

Hypoglycemia-Induced Changes in the Electroencephalogram: An Overview

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Lykke Blaabjerg, MSc, PhD¹ and Claus B. Juhl, MD, PhD^{1,2}

Abstract

Hypoglycemia is defined by an abnormally low blood glucose level. The condition develops when rates of glucose entry into the systematic circulation are reduced relative to the glucose uptake by the tissues. A cardinal manifestation of hypoglycemia arises from inadequate supply of glucose to the brain, where glucose is the primary metabolic fuel. The brain is one of the first organs to be affected by hypoglycemia. Shortage of glucose in the brain, or neuroglycopenia, results in a gradual loss of cognitive functions causing slower reaction time, blurred speech, loss of consciousness, seizures, and ultimately death, as the hypoglycemia progresses. The electrical activity in the brain represents the metabolic state of the brain cells and can be measured by electroencephalography (EEG). An association between hypoglycemia and changes in the EEG has been demonstrated, although blood glucose levels alone do not seem to predict neuroglycopenia. This review provides an overview of the current literature regarding changes in the EEG during episodes of low blood glucose.

Keywords

electroencephalography, electroencephalogram, EEG, diabetes, hypoglycemia, review

Hypoglycemia is usually defined by a blood glucose level below 70 mg/dL. As the glucose level drops, hormonal defense mechanisms, such as glucagon and epinephrine are normally activated, increasing the release of glucose from the liver and producing the typical hypoglycemic symptoms of, for example, sweating, tremor and dysphoria.¹ Spontaneous blood glucose values lower than 50 mg/dL may, however, frequently be measured in diabetes patients or following long-term fasting in healthy individuals with limited or no symptoms.^{1,2} Diabetes patients with a long diabetes duration or with tight glycemic control may experience recurrent episodes of hypoglycemia and lack typical warning symptoms even at very low glucose levels.³ These patients are considered as having impaired awareness of hypoglycemia and are at increased risk of developing severe hypoglycemia.

The rat brain has been shown to store a supply of glucose in the form of glycogen. Insulin-induced hypoglycemia promotes a gradual glycogenolysis, and when plasma glucose levels are below 36 mg/dL, the brain glucose concentration is close to zero.⁴ In the early stage, neuroglycopenia may be apparent only during systematic cognitive testing. As the blood glucose concentration falls, the cognitive function continues to decline, resulting in slower reaction time, blurred speech, loss of consciousness, seizures, and ultimately death.¹

The metabolic state of the brain cells can be measured by electroencephalography (EEG). EEG is traditionally measured

on the scalp, using surface electrodes at specified locations in accordance with the international 10-20 system.⁵ EEGs are often analyzed in the frequency domain, where signals are subjected to spectral analysis. For clinical purposes, EEG is subdivided into bandwidths denoted as beta (16-31 Hz), alpha (8-15 Hz), theta (4-7 Hz), and delta (<4 Hz), see Figure A1 and A2 in the appendix. Most of the cerebral signal observed in the scalp EEG falls in the range of 1-20 Hz.

Hypoglycemic episodes are associated with measurable changes in the EEG. Analysis of EEG changes as a predictor of severe hypoglycemia was proposed decades ago.⁶ The clinical applicability of a hypoglycemia alarm device based on analysis of EEG changes is reliant on the extent, reproducibility and spatial location of the EEG changes, as well as the time from onset of EEG changes to cognitive decline. This review provides an overview of what is currently known about the hypoglycemia-induced changes in the EEG on these matters.

¹HYPOSAFE A/S, Nymøllevej 6, 3540 Lyngø, Denmark

²Department of Endocrinology, Hospital South West Jutland, Esbjerg, Denmark

Corresponding Author:

Lykke Blaabjerg, MSc, PhD, HYPOSAFE A/S, Nymøllevej 6, 3540 Lyngø, Denmark.

Email: lb@hyposafe.com

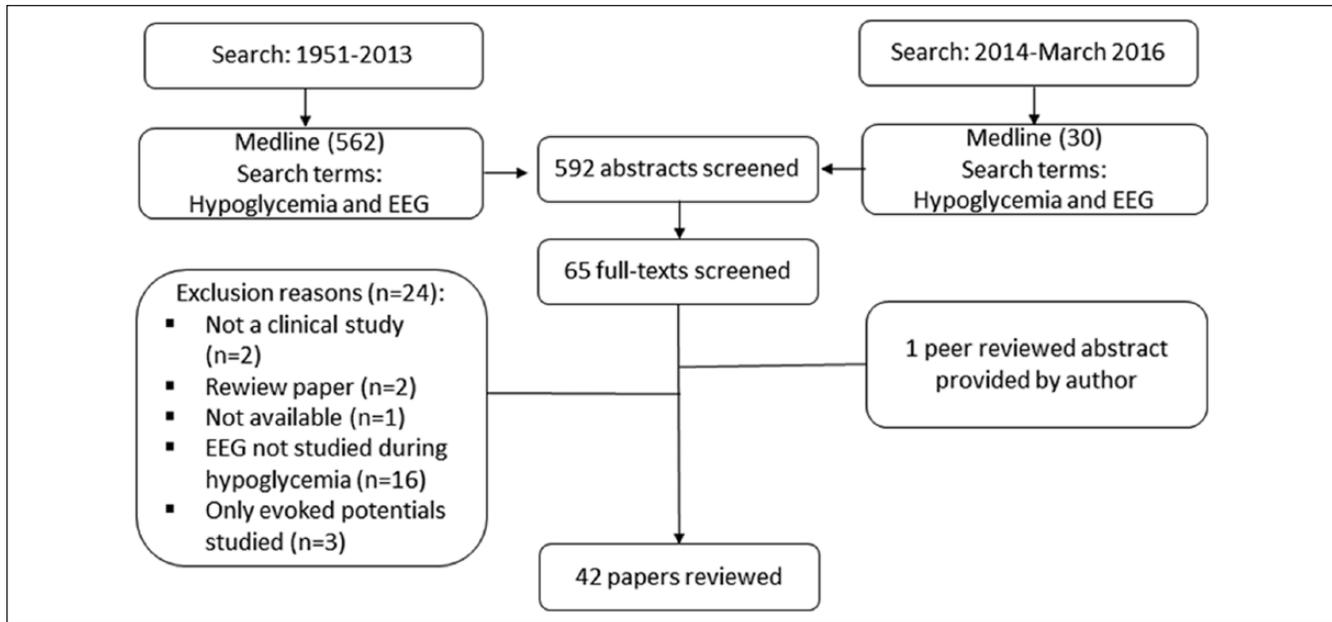


Figure 1. Search strategy and study selection.

Study Selection

The electronic database MEDLINE was searched in 2013 using the search terms “Hypoglycemia and EEG.” The search was repeated in March 2016. Studies included for review were English language studies investigating the clinical effect of hypoglycemia on the background EEG. Both medically induced and noninduced episodes of hypoglycemia were eligible, but only studies recording EEG during episodes of low blood glucose were included. Study selection was conducted independently by the 2 authors. Figure 1 illustrates stages of the study selection process, leading to the review of 65 full texts, with 42 publications matching the selection criteria.

EEG Parameters Affected by Hypoglycemia

Ross and Loeser⁷ were the first to record EEG time series simultaneously with blood glucose levels back in 1951. This was followed by Regan and Browne-Mayers,⁶ who observed a decrease in alpha frequencies and an increase in delta frequencies following insulin injection, with a gradual aggravation in the EEG changes as the hypoglycemia progressed—an association between hypoglycemia and changes in the EEG was demonstrated. Many others have since supported these observations (Table 1). An example of an EEG recorded during normoglycemia and hypoglycemia is shown in Figure 2.

Overall, the earliest abnormalities seen in response to hypoglycemia is an increase in the total EEG power and a generalized slowing of the frequency.^{6,9-18} More specifically, an increase in the power of the delta band and theta band relative to the total power is observed at the expense of the relative power in the alpha band.^{3,6,13-17,19-25} The centroid frequency of theta is often

increased, while the dominant alpha frequency or centroid frequency of alpha is reduced.^{15,19,20,25-28} This demonstrates that during the hypoglycemia onset, there is a power shift to the border area between alpha and theta band in the power spectra of EEG signals.²⁰ Hence, the alpha/theta ratio is a sensitive parameter for detecting changes in the EEG during hypoglycemia.²³ The generalized slowing is followed by abnormal spike changes^{3,10,29} and subsequent flattening of the EEG as the severity of hypoglycemia increases.³⁰ The changes in the EEG during hypoglycemia may not be identical in all patients, but they seem to be reproducible in each patient.³¹

Until now, most studies investigating EEG in diabetes patients have been univariate assessing hypoglycemia-induced EEG changes using linear spectral analysis. Recently, new ways of analyzing data have revealed new EEG parameters that are affected by hypoglycemia. Analyzing EEG signal complexity using nonlinear signal processing techniques has demonstrated a decrease in complexity of EEG when a state of hypoglycemia is entered.³² In addition, a decrease in the EEG coherence when passing from normoglycemia to hypoglycemia was observed by use of a multivariate model (ie, measuring synchronization between 2 signals in a multivariate data set).^{28,33}

Hypoglycemia-Induced EEG Changes During Sleep

During sleep, the cerebral activity is increasingly synchronized.⁵⁰ The EEG is then characterized by occurrence of slow wave pattern similar to the changes seen during daytime hypoglycemia.^{31,39,46} Since hypoglycemia in the awake state induces EEG changes similar to deep sleep, nocturnal hypoglycemia might be difficult to separate from the deep sleep pattern.⁴⁶ Nevertheless,

Table 1. Overview of Studies Investigating Hypoglycemia-Induced EEG Changes.

Author	Pub Year	N	Diabetes, healthy, other	Aware/unaware	Day/night	Nadir (mg/dL)	Delta power	Theta freq	Theta power	Alpha freq	Alpha power	Remarks
Hansen et al³⁴	2016	8	Diabetes	Day + night	37.8-41.4	↑	→ ^a	↑ ^b	→	→	↑ ^b	Children (6-12 years of age) ^a Decreased during sleep ^b No change during sleep
Rubega et al³³	2016	19	Diabetes	Day	41.0	nd	nd	↑	↑	↑	↑	
Rubega et al²⁸	2014											
Fabris et al³²												
Færch et al³⁵	2015	9	Diabetes	Day	46.8 ± 3.6	nd	nd	nd	→ ^c	→ ^c	nd	^c Unchanged centroid frequency (5-11 Hz)
Sejling et al^{36,37}	2015, 2014	23	Diabetes	Day	41.4 ± 0.9 aware 36.0 ± 0.7 unaware	nd	nd	↑	↑	→	→	
Nguyen et al^{19,20,26}	2013,2012, 2011	5	Diabetes	Night	38-45	nd	nd	↓ ^d	↑	↓	↑	Adolescents (12-18 years of age) ^d Decreased in some areas
Kristensen et al⁹	2013	11	Diabetes	Day	36.0	nd	nd	nd	nd	nd	nd	Overall decrease in EEG frequency
Larsen et al³⁸	2013	9	Diabetes	Day	30.6	↑ ^e	nd	↑ ^e	nd	↑ ^e	↑ ^e	^e Increased in some pt Overall decrease in EEG frequency
Remvig et al¹⁵	2012	35	Diabetes	Day	32.4	↑	↑	↑	→	↑	↑	
Snogdal et al³⁹	2012	10	Diabetes	Day + night	27.0-88.2 day 27.0-61.2 night	nd	nd	nd	nd	nd	nd	EEG changes detected in all pt
Nguyen & Jones²⁷	2010	6	Diabetes	Night	<60	→	nd	→	↑	→	→	Adolescents (12-18 years of age)
Juhl et al⁴⁰	2010	15	Diabetes	Day	28.8-48.4	nd	nd	nd	nd	nd	nd	EEG changes detected in all pt
Høi-Hansen et al⁴¹	2009	18	Diabetes	Day	39.6 ± 5.4	nd	nd	nd	nd	nd	nd	^f Decrease in alpha frequency in pt with high basal renin-angiotensin system activity
Iaione & Marques⁴²	2005	8	Diabetes	Day	37.8 ± 7.2	nd	nd	nd	nd	nd	nd	EEG changes detected by an EEG analyzing algorithm in most pt
Cox et al^{18,43}	2001, 2000	37	Diabetes	Day	39.6	nd	nd	↑	nd	nd	↓ ^g	^g Increase in total power, decrease in relative power
Osorio et al⁴⁴	1999	17	Healthy	Day	18-45	nd	nd	nd	nd	nd	nd	Overall decrease in EEG frequency in most pt
Bjørngaas et al²¹	1998	36	19 diabetes, 17 healthy	Day	43.2 ± 7.2 diabetes 50.4 ± 3.6 healthy	↑	nd	↑	nd	→	→	Children/adolescents (12-16.5 years of age)
Howorka et al¹⁶	1996	14	Diabetes	Day	18.0-39.6	↑	nd	↑	nd	↓	↓	
Lindgren et al²²	1996	10	Healthy	Day	45 ± 7.2	→	nd	→	nd	→	→	

(continued)

Table 1. (continued)

Author	Pub Year	N	Diabetes, healthy, other	Aware/unaware	Day/night	Nadir (mg/dL)	Delta power	Delta freq	Theta power	Theta freq	Alpha power	Alpha freq	Remarks
Tribl et al²³	1996	14	Diabetes	7/7	Day	32.6 ± 7.6	↑	↑ ^h	↑	↑ ^h	↓	↓	^h Increased centroid frequency in the combined delta and theta band in most areas
Heger et al¹⁴	1996	24	Diabetes	nd	Day	mean 34.2	↑	nd	↑	nd	↓	↓	EEG changes detected by an EEG analyzing algorithm in most pt
Gade et al⁴⁵	1994	16	Diabetes	nd	Night	<54.0	nd	nd	nd	nd	nd	nd	ⁱ Increased in some pt
Bendtsen et al^{31,46}	1992	8	Diabetes	nd	Night	25.2-34.2	↑ ⁱ	nd	↑ ⁱ	nd	nd	nd	ⁱ Increased in some pt
Amiel et al³	1991	17	9 diabetes, 2 insulinoma, 6 healthy	nd	Day	30.6-34.2	↑ ⁱ	nd	↑ ⁱ	nd	nd	nd	ⁱ Increased in some pt ^k Decreased ratio of fast to slow frequency band in some pt
Tallroth et al²⁴	1990	20	8 diabetes, 12 healthy	8/0 for diab	Day	28.8-41.4	↑	nd	↑	nd	↓	nd	
Chalew et al¹⁷	1989	5	Healthy	nd	Day	37.8 ± 5.4	↑	nd	↑	nd	→	nd	
Tamburrano et al²⁵	1988	8	Healthy	nd	Day	42.8 ± 2.9	nd	nd	nd	nd	↓	↓	
Pramming et al²⁹	1985	13	Diabetes	nd	Day	23.4-39.6	↑ ^k	nd	nd	nd	nd	nd	^k EEG changes detected in most pt
Harrad et al¹³	1985	11	5 diabetes, 6 healthy	nd	Day	32.2 ± 2.7	↑	nd	↑	nd	↓	nd	
Sperling⁷	1984	33	22 epilepsy, 11 healthy	na	Day	~30 healthy ~40 epilepsy	nd	nd	nd	nd	nd	nd	Diffuse EEG slowing in all healthy and most epilepsy pt
Erwin & Wilson¹²	1966	14	Psychiatric pt	nd	Day	5.4 acute 21.6 prolonged	nd	nd	nd	nd	nd	nd	Marked EEG slowing detected
Wilson et al¹¹	1965	20	Psychiatric pt	nd	Day	Mean 19.8	nd	nd	nd	nd	nd	nd	Marked EEG slowing detected
Green¹⁰	1963	51	Seizures/syncope pt	nd	Day	28.8-70.2	↑ ⁱ	nd	nd	nd	nd	nd	ⁱ Increased in some pt Detection of "slow waves" in some pt
Ziegler & Presthus⁴⁸	1957	24	Epilepsy/syncope pt	nd	Day	<15-54	nd	nd	nd	nd	nd	nd	EEG slowing detected in some pt
Regan & Browne-Mayers⁶	1956	10	Psychiatric pt	nd	Day	nd	nd	nd	↑	nd	nd	↓	Hypoglycemia to precoma and coma state
Ross & Loeser⁴⁹	1951	19	Functional hypoglycemia	nd	Day	16-70	nd	nd	nd	nd	nd	nd	EEG changes detected in some pt

Abbreviations: EEG, electroencephalography; freq, frequency; nd, not determined; pub year, publication year; pt, patient; ↑, increase; ↓, decrease; →, no change.

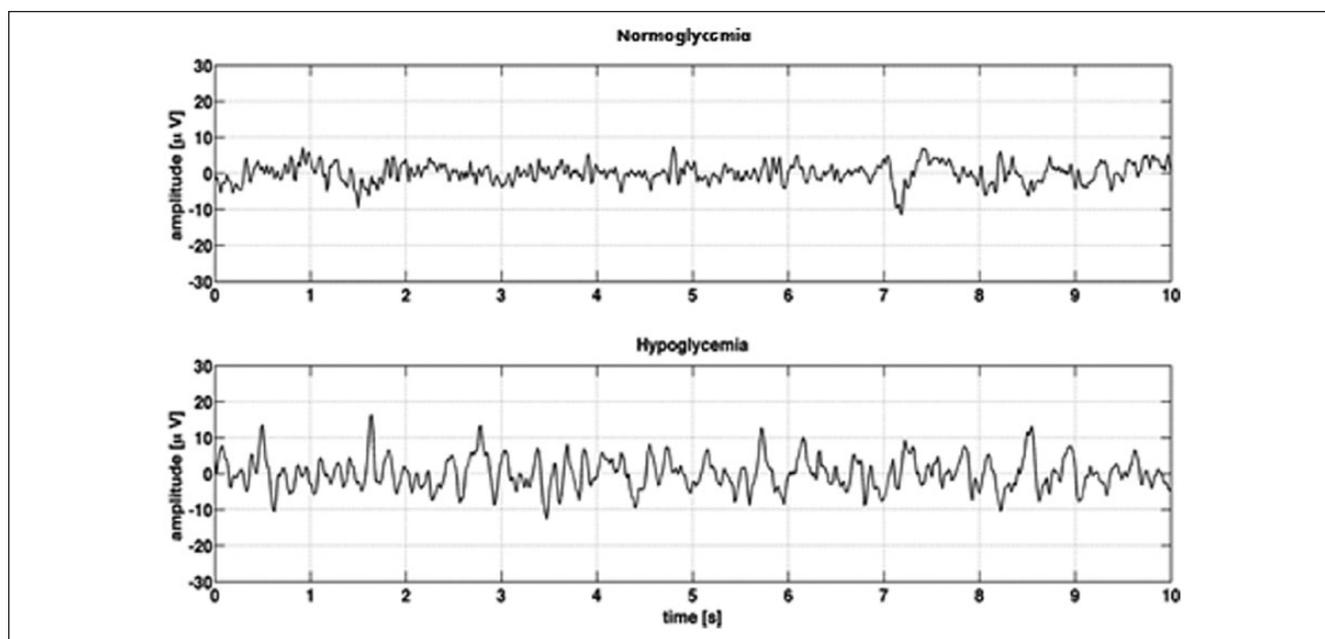


Figure 2. Examples of single channel EEG recordings during normoglycemia and hypoglycemia in the same person (daytime). The hypoglycemic EEG exhibits a lower frequency, which is more synchronized, leading to EEG of higher amplitude compared to the normoglycemic EEG. Adapted from Elsborg et al⁸ with permission.

when comparing the EEG during sleep in the hypoglycemic state to the normoglycemic sleeping state in adults or adolescents, EEG changes compatible with hypoglycemia are detected irrespective of sleep stage,³⁹ that is, a decrease in the centroid alpha, an increase in the centroid theta frequency,^{19,20,26,27} and increased theta and delta activity.³¹ This suggests that hypoglycemia-induced EEG changes overrule normal sleep patterns. As these changes are triggered at glucose levels similar to what is seen during daytime hypoglycemia, the brain seems equally sensitive toward changes in the blood glucose levels in the sleeping state.^{39,46}

A greater mixture of waveforms and frequencies characterizes the EEGs of children, with the relative predominance of these wave types varying with age. In children (6-12 years of age), hypoglycemia during sleep is associated with a decrease in the centroid delta frequency and an increase or decrease in the absolute amplitude depending on the sleep stage.³⁴ An EEG-based algorithm capable of distinguishing EEG sleep pattern from hypoglycemia during sleep in the adult was unable to do so during sleep in children, emphasizing that hypoglycemia-induced EEG changes during sleep in children resemble deep sleep patterns more than in adults.^{34,39}

Spatial Location of EEG Changes

Hypoglycemia-induced EEG changes have been reported in all cortical regions with no major interhemispheric asymmetry.^{11,20,23-25,29} Studies investigating a relatively mild hypoglycemia with blood glucose nadirs of ~43-54 mg/dL suggest that the anterior cerebral cortex is more sensitive to hypoglycemia than the posterior cortex.^{21,25} A

topographic maximum of slow frequencies is found in the frontal cortex at glucose levels of 50-60 mg/dL. During more profound hypoglycemia (30-50 mg/dL reached within <1 h) there is a shift toward the posterior parts of the brain,²³ and overall changes in the EEG are most pronounced in parietal-occipital and temporal regions at blood glucose nadirs of 36 mg/dL (reached within 1 h).²⁹ This suggests that the topographical maximum for EEG changes may change depending of the degree of hypoglycemia. Still others have been unable to detect any regional differences in the EEG changes at blood glucose levels of ~32-36 mg/dL.^{3,31} In these studies, glucose nadir was reached more slowly (after 2-3.5 h). Whether a slow decline in blood glucose leads to more diffusely distributed EEG changes, perhaps due to the general lack of metabolic fuel, remains to be determined.

Glycemic Threshold for EEG Changes

According to Pramming et al²⁹ signs of cortical dysfunction appeared at a blood glucose concentration of 36 mg/dL, and normal EEG was reestablished when the blood glucose exceeded this threshold. Other studies have since reported hypoglycemia-induced EEG changes at various levels of blood glucose. Significant changes in the EEG have been observed at glucose levels as high as 60-72 mg/dL in children, adolescents or adults with diabetes.^{16,19,21,23} At the other extreme, glucose values may drop to 29 mg/dL before significant changes in the EEG are apparent.³ There seems to be no correlation between the blood glucose concentration at the onset of EEG changes and age, duration of diabetes, hemoglobin A_{1c} concentration, initial blood glucose concentration and rate of decline in blood

glucose concentration.^{11,29,40,49} This suggests a highly individual critical glucose threshold for the onset of EEG changes. Clearly, glucose levels alone do not predict neurologic dysfunction.⁴⁴

EEG changes appear at a higher glucose level and are more pronounced in diabetes patients compared to healthy controls at the same hypoglycemic level.^{3,21,24} Furthermore, an association between hypoglycemia unawareness and an early shift toward lower frequencies has been reported during mild hypoglycemia,^{16,23} although unaware patients consistently did not show any clinical impairment.¹⁶ In agreement with this, intensively treated diabetes patients and insulinoma patients developed EEG changes at an early stage during hypoglycemia.³ This suggests a hierarchy with unaware diabetes patients being the most sensitive and healthy individuals the least sensitive toward changes in the blood glucose level. At more moderate levels of hypoglycemia, no difference is seen in hypoglycemia-induced EEG changes between aware and unaware patients.^{23,37}

According to Cox et al⁴³ the mental alertness, as reflected by a difference in relative power in the alpha and theta frequency band, is unrelated to the detection of significant neuroglycopenic and neurogenic symptoms. The early changes in the EEG in unaware diabetes patients during mild hypoglycemia may be seen as a protective phenomenon that shifts the threshold for eventual cerebral energy failure in hypoglycemia to lower plasma glucose levels. Slowing of the EEG pattern is associated with a decrease in cerebral metabolic rate for glucose and precedes severe cerebral energy derangements in rats.^{51,52} In addition, patients with type 1 diabetes, in particular those with impaired awareness, seem better able to maintain cerebral metabolism during hypoglycemia than healthy controls.⁵³ A detailed discussion of the changes in the brain metabolism during hypoglycemia is beyond the scope of the present review but has recently been reviewed elsewhere.⁵³

The time from onset of EEG changes to cognitive deficit is of interest if EEG is to be used as a cerebral surveillance tool to prevent further progression of hypoglycemia. When Regan et al⁶ induced hypoglycemia to a state of coma in psychiatric patients, EEG changes appeared 120 min before coma itself, at a time when the patients were often fully oriented. More subtle changes in vigilance were used to investigate this phenomenon in diabetic adults with a history of severe hypoglycemia or impaired awareness. Here, significant changes in the EEG appeared on average 29 min before serious signs of neuroglycopenia and adrenergic reactions (ranging from 3 to 113 min),⁴⁰ or 19 ± 3 min before major worsening of cognitive performance.¹⁶ In children with diabetes, the EEG changes were detected on average 18 min before glucose nadir (ranging from 0 to 55 min).³⁴ Although large interindividual variation is seen, this suggests that the onset of EEG changes in general occurs before the cognitive function is severely affected.

The Extent of EEG Changes

Several studies have reported 1 or more individuals who did not experience significant EEG changes during hypoglycemia,

- sometimes despite clear symptoms of hypoglycemia.^{22,29,44,47,54} Glucagon has been proposed as a defense mechanism, capable of protecting the brain against neuroglycopenia. This is based on studies showing absence of hypoglycemia-induced EEG changes during sleep in diabetes patients with a preserved counter-regulatory glucagon response.^{31,46} In support of this, a significant glucagon response was observed during daytime hypoglycemia in diabetes patients who did not exhibit any EEG changes.⁴¹ These patients were however characterized by having a low basal renin-angiotensin activity, implying other or additional discrepancies in the signal processing.

A correlation between the glucagon response and hypoglycemia-induced EEG changes is challenged by other studies, reporting EEG changes irrespective of the existence of a counter-regulatory glucagon response in patients with diabetes and in healthy individuals.^{9,25,37,40} The glucose nadir in individuals without detectable EEG changes varies from 29–40 mg/dL.^{22,29,41,42,44,46,47} Taking the great interindividual variation into consideration, 1 explanation for the lack of detectable EEG changes could be that the glucose level has not been sufficiently low in these individuals. Nevertheless, Ziegler and Presthus⁴⁸ reported remaining alpha activity and limited slow activity in the 4–7 Hz frequency range at very low blood glucose level, less than 15 mg/dL in a patient with epilepsy. In this study, the centroid frequency was not investigated. In addition, some patients had abnormal EEG before insulin injection, which may have masked any hypoglycemia-induced changes. Overall, the slowing of the EEG during hypoglycemia appears to be a general phenomenon. It is seen in adults as well as in children,^{15,21,26,34} in diabetes patients and healthy individuals,^{22,24,25,44} and regardless of whether hypoglycemia is medicine-induced or not.³¹

Reestablishment of EEG Pattern

Following insulin-induced hypoglycemia, glucose levels are typically restored in clinical studies by IV injection of glucose. During this recovery period, EEG reestablishes to pretreatment levels in diabetes patients as well as in nondiabetics.^{3,13,17,29} The glucose level at which the EEG slowing clears and the timing of clearance may vary between individuals just like the threshold for the onset of EEG changes.^{11,29} The EEG normalization has been reported to occur within 20–120 min after initiation of glucose infusion and often before plasma concentrations return to normoglycemic levels.^{19,24,29,44,46,47}

Howorka et al¹⁶ and Amiel et al³ found that as plasma glucose levels increased, the restoration of initial values of slow waves in unaware patients occurred earlier and at lower glucose levels compared to hypoglycemia aware patients. Irrecoverable alterations in the EEG signals following hypoglycemia were suggested by Nguyen et al,¹⁹ as reestablishment of the EEG did not happen consistently for all features in all patients 100 min after glucose induction. However, when assessing the acute effect of recent antecedent hypoglycemia on hypoglycemia-induced EEG changes, no difference in power or frequency distribution during hypoglycemia between the first and the second hypoglycemic episode was identified.³⁶

Conclusion

Although hypoglycemia is typically acknowledged based on blood glucose levels, the state of hypoglycemia becomes critical only once the brain experiences neuroglycopenia and brain functions fail. The EEG reflects the metabolic state of the brain, and changes in the EEG happen early in hypoglycemia. It is clear that the threshold for hypoglycemia-induced EEG changes varies between individuals. Whether it depends on cerebral glycogen levels, different rates of glucose transport into the brain cells, cerebral blood flow, or some other mechanism remains to be demonstrated. Despite this, hypoglycemia-induced EEG changes, such as an increase in overall power and a generalized slowing of cerebral activity, are seen symmetrically in all cerebral regions and occur irrespective of age, diabetes duration, awareness status, or antecedent episodes of hypoglycemia.

Appendix

Definitions

Centroid frequency can be referred as the center of gravity of the spectrum within each band. It is estimated as the frequency that subdivides the area under the spectral curve into 2 of equal size.

Coherence is a measure of synchronization between 2 signals based mainly on phase consistency; that is, 2 signals may have different phases, but high coherence occurs when this phase difference tends to remain constant.

Frequency Bands

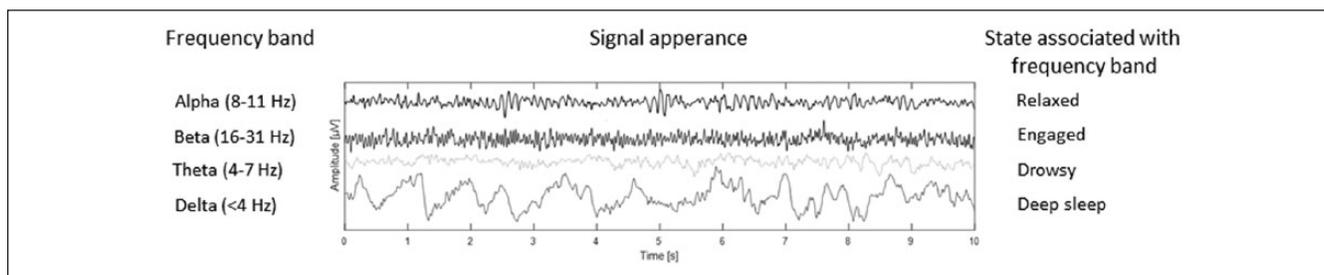


Figure A2. Frequency bands and associated mental states.

Examples of EEG frequency bands recorded in a healthy adult. To the right the mental states associated with frequency bands are described.

Abbreviations

EEG, electroencephalography; h, hour.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this

Electrode Position of the 10-20 System

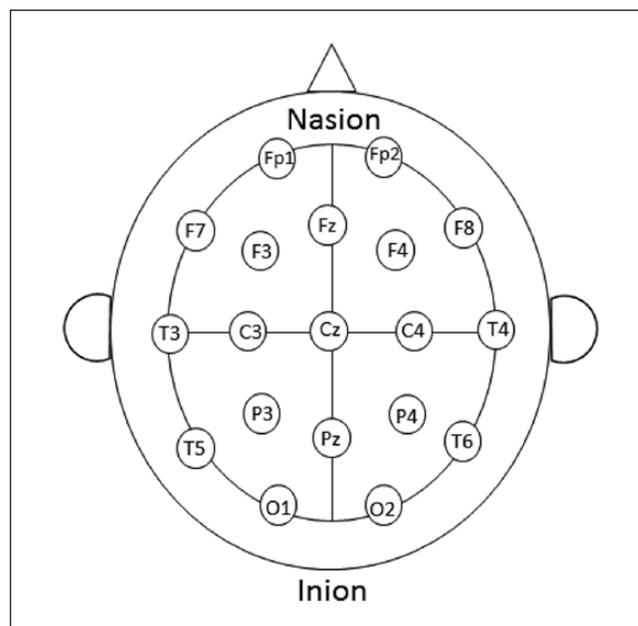


Figure A1. Electrode position of the 10-20 system.

A schematic presentation of the electrode position of the 10-20 system. F, T, C, P, and O refer to frontal, temporal, central, parietal, and occipital lobes, respectively. Z refers to an electrode placed on the midline and Fp to frontal polar sites. Even numbers represent electrodes positioned on the right hemisphere, whereas odd numbers represent electrodes positioned on the left hemisphere.

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References

1. Cryer PE. Hypoglycemia-associated autonomic failure in diabetes. *Am J Physiol Endocrinol Metab.* 2001;281:E1115-E1121.

2. Hojlund K, Wildner-Christensen M, Eshoj O, et al. Reference intervals for glucose, beta-cell polypeptides, and counter-regulatory factors during prolonged fasting. *Am J Physiol Endocrinol Metab.* 2001;280:E50-E58.
3. Amiel SA, Pottinger RC, Archibald HR, et al. Effect of antecedent glucose control on cerebral function during hypoglycemia. *Diabetes Care.* 1991;14:109-118.
4. Morgenthaler FD, Koski DM, Kraftsik R, Henry PG, Gruetter R. Biochemical quantification of total brain glycogen concentration in rats under different glycaemic states. *Neurochem Int.* 2006;48:616-622.
5. Klem GH, Lüders HO, Jasper HH, Elger C. The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl.* 1999;52:3-6.
6. Regan PF, Browne-Mayers AN. Electroencephalography, frequency analysis and consciousness; a correlation during insulin-induced hypoglycemia. *J Nerv Ment Dis.* 1956;124:142-147.
7. Ross IS, Loeser LH. Electroencephalographic findings in essential hypoglycemia. *Electroencephalogr Clin Neurophysiol.* 1951;3:141-148.
8. Elsborg R, Remvig L, Beck-Nielsen H, Juhl C. Detecting hypoglycemia by using the brain as a biosensor. In: Serra PA, ed. *Biosensors for Health, Environment and Biosecurity.* InTech; 2011. doi:10.5772/17018. <http://www.intechopen.com/books/biosensors-for-health-environment-and-biosecurity/detecting-hypoglycemia-by-using-the-brain-as-a-biosensor>
9. Kristensen PL, Pedersen-Bjergaard U, Kjaer TW, et al. Influence of erythropoietin on cognitive performance during experimental hypoglycemia in patients with type 1 diabetes mellitus: a randomized cross-over trial. *PLOS ONE.* 2013;8:e59672.
10. Green JB. The activation of electroencephalographic abnormalities by tolbutamide-induced hypoglycemia. *Neurology.* 1963;13:192-200.
11. Wilson WP, Short MJ, Deiss WP. The relationship of glucagon and EEG patterns in hypoglycemia. *J Psychiatr Res.* 1965;3:99-104.
12. Erwin CW, Wilson WP. Investigation of temporal lobe electrical activity during insulin hypoglycemia. *Int J Neuropsychiatry.* 1966;2:207-211.
13. Harrad RA, Cockram CS, Plumb AP, et al. The effect of hypoglycaemia on visual function: a clinical and electrophysiological study. *Clin Sci.* 1985;69:673-679.
14. Heger G, Howorka K, Thoma H, Tribl G, Zeitlhofer J. Monitoring set-up for selection of parameters for detection of hypoglycaemia in diabetic patients. *Med Biol Eng Comput.* 1996;34:69-75.
15. Remvig LS, Elsborg R, Sejling AS, et al. Hypoglycemia-related electroencephalogram changes are independent of gender, age, duration of diabetes, and awareness status in type 1 diabetes. *J Diabetes Sci Technol.* 2012;6:1337-1344.
16. Howorka K, Heger G, Schabmann A, et al. Severe hypoglycaemia unawareness is associated with an early decrease in vigilance during hypoglycaemia. *Psychoneuroendocrinology.* 1996;21:295-312.
17. Chalew SA, Sakamoto RN, McCarter R, et al. Quantitative monitoring of brain function, vital signs, and hormonal response during acute insulin-induced hypoglycemia. *J Clin Monit.* 1989;5:229-235.
18. Cox DJ, Gonder-Frederick LA, Kovatchev BP, Julian DM, Clarke WL. Progressive hypoglycemia's impact on driving simulation performance. Occurrence, awareness and correction. *Diabetes Care.* 2000;23:163-170.
19. Nguyen LB, Nguyen AV, Ling SH, Nguyen HT. Analyzing EEG signals under insulin-induced hypoglycemia in type 1 diabetes patients. *Conf Proc Annu Int Conf IEEE Eng Med Biol.* 2013;2013:1980-1983.
20. Nguyen LB, Nguyen AV, Ling SH, Nguyen HT. An adaptive strategy of classification for detecting hypoglycemia using only two EEG channels. *Conf Proc Annu Int Conf IEEE Eng Med Biol.* 2012;2012:3515-3518.
21. Bjørgaas M, Sand T, Vik T, Jorde R. Quantitative EEG during controlled hypoglycaemia in diabetic and non-diabetic children. *Diabet Med.* 1998;15:30-37.
22. Lindgren M, Eckert B, Stenberg G, Agardh CD. Restitution of neurophysiological functions, performance, and subjective symptoms after moderate insulin-induced hypoglycaemia in non-diabetic men. *Diabet Med.* 1996;13:218-225.
23. Tribl G, Howorka K, Heger G, et al. EEG topography during insulin-induced hypoglycemia in patients with insulin-dependent diabetes mellitus. *Eur Neurol.* 1996;36:303-309.
24. Tallroth G, Lindgren M, Stenberg G, Rosen I, Agardh CD. Neurophysiological changes during insulin-induced hypoglycaemia and in the recovery period following glucose infusion in type 1 (insulin-dependent) diabetes mellitus and in normal man. *Diabetologia.* 1990;33:319-323.
25. Tamburrano G, Lala A, Locuratolo N, et al. Electroencephalography and visually evoked potentials during moderate hypoglycemia. *J Clin Endocrinol Metab.* 1988;66:1301-1306.
26. Nguyen LB, Ling SSH, Jones TW, Nguyen HT. Identification of hypoglycemic states for patients with T1DM using various parameters derived from EEG signals. *Conf Proc Annu Int Conf IEEE Eng Med Biol.* 2011;2011:2760-2763.
27. Nguyen HT, Jones TW. Detection of nocturnal hypoglycemic episodes using EEG signals. *Conf Proc Annu Int Conf IEEE Eng Med Biol.* 2010;2010:4930-4933.
28. Rubega M, Sparacino G, Sejling AS, Juhl CB, Cobelli C. Decrease of EEG coherence during hypoglycemia in type 1 diabetic subjects. *Conf Proc Annu Int Conf IEEE Eng Med Biol.* 2015;2015:2375-2378.
29. Pramming S, Thorsteinsson B, Stigsby B, Binder C. Glycaemic threshold for changes in electroencephalograms during hypoglycaemia in patients with insulin dependent diabetes. *Br Med J Clin Res Ed.* 1988;296:665-667.
30. Auer RN. Progress review: hypoglycemic brain damage. *Stroke J Cereb Circ.* 1986;17:699-708.
31. Bendtson I, Gade J, Rosenfalck AM, et al. Nocturnal electroencephalogram registrations in type 1 (insulin-dependent) diabetic patients with hypoglycaemia. *Diabetologia.* 1991;34:750-756.
32. Fabris C, Sparacino G, Sejling AS, et al. Hypoglycemia-related electroencephalogram changes assessed by multiscale entropy. *Diabetes Technol Ther.* 2014;16:688-694.
33. Rubega M, Sparacino G, Sejling AS, Juhl CB, Cobelli C. Hypoglycemia-induced decrease of EEG coherence in patients with type 1 diabetes. *Diabetes Technol Ther.* 2016;18:178-184.

34. Hansen GL, Foli-Andersen P, Fredheim S, et al. Hypoglycemia-associated EEG changes in prepubertal children with type 1 diabetes [published online ahead of print February 25, 2016]. *J Diabetes Sci Technol*. 2016. doi:10.1177/1932296816634357.
35. Færch LH, Thorsteinsson B, Tarnow L, et al. Effects of angiotensin II receptor blockade on cerebral, cardiovascular, counter-regulatory, and symptomatic responses during hypoglycaemia in patients with type 1 diabetes. *J Renin-Angiotensin-Aldosterone Syst*. 2015;16:1036-1045.
36. Sejling AS, Kjaer TW, Pedersen-Bjergaard U, et al. Cerebral electrical activity during recurrent hypoglycemia in patients with type 1 diabetes and normal hypoglycemia awareness or hypoglycemia unawareness. *ADA 74th Sci Sess Webcast*; 2014. http://professional2.diabetes.org/Adv_SearchResult.aspx?congress=218&tit=&spk=sejling&ses=&kwd=&cgr=218&typ=10
37. Sejling AS, Kjaer TW, Pedersen-Bjergaard U, et al. Hypoglycemia-associated changes in the electroencephalogram in patients with type 1 diabetes and normal hypoglycemia awareness or unawareness. *Diabetes*. 2015;64:1760-1769.
38. Larsen A, Højlund K, Poulsen MK, Madsen RE, Juhl CB. Hypoglycemia-associated electroencephalogram and electrocardiogram changes appear simultaneously. *J Diabetes Sci Technol*. 2013;7:93-99.
39. Snogdal LS, Folkestad L, Elsborg R, et al. Detection of hypoglycemia associated EEG changes during sleep in type 1 diabetes mellitus. *Diabetes Res Clin Pract*. 2012;98:91-97.
40. Juhl CB, Højlund K, Elsborg R, et al. Automated detection of hypoglycemia-induced EEG changes recorded by subcutaneous electrodes in subjects with type 1 diabetes—the brain as a biosensor. *Diabetes Res Clin Pract*. 2010;88:22-28.
41. Høi-Hansen T, Pedersen-Bjergaard U, Andersen RD, et al. Cognitive performance, symptoms and counter-regulation during hypoglycaemia in patients with type 1 diabetes and high or low renin-angiotensin system activity. *J Renin-Angiotensin-Aldosterone Syst*. 2009;10:216-229.
42. Iaione F, Marques JLB. Methodology for hypoglycaemia detection based on the processing, analysis and classification of the electroencephalogram. *Med Biol Eng Comput*. 2005;43:501-507.
43. Cox DJ, Gonder-Frederick LA, Kovatchev BP, Clarke WL. Self-treatment of hypoglycemia while driving. *Diabetes Res Clin Pract*. 2001;54:17-26.
44. Osorio I, Arafah BM, Mayor C, Troster AI. Plasma glucose alone does not predict neurologic dysfunction in hypoglycemic nondiabetic subjects. *Ann Emerg Med*. 1999;33:291-298.
45. Gade J, Rosenfalck A, Bendtsen I. Detection of EEG patterns related to nocturnal hypoglycemia. *Methods Inf Med*. 1994;33:153-156.
46. Bendtsen I, Gade J, Thomsen CE, Rosenfalck A, Wildschjødztz G. Sleep disturbances in IDDM patients with nocturnal hypoglycemia. *Sleep*. 1992;15:74-81.
47. Sperling MR. Hypoglycemic activation of focal abnormalities in the EEG of patients considered for temporal lobectomy. *Electroencephalogr Clin Neurophysiol*. 1984;58:506-512.
48. Ziegler DK, Presthus J. Normal electroencephalogram at deep levels of hypoglycemia. *Electroencephalogr Clin Neurophysiol*. 1957;9:523-526.
49. Ross IS, Loeser LH. Electroencephalographic findings in essential hypoglycemia. *Electroencephalogr Clin Neurophysiol*. 1951;3:141-148.
50. Iber C, Ancoli-Isreal SL, Chesson A Jr, Quan S. *AASM Manual for the Scoring of Sleep and Associated Events*. Darien, IL: American Academy of Sleep Medicine; 2007.
51. Ghajar JB, Plum F, Duffy TE. Cerebral oxidative metabolism and blood flow during acute hypoglycemia and recovery in unanesthetized rats. *J Neurochem*. 1982;38:397-409.
52. Lewis LD, Ljunggren B, Ratcheson RA, Siesjö BK. Cerebral energy state in insulin-induced hypoglycemia, related to blood glucose and to EEG. *J Neurochem*. 1974;23:673-679.
53. Rooijackers HMM, Wiegers EC, Tack CJ, van der Graaf M, de Galan BE. Brain glucose metabolism during hypoglycemia in type 1 diabetes: insights from functional and metabolic neuroimaging studies. *Cell Mol Life Sci*. 2016;73:705-722.
54. Iaione F, Marques JL. Methodology for hypoglycaemia detection based on the processing, analysis and classification of the electroencephalogram. *Med Amp Biol Eng Amp Comput*. 2005;43:501-507.