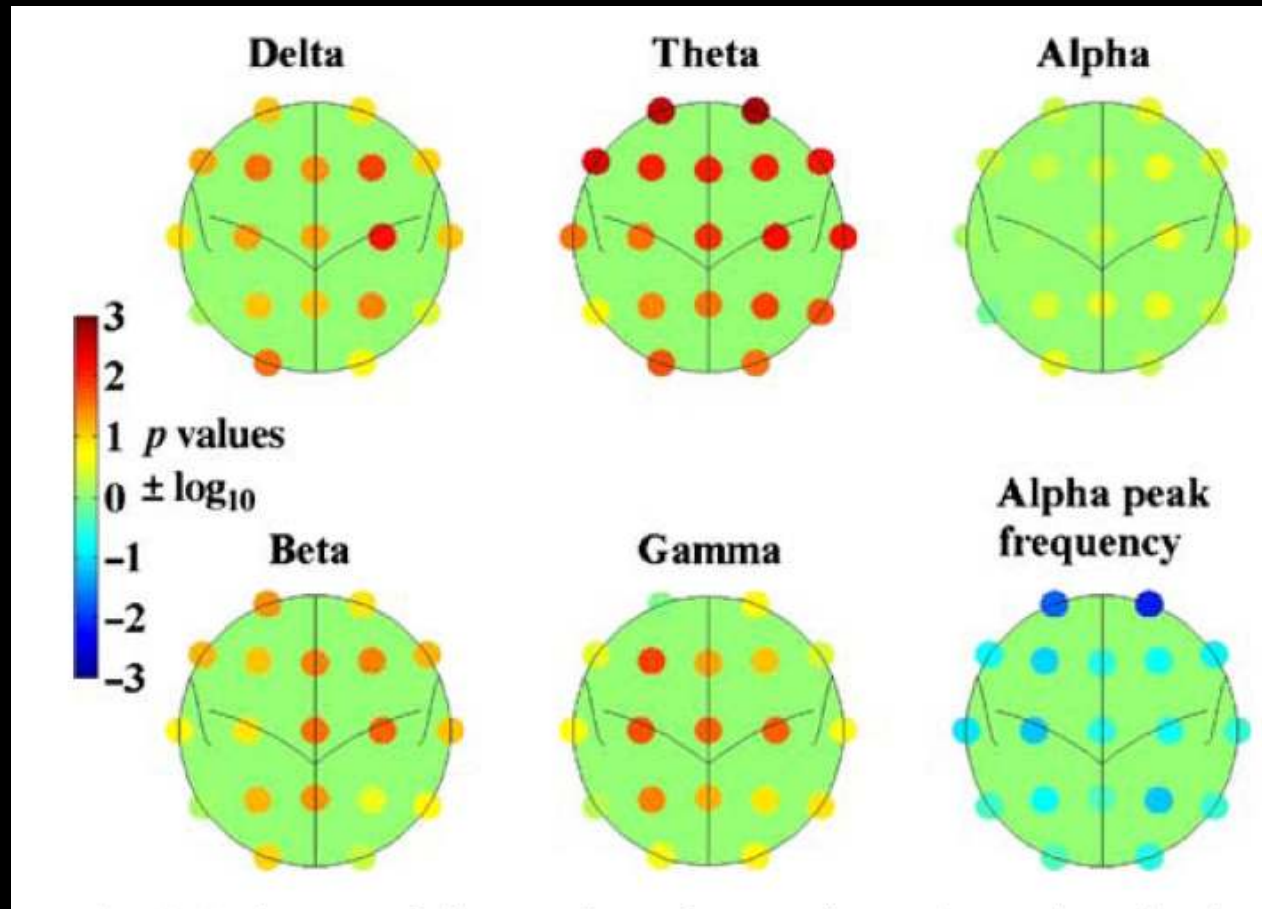
# Impact of recurrent hypoglycemia on EEG

- RH patients vs. controls



# Impact of recurrent hypoglycemia on EEG

- Correlation of number of severe hypoglycemic episodes on EEG power spectral parameters



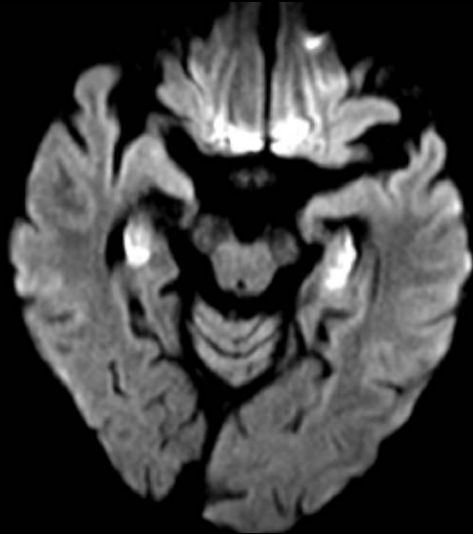
# Diffusion-weighted imaging in hypoglycemia

- Role of diffusion-weighted MR image (DWI) in the setting of hypoglycemic encephalopathy
  - Detection of brain regions of selective vulnerability to hypoglycemia
  - Detection of regions of early and subtle hypoglycemic brain damage
  - heralding overall prognosis in hypoglycemic encephalopathy, especially hypoglycemic coma
  - Areas of restricted diffusion does not necessarily indicate irreversible brain injury
  - Prompt recognition and early intervention potentially reverse brain injury

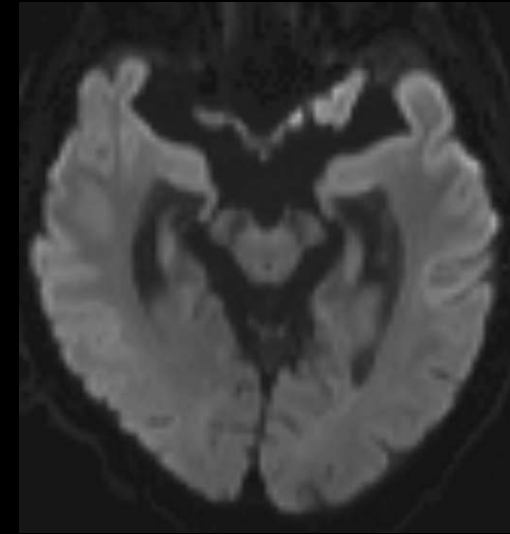
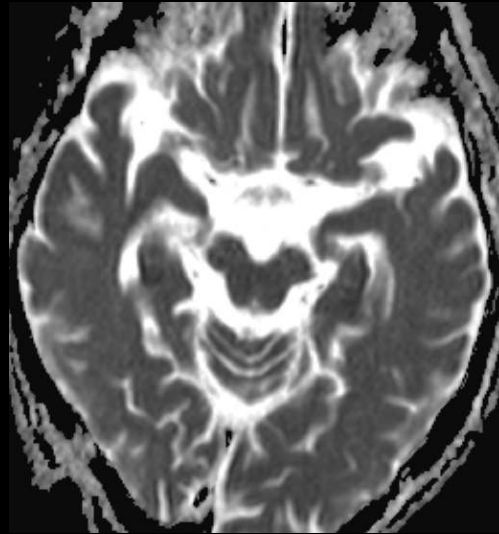


## Diffusion-weighted imaging in hypoglycemia

- A 63-year-old diabetic man on insulin therapy
  - Presenting with acute mental alteration (glucose, 16 mg/dl)
  - Permanent profound memory impairment and behavioral changes



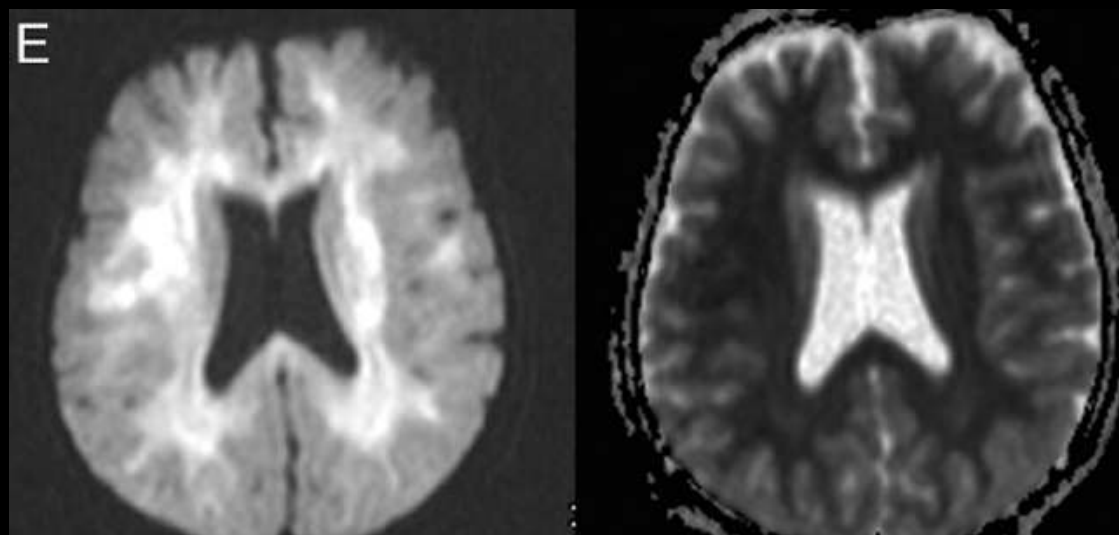
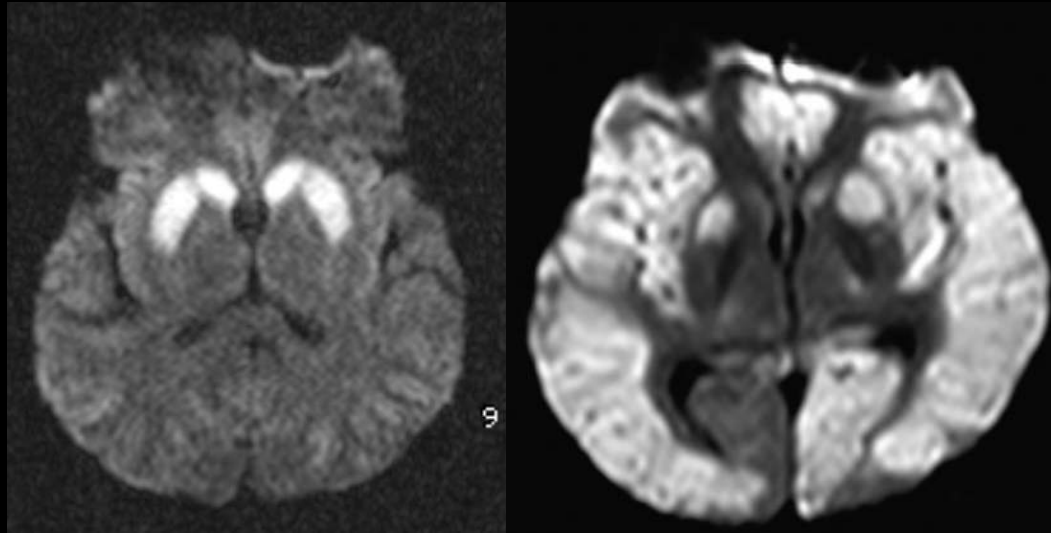
Initial DWI



1-year follow up DWI

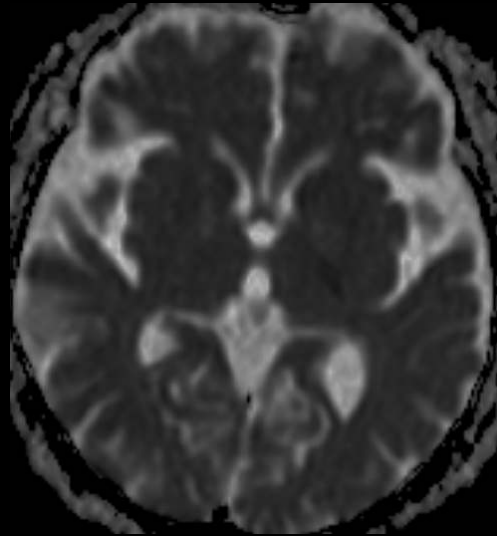
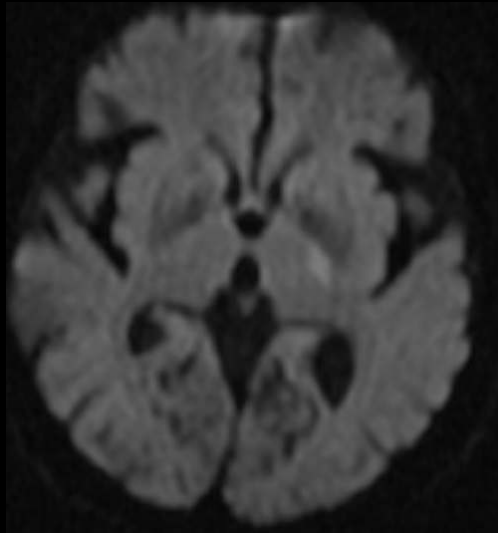
# Diffusion-weighted imaging in hypoglycemia

- DWI in patients presenting with hypoglycemic coma

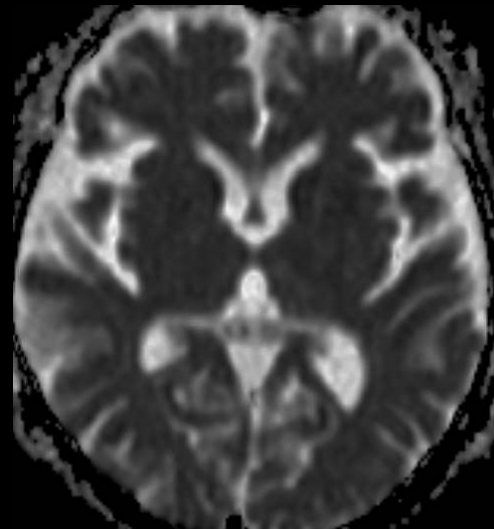
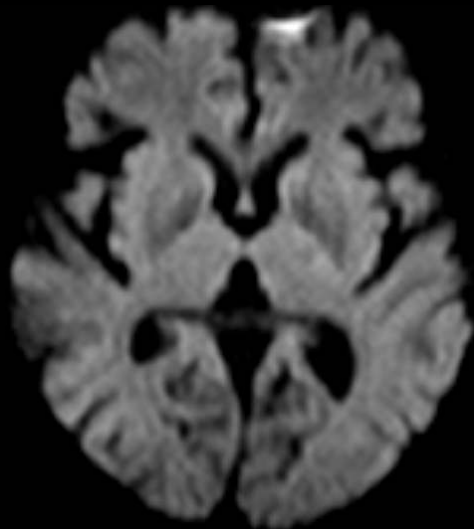


# Diffusion-weighted imaging in hypoglycemia

- DWI in hypoglycemic hemiparesis mimicking acute ischemic stroke



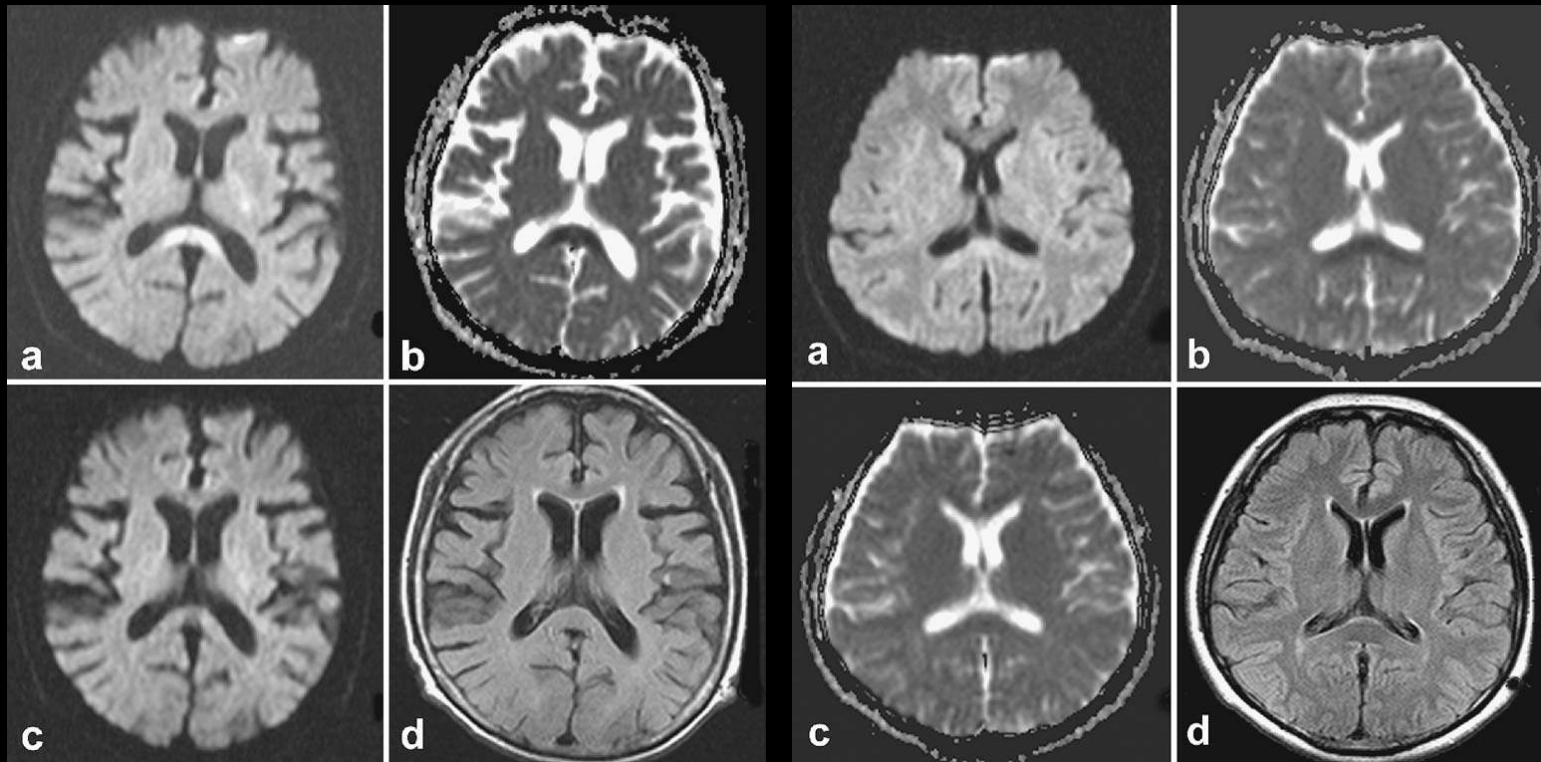
Initial DWI



DWI 2D later

# Diffusion-weighted imaging in hypoglycemia

- DWI in hypoglycemic patients presenting with acute disorientation and psychosis



78 yo woman (38 mg/dl)

42 yo man (28 mg/dl)

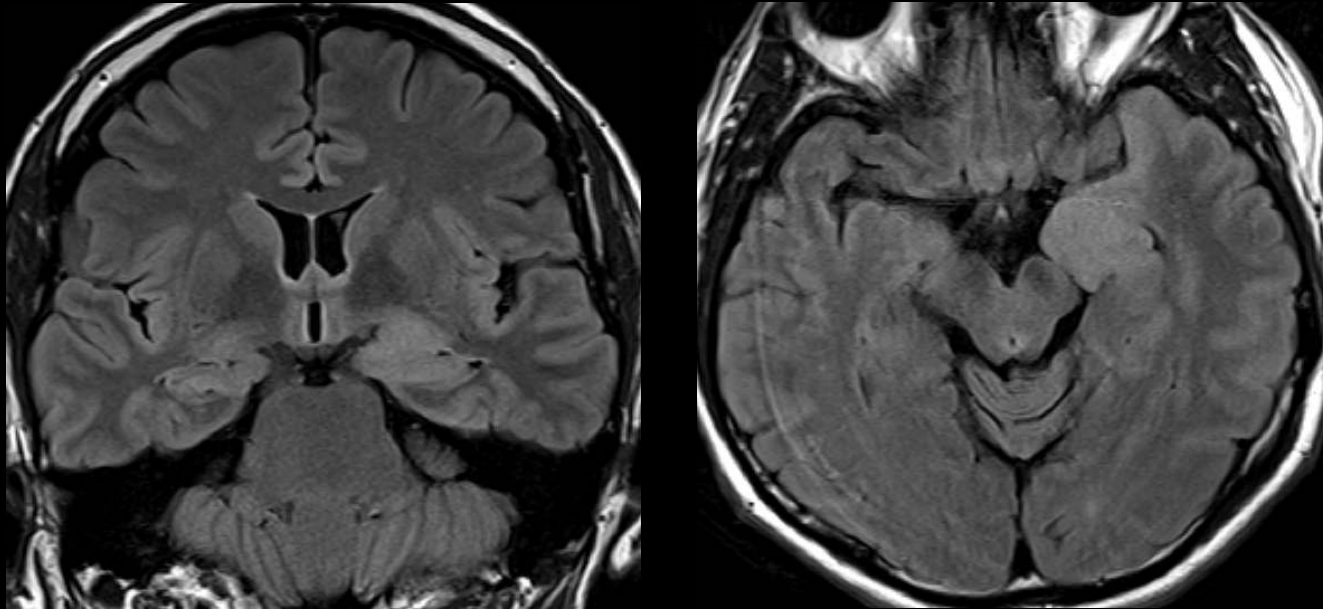
# A case

- A 50-year-old woman presenting with recurrent episodes of brief amnesia, unresponsiveness, abnormal behavior (automatism), brief confusion





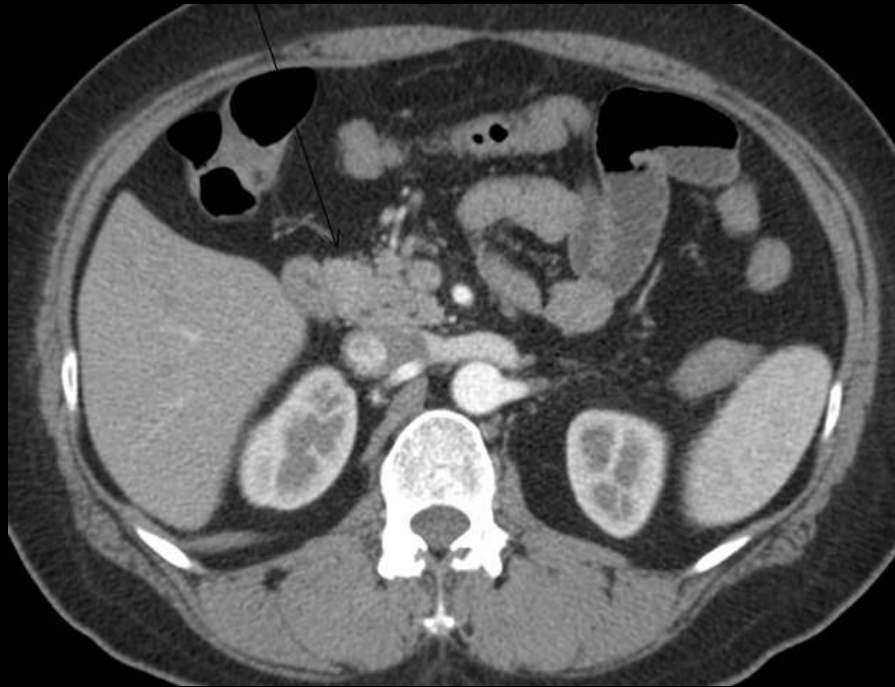
## A case



- A diagnosis of left temporal lobe epilepsy due to amygdala-hippocampal swelling (inflammation, limbic encephalitis)
- No response to antiepileptic medications

## A case

- Blood glucose of 21 mg/dl during the attack
- HbA1C 4.9

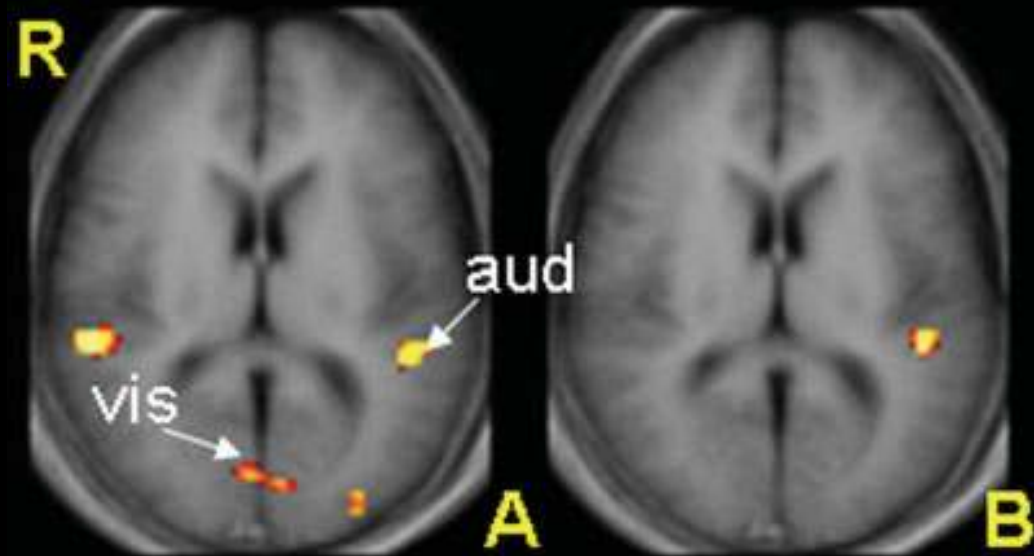
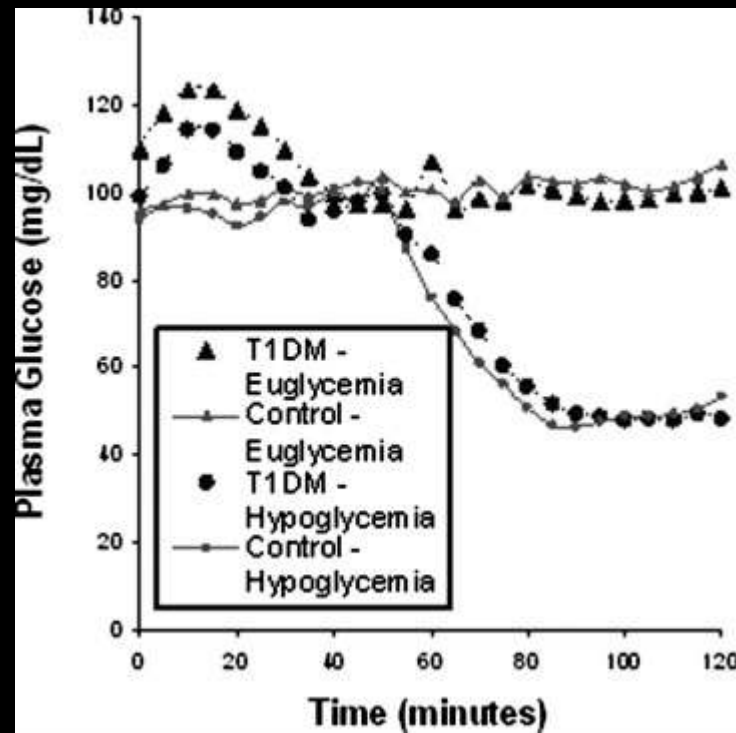


- She remained symptom-free after resection of pancreatic insulinoma



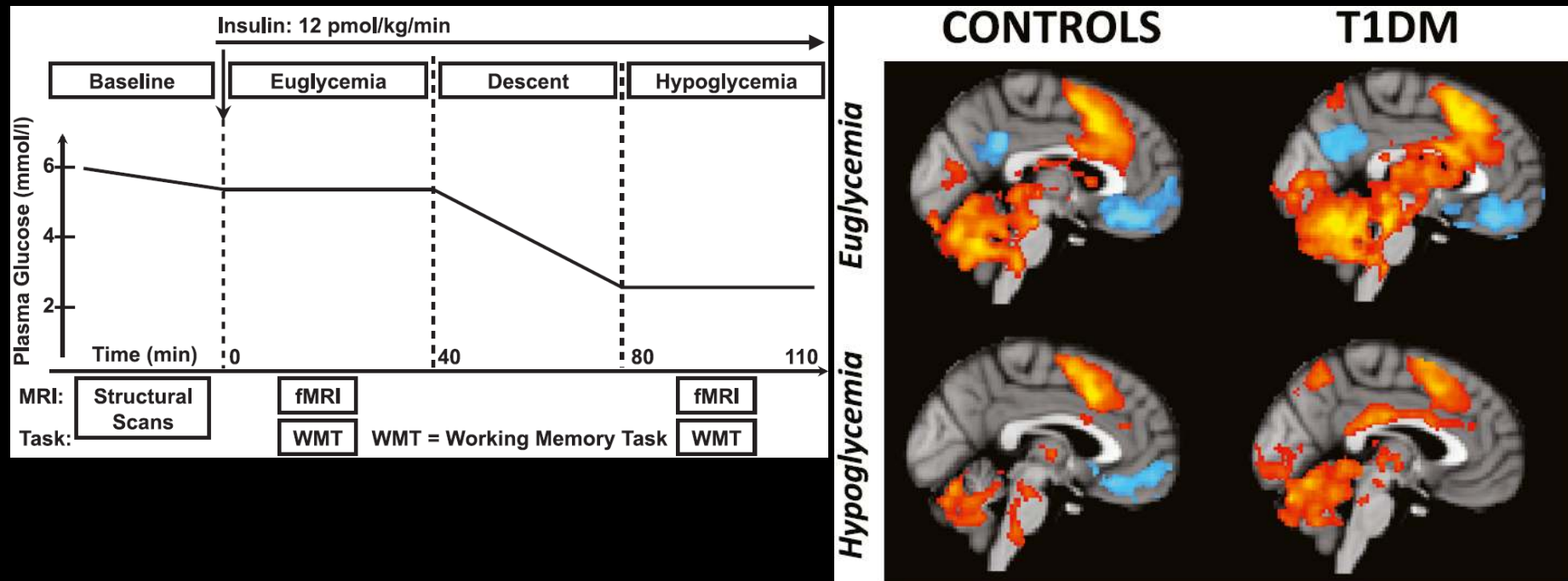
# Functional imaging in hypoglycemia

- Hypoglycemia reduces BOLD signal in auditory and visual cortices



# Functional imaging in hypoglycemia

- Brain activation during working memory is altered in patients with type 1 diabetes during hypoglycemia



# Hypoglycemia and cognition

- Induced hypoglycemia (36-54 mg/dl) impairs various cognitive functions (reaction time, arithmetical ability, verbal fluency, verbal and visual memory, attention/vigilance, coordination, planning)
- Increased latency and decreased amplitude of P300 during moderate hypoglycemia indicate slower information processing

**Table 1** Calculated glycaemic thresholds for cognitive dysfunction in healthy subjects derived from different studies

Study (reference)	Sample type	Blood glucose threshold (mmol/l)
Widom <i>et al.</i> [21]	Plasma	2.3
Mitrakou <i>et al.</i> [22]	Plasma	2.6
Fanelli <i>et al.</i> [23]	Plasma	2.7
Fanelli <i>et al.</i> [24]	Plasma	2.8
Fanelli <i>et al.</i> [25]	Plasma	2.9
Maran <i>et al.</i> [26]	Blood	2.9
Veneman <i>et al.</i> [27]	Plasma	3.0
Maran <i>et al.</i> [28]	Plasma	3.1

Holmes CS, Diabetes Care 1983; 6: 180–185

Blackman JD, Diabetes 1992;41:392-99

Lindgren M, Diabet Med 1995;13: 218–25

# Hypoglycemia and cognition

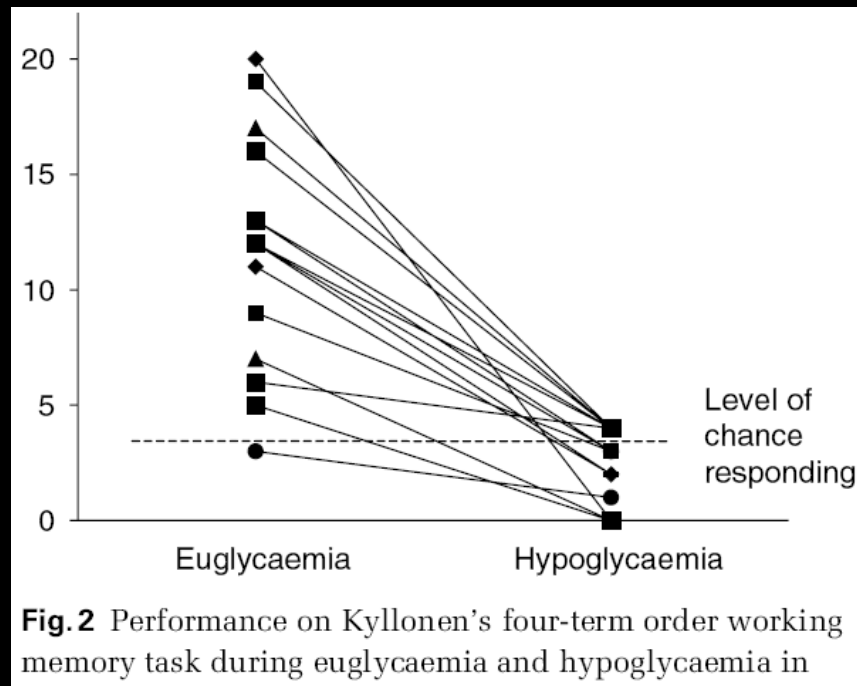
- Hypoglycemic symptoms and cognitive dysfunctions are immediate, but recovery is delayed even with restoration of euglycemia

Table 2—Symptoms and cognitive function during EU and HYPO

		Baseline	Plateau (min)			Recovery (min)		
			0	20	40	90	0	20
Total symptoms	EU	2 (1)	3 (1)	2 (1)	3 (1)	4 (1)	3 (1)	4 (2)
	HYPO	3 (1)	4 (1)	10 (2)*	16 (4)	23 (5)	11 (4)	8 (2)
Autonomic symptoms	EU	1 (0)	1 (1)	1 (0)	1 (0)	1 (1)	2 (1)	2 (1)
	HYPO	1 (0)	2 (1)	6 (1)*	9 (2)	14 (1)	6 (2)	5 (1)
Neuroglycopenic symptoms	EU	2 (1)	2 (1)	1 (1)	2 (1)	3 (1)	2 (1)	2 (1)
	HYPO	1 (1)	2 (1)	4 (1)*	7 (2)	9 (3)	5 (2)	3 (1)
Feeling abnormal score	EU	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	HYPO	0 (0)	0 (0)	2 (1)*	3 (1)	4 (1)	2 (1)	1 (1)
Stroop word (s)	EU	49 (3)	48 (2)	50 (3)	51 (4)	50 (3)	50 (2)	48 (3)
	HYPO	50 (2)	58 (3)*	59 (3)	60 (4)	65 (5)	56 (2)	53 (3)
Stroop color word score	EU	58 (4)	59 (3)	56 (4)	54 (3)	54 (3)	56 (93)	54 (4)
	HYPO	54 (3)	46 (3)*	46 (4)	44 (4)	43 (4)	49 (3)	50 (5)
4-Choice reaction (ms)	EU	388 (12)	397 (11)	392 (12)	414 (16)	444 (25)	412 (18)	397 (11)
	HYPO	422 (23)	477 (29)*	449 (18)	502 (40)	521 (37)	501 (27)	510 (25)

# Hypoglycemia and cognition

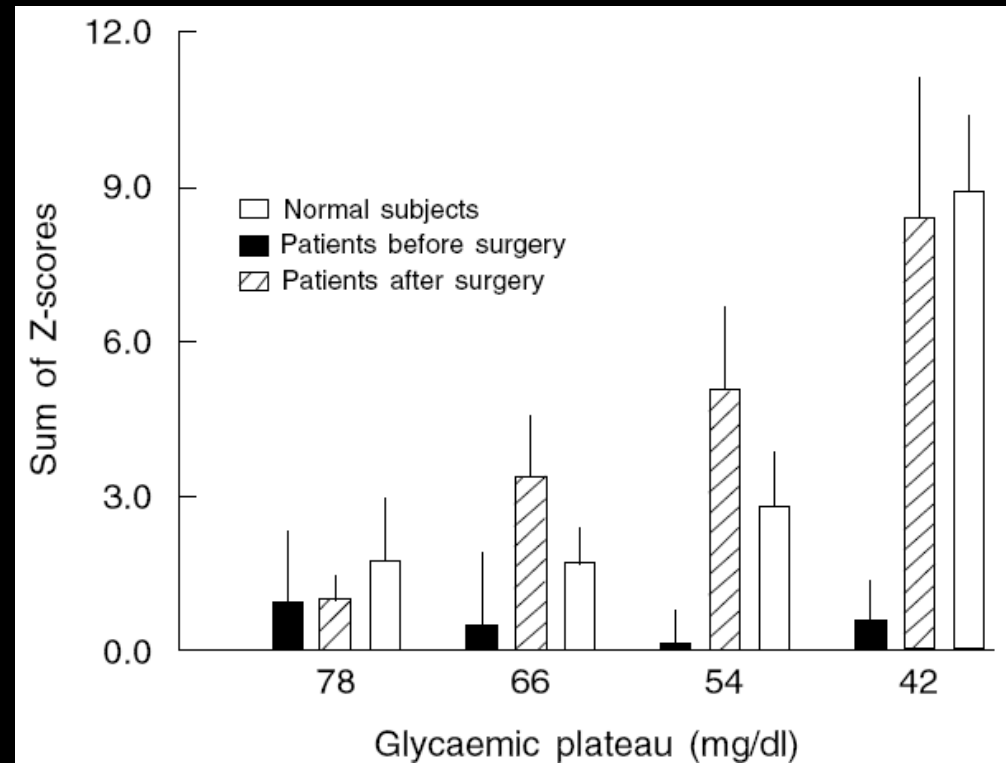
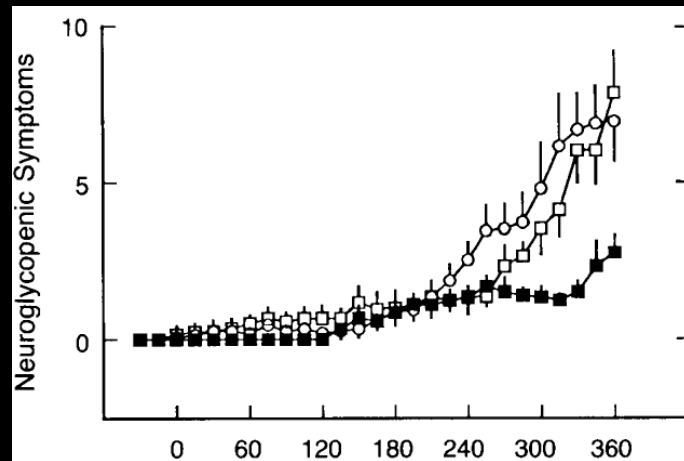
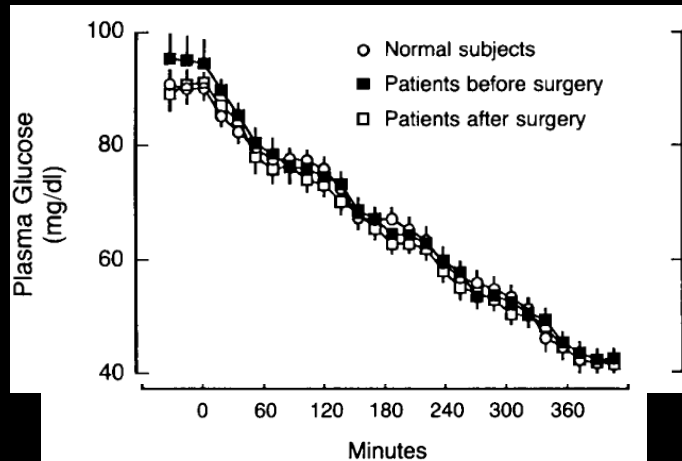
- Different sensitivity of cognitive process to hypoglycemia



- Threshold for deterioration of complex cognitive tasks (working memory, stroop, verbal and visual memory) is generally lower than simple tasks (finger tapping, reaction time)

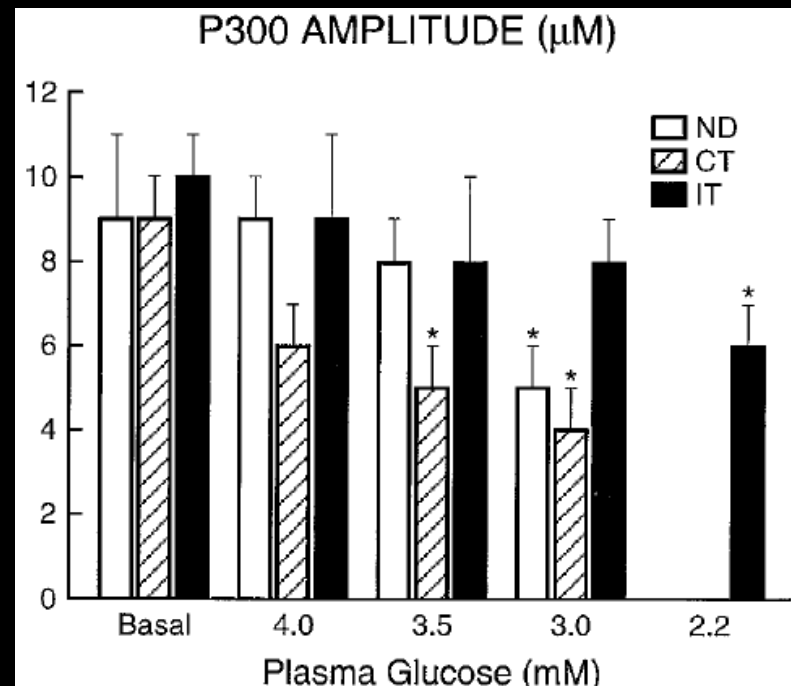
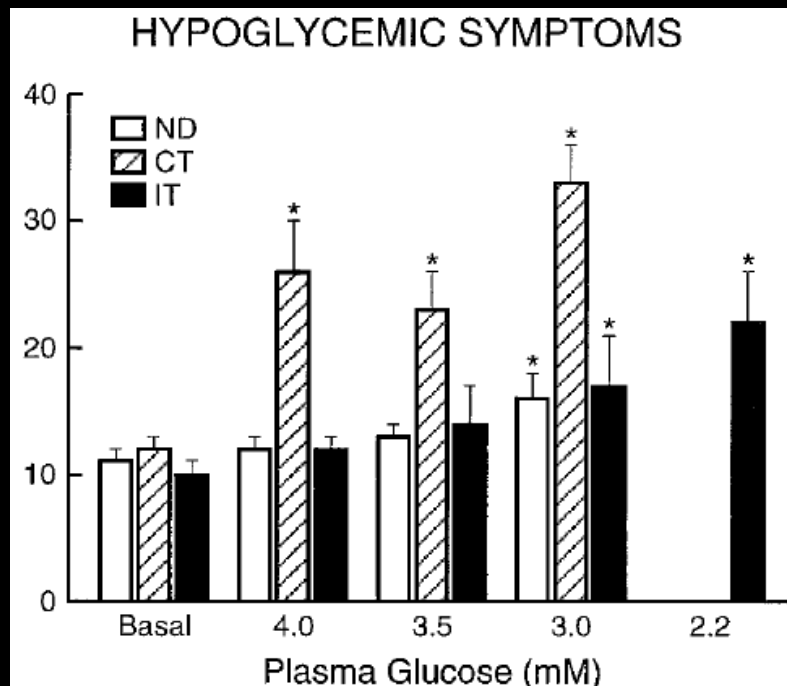
# Brain adaptation to hypoglycemia

- Reversibility of unawareness of hypoglycemia in patients with insulinoma



# Brain adaptation to hypoglycemia

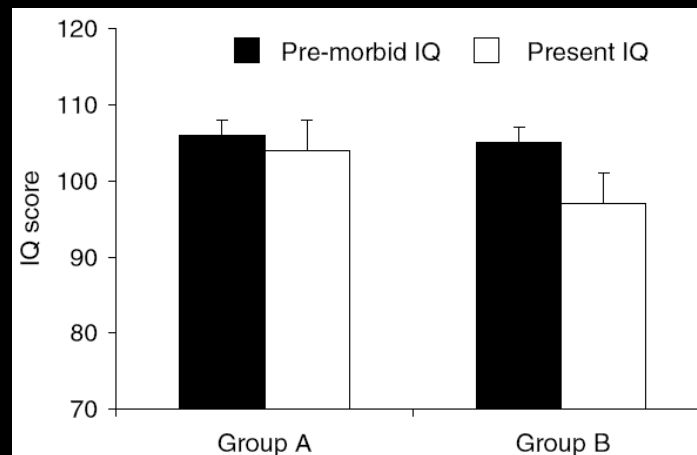
- Different adaptation to hypoglycemia in non-diabetic, conventionally treated diabetics, and intensively treated diabetics
- Intensively treated IDDM experience hypoglycemic symptoms at a lower glucose level than conventionally treated patients





# Long-term effects of hypoglycemia on cognition

- Selective vulnerability to hypoglycemia in frontal cortex and hippocampus
- RH episodes may cause subclinical brain damage, leading to cognitive impairment over time



**Fig. 4** Estimated pre-morbid IQ and present IQ in diabetic patients with no history of severe hypoglycaemia (group A) and with at least five episodes of severe hypoglycaemia (group B). Comparison for Group A is non-significant, for

- A significant correlation between the apparent decline in IQ and the frequency of major hypoglycemic attacks ( $r = -0.30$ ;  $P < 0.01$ )

# Long-term effects of hypoglycemia on cognition

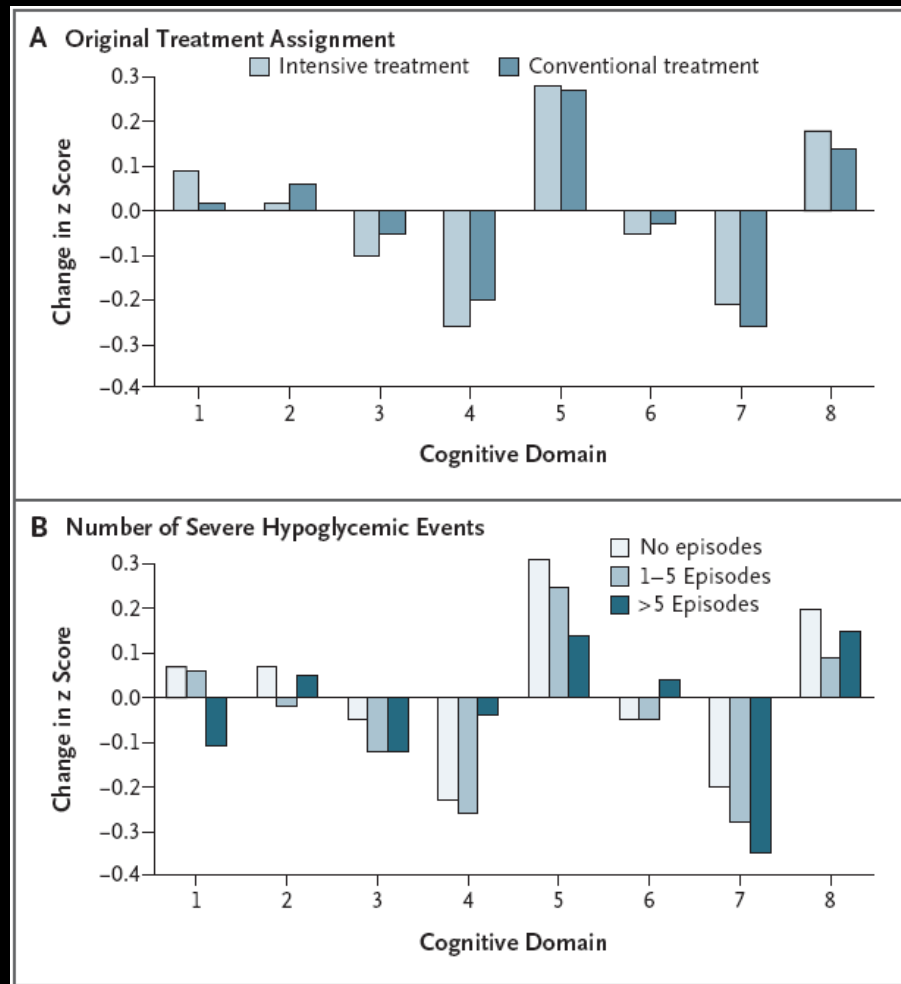
- A prospective study data from DCCT: lack of effects of RH on cognition

Table 2—Comparisons of cognitive score changes for groups with 0 (group 1) and five or more (group 2) hypoglycemic episodes

	Year 2	Year 5	Year 7	Year 9
<b>General ability</b>				
Group 1	-0.04 ± 0.23 (1,121)	-0.10 ± 0.28 (943)	0.91 ± 0.56 (371)	1.00 ± 0.90 (139)
Group 2	-3.32 ± 3.64 (8)	1.06 ± 1.51 (30)	4.50 ± 2.41 (30)	1.11 ± 2.16 (18)
P	0.24	0.46	0.08	0.97
Total sample size	1,301	1,256	561	249
<b>Spatial ability</b>				
Group 1	0.12 ± 0.30 (1,148)	-0.04 ± 0.33 (980)	0.32 ± 0.59 (391)	1.34 ± 1.01 (146)
Group 2	-3.47 ± 3.55 (8)	0.06 ± 1.89 (31)	1.76 ± 2.01 (32)	-0.74 ± 2.25 (19)
P	0.33	0.96	0.50	0.48
Total sample size	1,333	1,302	591	250
<b>Processing speed</b>				
Group 1	0.02 ± 0.30 (1,202)	0.18 ± 0.34 (1,010)	-0.40 ± 0.65 (397)	-0.27 ± 1.08 (152)
Group 2	0.03 ± 2.56 (8)	1.72 ± 2.05 (32)	4.41 ± 1.98 (34)	2.65 ± 3.17 (21)
P	1.00	0.43	0.04	0.35
Total sample size	1,395	1,342	601	258
<b>Verbal</b>				
Group 1	0.06 ± 0.31 (1,156)	-0.12 ± 0.35 (983)	1.15 ± 0.62 (380)	1.28 ± 0.93 (148)
Group 2	-3.32 ± 3.35 (8)	-0.04 ± 1.81 (32)	4.49 ± 2.42 (34)	-0.37 ± 1.96 (20)
P	0.37	0.97	0.13	0.53
Total sample size	1,343	1,309	581	254
<b>Memory</b>				
Group 1	-0.02 ± 0.32 (1,198)	0.18 ± 0.38 (1,005)	2.97 ± 0.64 (398)	1.88 ± 1.11 (153)
Group 2	-3.46 ± 3.90 (8)	0.75 ± 1.70 (31)	3.77 ± 2.11 (34)	3.33 ± 2.15 (20)
P	0.38	0.79	0.72	0.65
Total sample size	1,390	1,339	604	260

# Long-term effects of hypoglycemia on cognition

- No evidence of substantial declines in cognition in 1144 T1DM patients who were followed for 18 yrs



1. Problem solving
2. Learning
3. Immediate memory
4. Delayed recall
5. Spatial information
6. Attention
7. Psychomotor and mental efficiency
8. Motor speed

# Conclusions

- Hypoglycemia leads to brain damage and neurological symptoms, depending on the level of blood glucose
- Important role of EEG and DWI in diagnosis and prognostication of hypoglycemic encephalopathy
- Brain adaptation to hypoglycemia
- Cognitive consequence of acute hypoglycemia
- Long-term deleterious effect of recurrent hypoglycemia on cognitive functions ?