

## Brain changes in diabetes mellitus patients with gastrointestinal symptoms

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### Abstract

Diabetes mellitus is a common disease and its prevalence is increasing worldwide. In various studies up to 30%-70% of patients present dysfunction and complications related to the gut. To date several clinical studies have demonstrated that autonomic nervous system neuropathy and generalized neuropathy of the central nervous system (CNS) may play a major role. This systematic review provides an overview of the neurodegenerative changes that occur as a consequence of diabetes with a focus on the CNS changes and gastrointestinal (GI) dysfunction. Animal models where diabetes was induced experimentally support that the disease induces changes in CNS. Recent investigations with electroencephalography and functional brain imaging in patients with diabetes confirm these structural and functional brain changes. Encephalographic studies demonstrated that altered insular processing of sensory stimuli seems to be a key player in symptom generation. In fact one study indicated that the more GI symptoms the patients experienced, the deeper the insular electrical source was located. The electroencephalography was often used in combination with quantitative sensory testing

mainly showing hyposensitivity to stimulation of GI organs. Imaging studies on patients with diabetes and GI symptoms mainly showed microstructural changes, especially in brain areas involved in visceral sensory processing. As the electrophysiological and imaging changes were associated with GI and autonomic symptoms they may represent a future therapeutic target for treating diabetics either pharmacologically or with neuromodulation.

**Key words:** Diabetes mellitus; Gastrointestinal; Electroencephalogram; Magnetic resonance imaging; Brain

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**Core tip:** Investigation of the existing literature on diabetes patients with gastrointestinal (GI) symptoms indicates the presence of structural and functional brain changes. This was most consistent in electrophysiological studies, where especially changes in the insula seemed to correlate with GI symptoms. Imaging studies confirmed the electrophysiological findings showing microstructural changes in brain areas involved in visceral sensory processing. Due to these findings, future targets in treatment of GI symptoms in patients with diabetes may be based on modulation of central nervous system reorganisation, either pharmacologically or with afferent nerve stimulation.

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## INTRODUCTION

According to the World Health Organization diabetes mellitus (DM) is a common disease with a global prevalence estimated to be 9% among adults aged 18+ years. In various studies up to 30%-70% of DM patients complain of gastrointestinal (GI) dysfunction and complications<sup>[1-3]</sup>. This can be manifested as for example vomiting, diarrhoea, abdominal discomfort, constipation and faecal incontinence<sup>[4]</sup>. DM related GI dysfunction may also impair glucose control and increase the risk of malnutrition, which again leads to poor quality of life, weight loss and emptying of glucagon deposits<sup>[5]</sup>. Therefore it is of major importance to focus on the GI complications in patients with DM.

The GI symptoms have in several clinical studies been shown to relate to *peripheral* diabetic autonomic neuropathy, including the enteric nervous system<sup>[6]</sup>. However, as the neuropathy is generalized the central nervous system (CNS) may play a role as well. Hence, the cerebral complications of both type 1 and

type 2 diabetes have been referred to as "diabetic encephalopathy", a term introduced several decades ago<sup>[7]</sup>.

The pathophysiology behind generalized neuropathy is multifactorial, with metabolic, oxidative or immune-related damage of the neurons or glia cells as main factors. Apart from effects on the enteric nervous system that may lead to dysmotility, *etc.*, specific symptoms such as vomiting and nausea are mainly controlled from the brain. Therefore dysfunction of the CNS is mandatory to consider, when other reasons for vomiting and nausea have been ruled out. Furthermore, although some GI motility is present even in patients with severe CNS damage, it is partly centrally regulated, and therefore brain changes will invariably have an effect on gut function<sup>[8]</sup>.

What is already known on this area: (1) diabetes mellitus can cause peripheral and autonomic neuropathies; (2) 50% of patients with longstanding diabetes suffer from GI symptoms; and (3) the symptoms lead to severe socio-economic problems and reduced quality of life.

The aim of this review: (1) to update the literature about diabetes and brain changes in humans; and (2) to provide evidence that central neuroplastic and structural alterations may play a major role in diabetic patients with GI symptoms.

Several recent papers focusing on changes in the brain support the above considerations. Hence, in animals with diabetes, changes in the paraventricular nuclei of the hypothalamus as well as the dorsal motor nuclei have been found<sup>[9]</sup>. Changes in these areas are related to the function of the GI tract. In diabetes patients with GI symptoms changes of brain areas, which are involved in visceral sensory processing has been reported. Thus, novel methods used to treat vomiting in DM such as gastric electrical stimulation may exert its effects mainly *via* the brain since no clear effect and the gastric motor function is seen<sup>[10]</sup>. However significant knowledge gaps remain, but addressing central alterations may provide new insight which may guide future therapeutic targets for treatment of GI complications in DM<sup>[11]</sup>.

The aim of this review is to explore the current literature investigating brain changes in patients with DM and GI symptoms. Furthermore, the background for metabolic brain changes, neurophysiological and imaging methods will briefly be discussed.

## LITERATURE SEARCH

PubMed searches were performed for articles and abstracts published in English. There was no lower limit for the time of publication, but literature was searched up to January 2015. Although the focus of this review was studies in humans, animal studies are cited where they illustrate a point of importance. Medical sub-heading (MeSH) and free-text terms for "CNS", "brain", "electroencephalogram" (EEG), and "magnetic

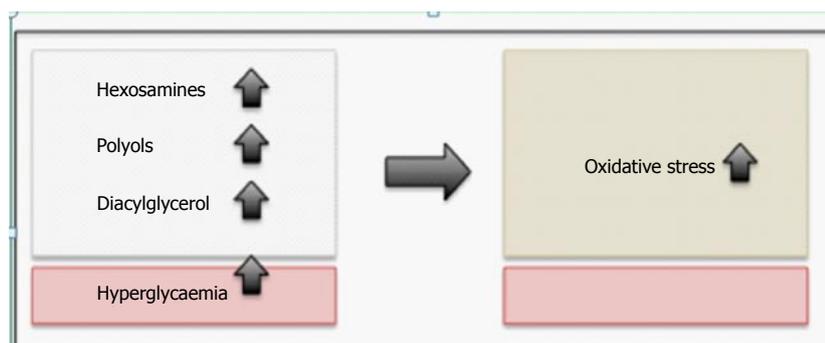


Figure 1 Hyperglycaemia leads to increased hexosamines, polyols and diacylglycerol within the cell, which can cause oxidative stress leading to cell damage.

resonance imaging (MRI)" were combined with "DM" and "GI symptoms". The authors reviewed titles and abstracts to identify studies examining brain changes in DM with GI symptoms. In addition to the structured literature search a manual search of references from articles included was also conducted. Thus, a number of articles not identified by the original search were included in this review if all other requirements were met. Mainly studies examining neurodegenerative changes in DM patients with GI symptoms were included. The level of evidence was not graded due to the exploratory nature of many of the studies.

## DIABETIC NEUROPATHY: THE PATHOPHYSIOLOGY

A multiple of factors appear to be involved in the pathogenesis of brain changes in DM. A widely held belief is that CNS changes are secondary to the peripheral neuropathy, because the reduced afferent activity may cause adaptive shrinking<sup>[12]</sup>. However, considerable controversy as to the underlying mechanism remain<sup>[13]</sup>, and an alternative hypothesis is that the CNS changes might indeed be a primary phenomenon. There are several potential causes for the direct changes such as fluctuations in insulin and blood sugar levels, as well as cerebrovascular alterations.

### *The hyperglycaemia hypothesis*

Most research focused on hyperglycaemia and hyperlipidaemia as main players to induce oxidative stress and pro-inflammatory mechanisms. Diabetes-related hyperglycaemia as well as hyperlipidaemia induce a number of pathological changes in neuronal tissue leading to oxidative stress and pro-inflammatory mechanisms, as shown in Figure 1<sup>[14,15]</sup>. Hyperglycaemia leads to elevated intracellular glucose and cellular toxicity. This glucotoxicity alters cell function in different ways leading to increased synthesis of polyols, diacylglycerol (which in turn activates protein kinase C) and hexosamines that accumulate intracellularly<sup>[16]</sup>. The exact mechanism by which these factors cause altered cell function is not yet clear, but they act in concert to induce oxidative stress<sup>[5]</sup>. Thus, levels of free radicals, such as superoxide and nitrogen species rise, especially in the mitochondria. Meanwhile, the ability to scavenge free radicals is reduced because of a depletion of the

proton donor nicotinamide-adenine-dinucleotide<sup>[14]</sup>.

These processes may also trigger an enzyme, poly(ADP-ribose) polymerase, of great importance to deoxyribonucleic acid repair, and thereby cause break-up of the deoxyribonucleic acid strands. A further consequence is the reduction of intracellular nicotinamide-adenine-dinucleotide, exacerbated by the polyol pathway induction. As an end result, adenosine triphosphate levels have been shown to reach critical low levels in, e.g., Schwann cells, possibly resulting in cell death<sup>[17]</sup>. Finally, a key enzyme in glycolysis (glyceraldehyde-3-phosphate dehydrogenase) is inhibited when the superoxide levels rise, which cause a reduction in the substrate flux into the mitochondria. However, glucose still enters the cell, which causes even more activity in the alternative metabolic routes, leading to further production of hexosamines, polyols, poly(ADP-ribose) polymerase and advanced glycation end products, thus closing the loop of a vicious cycle<sup>[18]</sup>. For further details see<sup>[17-19]</sup>.

The hyperglycaemia theory seems more valid for type 1 than type 2 DM. In line with this a Cochrane review showed that improved glucose control inhibits onset of neuropathy in type 1 DM, whereas it only had a modest, non-significant relative risk reduction in patients with type 2 DM after 4 years of follow-up. However, when patients were followed for 15-year the effect of increased glucose control showed significant risk reduction<sup>[20-22]</sup>. Although peripheral neuropathy was explored, the mechanisms are likely similar for other nerve tissues. Hence, the prevention of hyperglycemia is likely also of importance to protect the autonomic nervous system and the brain.

The altered function of the cell can also be caused by other factors. The intracellular non-enzymatic glycation of proteins gives rise to advanced glycation end-products, which in the extracellular matrix interacts with various receptors from matrix to endothelial receptors. This last mentioned interaction can lead to proinflammatory gene expression<sup>[19]</sup>.

### *The influence of severe hypoglycaemia*

Severe and prolonged hypoglycaemia can increase release of excitatory amino acids. The release may turn uncontrolled and trigger calcium influx, thereby leading to activation of proteolytic enzymes, causing neuronal damage<sup>[23]</sup>. However, the brain may utilise

other non-glucose resources such as ketone bodies and amino acids and hence be protected against the hypoglycaemic changes<sup>[7,24]</sup>. This is in contrast to the brain damage caused by ischemia and hypoxia. On the other hand, hypoglycaemia and the counter-regulatory hormonal responses are associated with an acute rise in haematocrit levels and blood viscosity, and this may influence capillary blood flow especially when structural changes of the vessels and metabolic pathways are already present<sup>[7]</sup>.

### **Insulin in the brain**

Insulin receptors are found throughout the brain. The systemic insulin level is increased in most type-1 DM patients due to exogenous insulin treatment. In healthy people insulin is produced in the pancreas, released into the portal circulation and passed on to the liver, where it exerts its prime metabolic effects. When patients with diabetes are treated with exogenous insulin it is absorbed directly into the systemic circulation. This results in 200% increased insulin level in the blood, depending on the injected insulin dose<sup>[7,25]</sup>. Insulin is thought to modulate glucose utilisation in specific brain areas, such as hippocampus with a central role for memory function, and in this way it may affect cognitive functions. Furthermore, brain insulin plays a role in satiety signalling and possible neurodegenerative disorders such as Alzheimer disease<sup>[26]</sup>.

### **Cerebrovascular alterations**

Diabetes is associated with both functional and structural alterations of the cerebral vascular system, which can for example increase the risk of stroke<sup>[7]</sup>. Early changes DM is the reduced neuronal blood flow in the vasa nervorum, which can cause neurophysiological changes, such as endotheliopathy<sup>[19]</sup>. Pathogenically, reduced availability of vasodilating molecules, in particular nitric oxide due to its binding to superoxide forming peroxynitrite, play a central role<sup>[16]</sup>. Secondly, vasoconstrictive factors such as sympathetic tone and angiotensin II levels are increased. Thirdly, increased arterio-venous shunting reduces endoneurial blood flow<sup>[27]</sup>. Later on, structural changes such as pericyte degeneration, capillary membrane thickening and decreased capillary density may occur in the brain<sup>[28]</sup>.

Studies regarding cerebrovascular reactivity in type-1 diabetes patients show that the normal increase in blood flow after administration of dilatory stimuli is impaired in DM patients. The impairment is more severe in patients with diabetes with longer disease duration or who have other complications<sup>[29]</sup>. Cerebral vasoreactivity and accompanying changes in blood flow are important in the preservation of adequate perfusion during abnormal events such as hypotension, hypoxia, hypercapnia and hypoglycaemia, all of which are prevalent in diabetes patients. Loss of these important regulatory mechanism may therefore have detrimental effects on the brain<sup>[7]</sup>.

Besides the above described mechanisms, additional

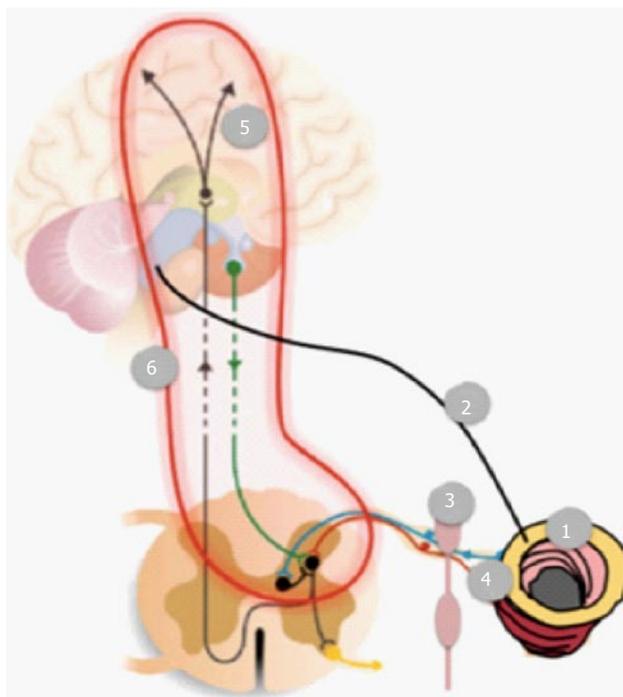
factors, such as disruption of normal endoplasmatic reticulum functioning and the role of autoantibodies may play a role, but will not be further explained here<sup>[27,30,31]</sup>. Finally, it is important to realize that the relative contribution of different factors varies between individuals (depending on characteristics such as sex, age, co-morbidity and stage of disease) and that all these factors interact<sup>[32]</sup>.

## **THE GI SYMPTOMS**

The above theories may lead to better understanding of the brain-gut axis and GI symptoms seen in DM. In the following section the most relevant symptoms will be described.

Fifty percent of DM patients are affected with peripheral neuropathy<sup>[33]</sup>. Diabetic autonomic neuropathy can cause abnormal organ function with symptoms such as urinary incontinence, sexual dysfunction, gastroparesis and nocturnal diarrhoea. Both the parasympathetic and the sympathetic nerves are affected, but in the early stages the vagal nerve seems to be the most vulnerable<sup>[34]</sup>. The vagal nerve has among others a great impact in regulating heart function, which - when damaged - can result in tachycardia and other dysrhythmias. When the sympathetic nerves degenerate the heart rate may fall slightly, but in general diabetes patients with autonomic neuropathy have a resting tachycardia. Furthermore, they may have an impaired adaptability of the heart rate (reduced heart rate variability).

The autonomic nervous system does also have a great impact on GI function. Epidemiological studies have indicated a high prevalence of GI complaints in DM patients<sup>[1-3]</sup>, and as mentioned in the introduction, up to 40% with longstanding diabetes suffer from GI symptoms such as nausea and vomiting<sup>[1,4]</sup>. Abdominal discomfort is also a common symptom, which in severe cases may lead to weight loss and malnutrition. Diarrhoea can be a consequence of abnormal gut motor function, but may also be related to small intestinal bacterial overgrowth and adverse effects to various drugs<sup>[1-3]</sup>. Another prevalent GI symptom is delayed gastric emptying, which can lead to nausea, vomiting and weight loss<sup>[35]</sup>. The peripheral and central neuropathy may in theory also give rise to pain *per se*. Pain is a cardinal symptom of peripheral somatic nerve damage in diabetics, and it is a typical neuropathic pain type. In DM peripheral neuropathy is prevalent and can occur spontaneously or provoked by noxious or non-noxious stimuli<sup>[36]</sup>. As a parallel, in patients with pancreatitis where the visceral nerves are also destroyed, neuropathy may play a major role in the GI symptoms<sup>[37]</sup>. Thus, although speculative, peripheral visceral neuropathy in DM may therefore result in abdominal pain. As central nerve lesions in humans such as in spinal cord injuries and stroke also may give rise to pain, diabetic encephalopathy may also lead to symptoms *per se*<sup>[38,39]</sup>.



**Figure 2** Schematic representation of the possible nerve pathways and mechanisms that theoretical can contribute to gastrointestinal symptoms in diabetics. (1) Vascular and degenerative changes in the enteric nervous system; Autonomic neuropathy affecting (2) the vagal nerve and (3) sympathetic pathways; (4) Affection of visceral (and somatic in case the peritoneum is involved) afferents mediating sensations such as pain; (5) Structural and functional changes in the brain (and spinal cord), together with (6) affection of spino-bulbo-spinal loops.

The relationship between the visceral nerves and the brain is illustrated in Figure 2. The gut changes in DM may however, also be related to changes in the CNS as motility is partly influenced by interaction with several brain areas<sup>[8]</sup>. For example has damage to the dorsal motor nucleus and the paraventricular nucleus of hypothalamus in animals been found of importance for nerves controlling the gut<sup>[9]</sup>, and a pathway including the area postrema, nucleus tractus solitaries and the dorsal motor nucleus of the vagal nerve has been shown to have great impact in controlling gut function including motility<sup>[9]</sup>. Such changes in motility may indirectly lead to symptoms<sup>[38,39]</sup>.

Other symptoms that may relate to diabetic affection of the brain are cognitive dysfunction. This is most marked in patients with an early onset of diabetes. When having type 1 diabetes it is most evident in the domains of psychomotor speed, mental flexibility and general intelligence. Hence, the performance on these domains in patients with diabetes is 30%-40% of that in healthy control subjects<sup>[40]</sup>.

## DIABETES AND THE CNS

### *Brain changes in animals*

Changes within the brain in DM have been investigated in both animals and humans. Although not the focus of this review, a few selected animal studies are shown

in Table 1. In animals such as rats with long-term streptozotocin-induced diabetes increased abnormality in the neuron cells and blood vessels within the brain have been found. Findings were altered Golgi bodies, mitochondria and endoplasmic reticulum cisterns, concurrent with superoxide dismutase inactivation and aldose reductase accumulation<sup>[41]</sup>. Besides this, changes in dorsal motor and paraventricular nuclei of the hypothalamus have been reported in animal models, both of great importance for controlling the part of the autonomic nerves that innervate the gut<sup>[9]</sup>. Additionally, protein kinase C was found increased, which may cause altered cell functioning as explained in section (The hyperglycaemia hypothesis)<sup>[42]</sup>. However, it is not yet clear to which extend the GI mechanisms are caused by the central neuropathy. Some changes in the gut function may be explained by neurotoxicity of streptozotocin at specific locations in the brain, which could have great impact on the regulation of the gut. When having this in mind the choice of animal model is critical if wrong conclusions are to be avoided and relevance to human disease to be maintained<sup>[9]</sup>. Animal models can inform us of some of the pathophysiological and pathogenic aspects of human disease. An advantage is that they may compare to human cases even though the animal does not necessarily have the same symptoms as in a human condition. On the other hand, major differences in morphology and function between rodent and human brains do exist, making the results of animal studies difficult to translate to humans.

As outlined above, the differences between human and animal brains make it important to focus on human research. Here, methods such as quantitative sensory testing (QST), electrophysiology or imaging can be used to explore functional and structural brain changes in humans with diabetes and GI symptoms, which will be elaborated further on in the next sections.

### **QST - methodology**

Clinical assessment of the sensory system in patients is affected by, *e.g.*, general malaise, additional pathophysiological influences, or co-medications. QST is a discipline to evoke sensations such as pain under controlled circumstances<sup>[43]</sup>. This is advantageous as it encompasses many of the problems seen in the clinical situation and offers the opportunity to explore the sensory system more objectively. QST can for example determine the vibration sensation threshold and the pain thresholds for cold and warm temperatures by stimulating the skin, but can also be used in the deeper tissues such as muscles and viscera. In many of the studies investigated in this review, the oesophagus has been investigated. The methods are also able to selectively activate different nerve pathways to mimic the clinical situation such as with the multimodal probe that can be used in the oesophagus and rectum<sup>[44]</sup>. Following standardised sensory stimulation there are several ways to measure the response. Psychophysical methods such as intensity ratings

Table 1 Animal models of diabetes

Ref.	Methods	Results
Bhardwaj <i>et al</i> <sup>[42]</sup>	Signal transduction in brains was investigated in rats with 1-3 mo of induced diabetes	Protein kinase A and C were increased and calcium/calmodulin dependent protein kinase II decreased
Li <i>et al</i> <sup>[81]</sup>	Proteins were extracted from brain tissues of control rats and type 1 diabetic rats	The proteomic identification could be a useful tool for understanding of diabetic encephalopathy mechanisms
Yang <i>et al</i> <sup>[41]</sup>	Rats were randomized into a control and a DM group and neuron and vessel changes were examined with electron microscopy	Increasing abnormality in the neurons and blood vessels were seen that correlated to the length of diabetes
Ramos-Rodriguez <i>et al</i> <sup>[82]</sup>	Brain morphology was analyzed in mice	Hippocampal and cortical atrophy was found as well as cell proliferation and neurogenesis impairment

DM: Diabetes mellitus.

are most frequently used, but they give no detailed information about the brains response that can be explored with electrophysiological or imaging methods. Findings from experimental pain can be used to getting greater knowledge of a disease and pharmacological mechanisms, and clinical pain symptoms may help explaining results from experimental pain studies.

### Findings with QST

QST has been used in several studies to investigate diabetes patients with GI symptoms, as seen in Table 2. The most consistent result to painful gut stimulation in DM was hyposensitivity. Two studies found that DM patients had hyposensitivity to painful sensation evoked in the esophagus<sup>[11,45]</sup>. When using rectosigmoid electrostimulation hyposensitivity to painful stimulation was also found<sup>[4]</sup>. However in another study the authors found no significant differences in sensory or pain threshold to esophageal stimulations between DM patients and healthy controls, and findings are therefore not absolutely consistent<sup>[46]</sup>. In a study where the effect of acute hyperglycaemia was tested, increased gut sensitivity was seen. Hyperglycaemia is thought to affect the nerves, however it had no effect on the sensation in the patients<sup>[47]</sup>. The hyposensitivity seen in DM strongly supports the presence of peripheral neuropathy and it seems to be generalized to several gut segments. Hence, in comparison with healthy controls, Søfteland *et al*<sup>[48]</sup> found evidence of decreased cutaneous and rectal sensations in diabetes patients with sensorimotor neuropathy and increased GI symptoms. Rectal and cutaneous sensitivities were correlated and associated with abnormal heart rate variability supporting that all fibre types were affected. Another QST study in patients with longstanding DM, showed evidence of generalized neuronal damage manifested as sensorimotor, autonomic and central neuropathies, and the degree of peripheral hypoesthesia was associated to both heart rate variability and impaired conditioned pain modulation<sup>[49]</sup>. Pain and other conscious sensations are processed in the brain and traditionally a "bottom-up" model has been suggested; *i.e.*, damage to the peripheral nerve causes central reorganization<sup>[4]</sup>. On the other hand, it cannot be excluded that spinal, brainstem or brain changes due to central neuropathy alone may contribute to the

generalized sensory changes.

QST can also be used to evoke referred pain. This is partly due to convergence between visceral and somatic afferents in the dorsal horn of the spinal cord, and any central hyperexcitability will increase the size of the referred pain area<sup>[50-53]</sup>. As increases in the referred pain areas were seen following stimulation of the upper gut in DM, this indicates a widely distribution of central sensitization.

### Electroencephalography - methodology

EEG is the recording of electrical activity on the scalp produced by activation of neurons in the brain. The activity can basically be recorded as either evoked potentials following an external stimulus, or in the resting state<sup>[54]</sup>. In both types of recordings, the EEG can be used to study normal pain processing and to identify alterations of pain processing in different patient groups<sup>[54]</sup>. Most studies used evoked brain potentials (EPs), the concept illustrated in Figure 3. The advantage of EPs is that they can detect neuronal activity with very high temporal resolution, thereby making analysis of the primary sensory-specific upstream activation of brain centres possible. This is of major importance as these activations take place within the first 200 ms after stimulation of the periphery<sup>[54]</sup>. Compared with methods based on hemodynamic and metabolic changes (positron emission tomography and functional MRI) EPs have a better time resolution (ms) and with the newest models the corresponding brain sources can be modelled with a spatial resolution of a few mm<sup>[54,55]</sup>.

Electrical stimulation is often used to activate the nervous system but it is unspecific as it bypasses peripheral receptors and depolarizes all types of nerve fibres. In the gut electrical stimulation primarily activates A $\delta$  fibers although the majority are unmyelinated C-fibres, but the electrical stimulus is still to be favored due to the high temporal accuracy. Recently methods such as rapid balloon distension, which is a more natural stimulus, have been developed, but they have never been used in patients with diabetes<sup>[56]</sup>. Furthermore, EPs have been recorded following non-visceral sources such as auditory, visual and somatosensory stimuli, and abnormal response in the brain has been observed in patients with type 1 and 2 diabetes<sup>[7]</sup>. There has been

**Table 2 Findings with quantitative sensory testing and evoked brain potentials in patients with diabetes and gastrointestinal symptoms**

Ref.	Method	Results
Frøkjær <i>et al</i> <sup>[11]</sup>	12 healthy controls and 12 type-1 diabetes patients with proven autonomic neuropathy and severe GI symptoms had their sensitivity to stimulations in the oesophagus and duodenum assessed	A 46% increase in the somatic referred pain areas, indicating central hyper excitability. The results also indicated that the sensory nerves in the GI tract were widely affected. Furthermore it is suggested that future targets in the treatment of GI symptoms in DM patients could be based on modulation of the central nervous system excitability
Frøkjær <i>et al</i> <sup>[63]</sup>	14 type-1 diabetes patients with autonomic neuropathy and GI symptoms and 15 healthy volunteers had their sensitivity to electrical oesophageal and median nerve stimulations assessed by using an euglycemic-hyperinsulinemic clamp. The EPs were also collected	GI symptoms correlated with characteristics of brain potentials in the DM patients. These results indicate a change in peripheral visceral nerves as well as in the central nervous system
Frøkjær <i>et al</i> <sup>[47]</sup>	Evoked potentials to oesophageal and median nerve stimulations were recorded in 14 type-1 diabetes patients with GI symptoms	The study concluded that acute hyperglycaemia had no effect on the brain activation of visceral and somatic stimulations
Frøkjær <i>et al</i> <sup>[62]</sup>	15 healthy volunteers and 14 type-1-diabetes patients with autonomic neuropathy and related GI symptoms had their EPs recorded following painful oesophageal electrical stimulation	Evidence of altered central processing to visceral stimulation in diabetes was found. Compared to controls, the patients with diabetes had a posterior shift of the electrical sources in the anterior cingulate cortex, and additional sources close to the posterior insula and in medial frontal gyrus
Frøkjær <i>et al</i> <sup>[45]</sup>	Ultrasound monitored oesophageal distension was used to study 17 patients with longstanding DM and GI symptoms and 13 healthy controls	The reduced sensitivity was associated with the presence of peripheral neuropathy. This indicates a coexisting change within the visceral and somatic neuropathy
Brock <i>et al</i> <sup>[64]</sup>	14 type-1 diabetes patients with diabetes autonomy neuropathy and 15 healthy volunteers underwent multichannel EEG during painful electrical stimulation of the lower esophagus	Central neuroplastic changes within DM patients were found in the insular region, and it was suggested that the GI symptoms are due to the abnormal insular processing
Lelic <i>et al</i> <sup>[46]</sup>	Electrical stimulation of the rectum was done in 12 healthy controls and 12 type 1 diabetes patients with GI symptoms while having their EPs recorded	Changes in the cingulate-operculum brain network were found in DM patients with GI symptoms. Changes could serve as a biomarker of disturbed sensory visceral processing and GI symptoms in patients with diabetes
Brock <i>et al</i> <sup>[4]</sup>	15 healthy volunteers and 15 diabetes patients with GI symptoms and clinical suspicion of autonomic neuropathy were included. Electrical source analysis to painful recto-sigmoid electrostimulations was modelled	Patients with autonomic neuropathy and GI symptoms had evidence for altered brain activation and dysregulation of the central regulation of the autonomic nervous system, which could explain appearance and persistence of upper GI symptoms
Søfteland <i>et al</i> <sup>[48]</sup>	16 healthy controls and 20 DM patients with sensorimotor polyneuropathy had their heart rate variability and peripheral tactile thresholds recorded and underwent a cold-pressor-test	The patients in this study suffered from generalized polyneuropathy evident as autonomic neuropathy, peripheral hypoesthesia and central changes manifested as impaired conditioned pain modulation
Lelic <i>et al</i> <sup>[61]</sup>	EPs to electrical esophageal stimulation were achieved in 23 diabetes patients with upper GI symptoms and 27 healthy controls. Network analysis between active sources were performed	There was a reorganisation in the opercular cortex, which was correlated with GI symptoms. It was proposing that the changes in the operculo-cingulate cortex could help explain the development and maintenance of GI symptoms in diabetes patients

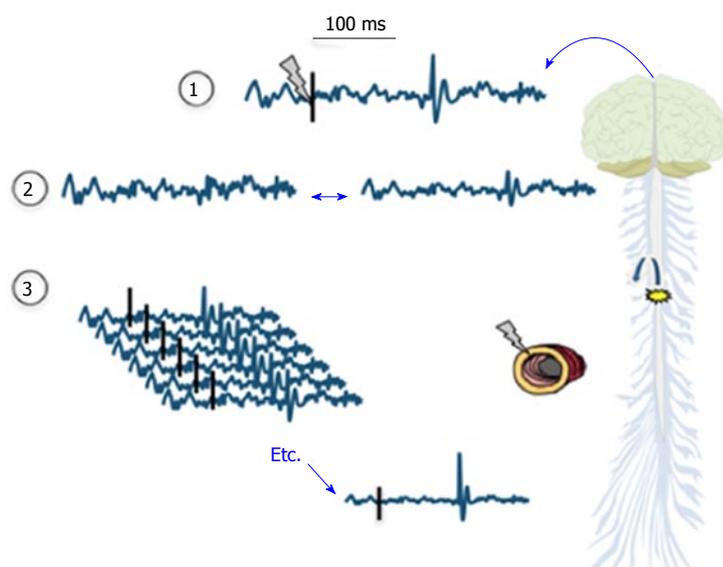
EPs: Evoked brain potentials; GI: Gastrointestinal; EEG: Electroencephalography; DM: Diabetes mellitus.

focus on the so-called late responses as reflected in the P300 wave of somatosensory stimuli, where the latency was increased in DM patients, and it has been hypothesized that evoked potential changes may appear before cognitive dysfunction develops<sup>[57]</sup>. The resting EEG has also been used to investigate the brain in patients with diabetes. This has revealed differences in brain connectivity and information flow, but the changes were not related to the evoked potentials or cognitive functions, and hence assess other functions of the brain<sup>[57,58]</sup>. More sophisticated analyses have confirmed that resting EEG synchronization and complexity is also related to cognitive function and blood glucose level<sup>[59,60]</sup>. However, resting EEG has not been used to explore neuropathy or GI changes and hence it will not be elaborated further in this review. Recently the neurophysiological changes using EPs to visceral organs

in patients with GI symptoms have been investigated and these will be presented below.

### **Findings with electroencephalography**

Studies with EPs have shown evidence of altered central processing to visceral stimulation in diabetes patients with GI symptoms and the findings were repeated in several studies<sup>[61,62]</sup>. Table 2 shows an overview of the different studies. Using evoked potentials to stimulation of recto-sigmoid and esophagus the latencies of the EPs at vertex were increased and amplitudes reduced in DM patients with major variability between patients<sup>[62]</sup>. In recent studies where multiple channels (64-128) were recorded the authors were able to model the corresponding brain sources<sup>[2]</sup>. Compared with controls, the patients had a posterior shift of the electrical sources in the anterior cingulate cortex to oesophageal stimulation,



**Figure 3** Evoked potentials are recorded following a peripheral stimulus as indicated with the grey “lightning” and ideally a corresponding activity can be seen following 80-90 ms as an evoked potential. However, as illustrated in (2) the amplitudes of the evoked potential tend to be low and often comparable to the amplitudes of spontaneous electroencephalogram. In order to decode the evoked potentials from the background electroencephalographic activity and noise, signal averaging is necessary as illustrated in (3). Provided enough of recorded trials, the evoked potentials become bigger in amplitude and therefore visible and the random background activity cancel out. Then, the EP latencies and amplitudes of the peaks can be analyzed by visual inspection. When many (64-128) electrodes are used the corresponding brain sources can be computed based on the surface electroencephalographic recordings. EP: Evoked brain potential.

and additional sources close to the medial frontal gyrus and posterior insula<sup>[62]</sup>. Another study conducted with a similar method found that the GI symptoms correlated with characteristics of brain potentials in the diabetes patients<sup>[63]</sup>. Furthermore a study conducted by the same group showed that DM patients had an anterior shift in insular and cingulate source localizations compared to healthy controls<sup>[64]</sup>. As the insula is considered one of the main centres from where the upstream activation of visceral information is controlled, this may have major importance for our understanding of GI symptoms in DM. In fact the research showed that the more GI symptoms (vomiting, nausea, early satiety, diarrhoea, abdominal pain and/or constipation) the patients experienced, the more anteriorly the insular source was located<sup>[64]</sup>.

GI symptoms and their development and maintenance were also found to correlate with reorganization within the opercular cortex localised between the insula and secondary somatosensory cortex<sup>[61]</sup>. Another study explored the communication between different brain regions. The changes in networks were correlated to severity of upper GI symptoms and life quality. It was concluded that changes in the networks could also serve as a biomarker of disturbed sensory visceral processing and GI symptoms in patients with diabetes<sup>[46]</sup>.

### Imaging methods

Another method is brain imaging where magnetic resonance (MR) is the dominating method. The contrast between grey and white matter in MRI makes it the optimal choice for many conditions of the CNS including demyelination. A specific way of analysing MR images is volumetry where the total brain volume is determined by summing the grey and white matter pixels, then multiplying by the voxel dimension. With this method, a more precise estimate of atrophy can be accessed<sup>[65]</sup>. Another MRI method used in some of the studies in this review is functional magnetic

resonance (fMRI) with measurement of blood oxygen level dependent contrasts (BOLD). It measures brain activity by detecting changes in blood oxygenation. It infers regional changes in brain activity, and thereby it reflects whether a specific brain region is engaged to a time-linked neurobehavioral or neurocognitive task. It has been of great importance in mapping regions in the brain linked to specific functions<sup>[66]</sup>. More specifically it is a great method to examine the superficial layers of the brain because of the excellent spatial resolution (2-5 mm), but limitations are seen in the deeper structures, such as brainstem and thalamus because of pulsation artefacts. fMRI has the possibility to take individual characteristics and anatomy into account, which can be a major advantage. Furthermore, fMRI operates in a non-radioactive and non-invasive radioactive environment, allowing subjects to be studied repetitively<sup>[54]</sup>. Though there are many advantages of fMRI there are some limitations, for example the fMRI is clearly inferior in temporal resolution compared to EEG/MEG, meaning that in pain studies fMRI is not a specific tool for investigating the primary neuronal activity directly related to the painful stimuli. Additionally, the fMRI activity to GI stimulation is not stimulus-specific. Hence, anticipation of stimuli can trigger similar activity and repeated activation can result in habituation<sup>[54]</sup>. Another imaging method is diffusion tensor imaging (DTI)<sup>[67]</sup>. It measures the directionality and magnitude of water diffusion in tissues. The mechanism behind neurostructural changes is not clear but it is the general belief that the integrity of axonal membrane and myelin sheaths is reflected by restriction of diffusion perpendicular to the fibres. The intra-axonal structures, such as microtubules, are thought reflected by diffusion parallel to the fibres. DTI measures the magnitude [described by the apparent diffusion coefficient (ADC)] and directionality [described as fractional anisotropy (FA)] of water diffusion in tissues. Reduced ADC values are seen in variety of CNS insults such as stroke and

trauma, whereas reduced FA is often seen in schizophrenia, Alzheimer's disease and depression<sup>[68]</sup>.

The last method relevant for this review is the arterial spin labelling, which allows the measurement of whole brain blood flow in absolute units through the use of magnetically labelled endogenous water in blood acting as a diffusible tracer<sup>[54]</sup>. This method makes it possible to track the temporal dynamics of the neural activation induced by pain. It is a suitable method to measure the brain's response to tonic stimuli and symptoms since it is more sensitive than fMRI to changes in neural activation when stimulus duration exceeds 1 min<sup>[54]</sup>.

### Imaging findings

Brain MRI conducted in diabetics has been used in different contexts. Most studies have been done in non-selected patients - *i.e.*, without GI symptoms. In type 2 DM atrophy of the brain is mostly found in areas responsible for verbal, visual memory, executive functioning and information processing, and this may link to an increased risk for developing dementia<sup>[40]</sup>. There has also been found cortical atrophy in type-2 diabetes patients, resembling patterns in preclinical Alzheimer's disease<sup>[69]</sup>. Cerebral dysfunction has been convincingly shown in patients with type 1 and 2 diabetes, but few neuroradiological studies have been conducted in patients with autonomic and GI symptoms<sup>[70]</sup>. Due to the sparse imaging research with focus on GI problems and diabetes this review has included few studies regarding general brain changes, as well as studies where brain changes, were comparable to those in animal studies with a correlate to GI symptoms. Generally, as shown in Table 3 structural changes with central atrophy has been reported in patients with DM. One study on type 2 diabetes patients found cortical and subcortical atrophy involving frontal and temporal brain regions, with diminished vasoreactivity and regional cerebral perfusion<sup>[71]</sup>. This supports that uncontrolled diabetes may further contribute to hypoperfusion and atrophy. More specifically MR has also been used to discover a larger lateral ventricular volume with larger white matter lesion. However, no white matter volume difference was found, which is opposite the grey matter shrinkage in the DM patients<sup>[72]</sup>. In another study with MR imaging the focus was atrophy and aging, and in midlife diabetes was associated with subcortical infarctions. More specifically a reduced hippocampal volume, whole brain volume atrophy, and mild cognitive impairment were found<sup>[73]</sup>. The reduced hippocampal volume has been confirmed in different studies including animal studies<sup>[9,69,73,74]</sup>. On the other hand a study that looked into the macrostructural brain alterations found no overall alterations with standard evaluations of the images, and it may be that the macrostructural brain changes are limited in well-treated type-1 diabetes patients<sup>[75]</sup>. It has also been suggested that the

radiological appearance of the brain in patients with diabetes resembles that of normal ageing, but appears to develop at a younger age than in healthy controls<sup>[7]</sup>. In one study investigating the effect of diabetes on brain atrophy and cognitive impairment, pathological findings were only significant in women. The differences between the genders were an unexpected finding and need to be investigated in more detail<sup>[72]</sup>.

Changes in cerebral blood flow in type 2 diabetes have also been investigated with arterial spin labelling<sup>[71]</sup>. Type 2 diabetes were associated with cortical and subcortical atrophy involving frontal and temporal brain regions and with diminished vasoreactivity and regional cerebral perfusion. Additionally the same study found that uncontrolled diabetes might further contribute to hypoperfusion and atrophy.

In patients with DM and GI symptoms a study used cortical volumetry and found reduced cortical thickness of the postcentral and superior parietal gyrus in patients. Those with peripheral neuropathy showed reduction in right postcentral gyrus cortical thickness compared to patients without neuropathy<sup>[74]</sup>. DTI has also been used to investigate more subtle changes in the brain. More specifically a study found that patients with long-standing DM and GI symptoms have microstructural changes in brain areas involved in visceral sensory processing. This could be related to DM-induced brain changes specific for the gut, although, *e.g.*, insular changes may also be important in dysregulation of other functions<sup>[68]</sup>. The microstructural changes were for some areas correlated to GI parameters such as bloating and presence of gastroparesis, together with other autonomic dysfunctions and therefore may be involved in the pathogenesis of GI symptoms. However, even though the few studies in MR are consistent and microstructural alterations were found in diabetes patients with GI symptoms, they still need confirmation in other studies.

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## POTENTIAL EFFECTS OF ANTIDIABETIC TREATMENT

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Many antidiabetics can potentially protect against harmful changes in the CNS. Hence, according to the pathophysiology section above improved blood sugar control and sparing of exogenous insulin will likely result in less neuronal damage. Furthermore, new antidiabetics such as the incretin hormone GLP-1 may be beneficial. Despite its insulinotropic actions it has many unexplored extra-pancreatic effects. Hence, GLP-1 receptors are, in addition to the pancreas, found in the heart, lungs, kidneys and elsewhere in the GI tract, and its function in many of these locations is not yet fully understood<sup>[76]</sup>. In the CNS it primarily affects stimulation of glucose-dependent insulin secretion<sup>[77]</sup> and inhibition of glucagon secretion<sup>[78]</sup>. Interestingly, GLP-1 also acts as a neuropeptide with direct effect on regulation of vagal activity, consequently modulating

**Table 3** Imaging findings in patients with diabetes

Ref.	Method	Results
Jongen <i>et al</i> <sup>[72]</sup>	MR images of 99 DM patients and 46 controls	Larger lateral ventricular volume with white matter lesion and smaller great matter volume was seen in the diabetes patients. The effect of diabetes on brain atrophy where only significant in women
Kodl <i>et al</i> <sup>[83]</sup>	25 type-1 diabetes patients and controls were scanned with a diffusion tensor imaging protocol	White matter microstructural deficits in patients with longstanding diabetes type-1 were found. The deficits correlated with the neurocognitive tests
Last <i>et al</i> <sup>[71]</sup>	Cerebral blood flow was examined in 26 diabetes patients and 25 controls using continuous arterial spin labeling imaging during baseline, CO <sub>2</sub> rebreathing and hyperventilation	Type-2 diabetes was associated with cortical and subcortical atrophy involving frontal and temporal brain regions and with diminished vasoreactivity and regional cerebral perfusion. Uncontrolled diabetes may further contribute to hypoperfusion and atrophy
Kamiyama <i>et al</i> <sup>[74]</sup>	Voxel-based morphometric analysis was performed on 28 diabetes patients and 28 controls	Diabetes patients had hippocampal region atrophy and whole-brain atrophy
Northham <i>et al</i> <sup>[84]</sup>	MRI and IQ test were performed on 106 type-1 diabetes patients and 75 control subjects at baseline and then a 12-yr follow-up	DM subjects had lower verbal and full scale IQs, a decreased gray matter in bilateral thalami and right parahippocampal gyrus and insular cortex. White matter was decreased in bilateral parahippocampus, left temporal lobe, and middle frontal area
van Elderen <i>et al</i> <sup>[32]</sup>	Cognitive function test and MRI was conducted on 438 control subjects and 89 DM patients aged 70-82 yr	Elderly DM patients have accelerated progression of brain atrophy with significant consequences in cognition compared to the control subjects
Frøkjær <i>et al</i> <sup>[68]</sup>	MR scanning was performed in 23 controls and 26 patients with DM and GI symptoms and diffusion tensor imaging was performed	Diabetes patients had microstructural changes in brain areas involved in visceral sensory processing. This could be related to generalized DM-induced brain changes
Rosebud <i>et al</i> <sup>[73]</sup>	MRI on 51437 subjects including 214 with diabetes was performed	Midlife diabetes was associated with subcortical infarctions. Reduced hippocampal volume, whole brain volume and mild cognitive impairment were registered in diabetes patients
Frøkjær <i>et al</i> <sup>[75]</sup>	20 healthy controls and 15 patients with longstanding type 1 diabetes mellitus were scanned and cortical thickness was assessed based on a cortical segmentation method	Reduced cortical thickness of superior parietal and postcentral gyrus. No overall macrostructural brain alterations were detected, but the authors concluded that cortical thinning involving sensory related areas might be important in diabetes

MR: Magnetic resonance; MRI: Magnetic resonance imaging; GI: Gastrointestinal; IQ: Intelligence quotient; DM: Diabetes mellitus.

the homeostatic regulation of the gut<sup>[78]</sup>. Recently, potential neuroprotective function through activation of the GLP-1 axis has received more attention<sup>[79]</sup>, and GLP-1 expression has been identified in neurons of the nodose ganglion including sensory afferents critical to many autonomic reflexes. Furthermore, diabetes patients with autonomous neuropathy were shown to have altered incretin effect as compared to patients without neuropathy<sup>[80]</sup>. Therefore - although it is not recommended to use GLP-1 agonists in patients with diabetic gastroparesis - such drugs may be neuroprotective and human studies are highly warranted.

## CONCLUSION

Investigation of the existing literature on diabetes patients with GI symptoms indicates the presence of structural and functional brain changes. This association was most consistent in EEG studies, but this may relate to the greater amount of papers using this technique. Especially changes in the insula seemed to correlate with GI symptoms. In fact there was evidence that the more GI symptoms the patients experienced, the more changes in insular source was seen, and communications between the insula and other brain regions were malfunctioning. The EEG was often used in combination with QST, which mainly indicated

visceral hyposensitivity in the patients with diabetes and GI symptoms. Imaging studies on diabetes patients with GI symptoms indicated microstructural changes in brain areas involved in visceral sensory processing. Due to these findings, future targets in treatment of GI symptoms may be based on modulation of the CNS reorganisation, either pharmacologically or with afferent nerve stimulation.

## REFERENCES

- 1 **Bytzer P**, Talley NJ, Leemon M, Young LJ, Jones MP, Horowitz M. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults. *Arch Intern Med* 2001; **161**: 1989-1996 [PMID: 11525701]
- 2 **Ricci JA**, Siddique R, Stewart WF, Sandler RS, Sloan S, Farup CE. Upper gastrointestinal symptoms in a U.S. national sample of adults with diabetes. *Scand J Gastroenterol* 2000; **35**: 152-159 [PMID: 10720112]
- 3 **Ko GT**, Chan WB, Chan JC, Tsang LW, Cockram CS. Gastrointestinal symptoms in Chinese patients with Type 2 diabetes mellitus. *Diabet Med* 1999; **16**: 670-674 [PMID: 10477212]
- 4 **Brock C**, Søfteland E, Gunterberg V, Frøkjær JB, Lelic D, Brock B, Dimcevski G, Gregersen H, Simrén M, Drewes AM. Diabetic autonomic neuropathy affects symptom generation and brain-gut axis. *Diabetes Care* 2013; **36**: 3698-3705 [PMID: 24026548 DOI: 10.2337/dc13-0347]
- 5 **Koppen BM**, Stanton BA. *Berne & Levy Physiology*, 6th Updated Edition, with Student Consult Online Access 6th Edition. Mosby, 2010: 693
- 6 **Deguchi T**, Nishio Y, Takashima H. Diabetes mellitus and

- autoimmune neuropathy. *Brain Nerve* 2014; **66**: 135-147 [PMID: 24523312]
- 7 **Brands AM**, Kessels RP, de Haan EH, Kappelle LJ, Biessels GJ. Cerebral dysfunction in type 1 diabetes: effects of insulin, vascular risk factors and blood-glucose levels. *Eur J Pharmacol* 2004; **490**: 159-168 [PMID: 15094082 DOI: 10.1016/j.ejphar.2004.02.053]
  - 8 **Browning KN**, Travagli RA. Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions. *Compr Physiol* 2014; **4**: 1339-1368 [PMID: 25428846 DOI: 10.1002/cphy.c130055]
  - 9 **Horowitz M**, Samsom M. *Gastrointestinal Function in Diabetes Mellitus*. Wiley Online Library, 2004: 44-45, 67 [DOI: 10.1002/0470013877]
  - 10 **Frøkjær JB**, Ejskjaer N, Rask P, Andersen SD, Gregersen H, Drewes AM, Funch-Jensen P. Central neuronal mechanisms of gastric electrical stimulation in diabetic gastroparesis. *Scand J Gastroenterol* 2008; **43**: 1066-1075 [PMID: 18609155 DOI: 10.1080/00365520802028221]
  - 11 **Frøkjær JB**, Andersen SD, Ejskjaer N, Funch-Jensen P, Arendt-Nielsen L, Gregersen H, Drewes AM. Gut sensations in diabetic autonomic neuropathy. *Pain* 2007; **131**: 320-329 [PMID: 17521809 DOI: 10.1016/j.pain.2007.04.009]
  - 12 **Apkarian AV**, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, Gitelman DR. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci* 2004; **24**: 10410-10415 [PMID: 15548656 DOI: 10.1523/jneurosci.2541-04.2004]
  - 13 **Selvarajah D**, Wilkinson ID, Davies J, Gandhi R, Tesfaye S. Central nervous system involvement in diabetic neuropathy. *Curr Diab Rep* 2011; **11**: 310-322 [PMID: 21667355 DOI: 10.1007/s11892-011-0205-z]
  - 14 **Tomlinson DR**, Gardiner NJ. Glucose neurotoxicity. *Nat Rev Neurosci* 2008; **9**: 36-45 [PMID: 18094705]
  - 15 **Chowdhury SK**, Smith DR, Fernyhough P. The role of aberrant mitochondrial bioenergetics in diabetic neuropathy. *Neurobiol Dis* 2013; **51**: 56-65 [PMID: 22446165 DOI: 10.1016/j.nbd.2012.03.016]
  - 16 **Hosseini A**, Abdollahi M. Diabetic neuropathy and oxidative stress: therapeutic perspectives. *Oxid Med Cell Longev* 2013; **2013**: 168039 [PMID: 23738033 DOI: 10.1155/2013/168039]
  - 17 **Obrosova IG**, Drel VR, Pacher P, Ilnytska O, Wang ZQ, Stevens MJ, Yorek MA. Oxidative-nitrosative stress and poly(ADP-ribose) polymerase (PARP) activation in experimental diabetic neuropathy: the relation is revisited. *Diabetes* 2005; **54**: 3435-3441 [PMID: 16306359]
  - 18 **Edwards JL**, Vincent AM, Cheng HT, Feldman EL. Diabetic neuropathy: mechanisms to management. *Pharmacol Ther* 2008; **120**: 1-34 [PMID: 18616962 DOI: 10.1016/j.pharmthera.2008.05.005]
  - 19 **Sytze Van Dam P**, Cotter MA, Bravenboer B, Cameron NE. Pathogenesis of diabetic neuropathy: focus on neurovascular mechanisms. *Eur J Pharmacol* 2013; **719**: 180-186 [PMID: 23872412 DOI: 10.1016/j.ejphar.2013.07.017]
  - 20 **Callaghan BC**, Little AA, Feldman EL, Hughes RA. Enhanced glucose control for preventing and treating diabetic neuropathy. *Cochrane Database Syst Rev* 2012; **6**: CD007543 [PMID: 22696371 DOI: 10.1002/14651858.CD007543.pub2]
  - 21 **Linn T**, Ortac K, Laube H, Federlin K. Intensive therapy in adult insulin-dependent diabetes mellitus is associated with improved insulin sensitivity and reserve: a randomized, controlled, prospective study over 5 years in newly diagnosed patients. *Metabolism* 1996; **45**: 1508-1513 [PMID: 8969284]
  - 22 The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; **329**: 977-986 [PMID: 8366922 DOI: 10.1056/nejm199309303291401]
  - 23 **Perros P**, Deary IJ, Sellar RJ, Best JJ, Frier BM. Brain abnormalities demonstrated by magnetic resonance imaging in adult IDDM patients with and without a history of recurrent severe hypoglycemia. *Diabetes Care* 1997; **20**: 1013-1018 [PMID: 9167117]
  - 24 **Chabriat H**, Sachon C, Lévassieur M, Grimaldi A, Pappata S, Rougemont D, Masure MC, De Recondo A, Samson Y. Brain metabolism after recurrent insulin induced hypoglycaemic episodes: a PET study. *J Neurol Neurosurg Psychiatry* 1994; **57**: 1360-1365 [PMID: 7964812]
  - 25 **Nijs HG**, Radder JK, Poorthuis BJ, Krans HM. Insulin resistance in type 1 (insulin-dependent) diabetes: dissimilarities for glucose and intermediary metabolites. *Diabetes Res* 1990; **15**: 15-19 [PMID: 2132195]
  - 26 **Kleinridders A**, Ferris HA, Cai W, Kahn CR. Insulin action in brain regulates systemic metabolism and brain function. *Diabetes* 2014; **63**: 2232-2243 [PMID: 24931034 DOI: 10.2337/db14-0568]
  - 27 **Cameron NE**, Eaton SE, Cotter MA, Tesfaye S. Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. *Diabetologia* 2001; **44**: 1973-1988 [PMID: 11719828 DOI: 10.1007/s001250100001]
  - 28 **Johnson PC**, Brendel K, Meezan E. Thickened cerebral cortical capillary basement membranes in diabetics. *Arch Pathol Lab Med* 1982; **106**: 214-217 [PMID: 6896132]
  - 29 **Fülesdi B**, Limburg M, Bereczki D, Michels RP, Neuwirth G, Legemate D, Valikovic A, Csiba L. Impairment of cerebrovascular reactivity in long-term type 1 diabetes. *Diabetes* 1997; **46**: 1840-1845 [PMID: 9356034]
  - 30 **Cameron NE**. Role of endoplasmic reticulum stress in diabetic neuropathy. *Diabetes* 2013; **62**: 696-697 [PMID: 23431013 DOI: 10.2337/db12-1469]
  - 31 **Knopp M**, Rajabally YA. Common and less common peripheral nerve disorders associated with diabetes. *Curr Diabetes Rev* 2012; **8**: 229-236 [PMID: 22283678]
  - 32 **van Elderen SG**, de Roos A, de Craen AJ, Westendorp RG, Blauw GJ, Jukema JW, Bollen EL, Middelkoop HA, van Buchem MA, van der Grond J. Progression of brain atrophy and cognitive decline in diabetes mellitus: a 3-year follow-up. *Neurology* 2010; **75**: 997-1002 [PMID: 20837967 DOI: 10.1212/WNL.0b013e3181f25f06]
  - 33 **Tesfaye S**, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, Lauria G, Malik RA, Spallone V, Vinik A, Bernardi L, Valensi P. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010; **33**: 2285-2293 [PMID: 20876709 DOI: 10.2337/dcl10-1303]
  - 34 **Schönauer M**, Thomas A, Morbach S, Niebauer J, Schönauer U, Thiele H. Cardiac autonomic diabetic neuropathy. *Diab Vasc Dis Res* 2008; **5**: 336-344 [PMID: 18958844 DOI: 10.3132/dvdr.2008.047]
  - 35 **Olausson EA**, Brock C, Drewes AM, Grundin H, Isaksson M, Stotzer P, Abrahamsson H, Attvall S, Simrén M. Measurement of gastric emptying by radiopaque markers in patients with diabetes: correlation with scintigraphy and upper gastrointestinal symptoms. *Neurogastroenterol Motil* 2013; **25**: e224-e232 [PMID: 23316944 DOI: 10.1111/nmo.12075]
  - 36 **Ktirji B**, Koontz D. Disorders of Peripheral Nerves. *Bradley's Neurology in Clinical Practice*, 2013-2014
  - 37 **Poulsen JL**, Olesen SS, Malver LP, Frøkjær JB, Drewes AM. Pain and chronic pancreatitis: a complex interplay of multiple mechanisms. *World J Gastroenterol* 2013; **19**: 7282-7291 [PMID: 24259959 DOI: 10.3748/wjg.v19.i42.7282]
  - 38 **Drewes AM**, Andreasen A, Poulsen LH. Valproate for treatment of chronic central pain after spinal cord injury. A double-blind crossover study. *Paraplegia* 1994; **32**: 565-569 [PMID: 7970862 DOI: 10.1038/sc.1994.89]
  - 39 **Hansen AP**, Marcussen NS, Klit H, Andersen G, Finnerup NB, Jensen TS. Pain following stroke: a prospective study. *Eur J Pain* 2012; **16**: 1128-1136 [PMID: 22407963 DOI: 10.1002/j.1532-2149.2012.00123.x]
  - 40 **Biessels GJ**, Reijmer YD. Brain changes underlying cognitive dysfunction in diabetes: what can we learn from MRI? *Diabetes* 2014; **63**: 2244-2252 [PMID: 24931032 DOI: 10.2337/db14-0348]
  - 41 **Yang H**, Fan S, Song D, Wang Z, Ma S, Li S, Li X, Xu M, Xu M, Wang X. Long-term streptozotocin-induced diabetes in rats leads to severe damage of brain blood vessels and neurons via enhanced

- oxidative stress. *Mol Med Rep* 2013; **7**: 431-440 [PMID: 23232924 DOI: 10.3892/mmr.2012.1227]
- 42 **Bhardwaj SK**, Sandhu SK, Sharma P, Kaur G. Impact of diabetes on CNS: role of signal transduction cascade. *Brain Res Bull* 1999; **49**: 155-162 [PMID: 10435778]
- 43 **Olesen AE**, Andresen T, Staahl C, Drewes AM. Human experimental pain models for assessing the therapeutic efficacy of analgesic drugs. *Pharmacol Rev* 2012; **64**: 722-779 [PMID: 22722894 DOI: 10.1124/pr.111.005447]
- 44 **Drewes AM**, Schipper KP, Dimcevski G, Petersen P, Andersen OK, Gregersen H, Arendt-Nielsen L. Multimodal assessment of pain in the esophagus: a new experimental model. *Am J Physiol Gastrointest Liver Physiol* 2002; **283**: G95-103 [PMID: 12065296 DOI: 10.1152/ajpgi.00496.2001]
- 45 **Frøkjær JB**, Brock C, Brun J, Simrén M, Dimcevski G, Funch-Jensen P, Drewes AM, Gregersen H. Esophageal distension parameters as potential biomarkers of impaired gastrointestinal function in diabetes patients. *Neurogastroenterol Motil* 2012; **24**: 1016-e544 [PMID: 22738347 DOI: 10.1111/j.1365-2982.2012.01966.x]
- 46 **Lelic D**, Brock C, Søfteland E, Frøkjær JB, Andresen T, Simrén M, Drewes AM. Brain networks encoding rectal sensation in type 1 diabetes. *Neuroscience* 2013; **237**: 96-105 [PMID: 23384609 DOI: 10.1016/j.neuroscience.2013.01.049]
- 47 **Frøkjær JB**, Søfteland E, Graversen C, Dimcevski G, Drewes AM. Effect of acute hyperglycaemia on sensory processing in diabetic autonomic neuropathy. *Eur J Clin Invest* 2010; **40**: 883-886 [PMID: 20624170 DOI: 10.1111/j.1365-2362.2010.02335.x]
- 48 **Søfteland E**, Brock C, Frøkjær JB, Brøgger J, Madácsy L, Gilja OH, Arendt-Nielsen L, Simrén M, Drewes AM, Dimcevski G. Association between visceral, cardiac and sensorimotor polyneuropathies in diabetes mellitus. *J Diabetes Complications* 2014; **28**: 370-377 [PMID: 24355661 DOI: 10.1016/j.jdiacomp.2013.10.009]
- 49 **Brock C**, Søfteland E, Frøkjær JB, Drewes AM, Nielsen LA. Associations between Sensorimotor, Autonomic and Central Neuropathies in Diabetes Mellitus. *J Diabetes Metab* 2014; **5**: 390 [DOI: 10.4172/2155-6156.1000390]
- 50 **Drewes AM**, Reddy H, Pedersen J, Funch-Jensen P, Gregersen H, Arendt-Nielsen L. Multimodal pain stimulations in patients with grade B oesophagitis. *Gut* 2006; **55**: 926-932 [PMID: 16091554 DOI: 10.1136/gut.2005.067769]
- 51 **Reddy H**, Staahl C, Arendt-Nielsen L, Gregersen H, Drewes AM, Funch-Jensen P. Sensory and biomechanical properties of the esophagus in non-erosive reflux disease. *Scand J Gastroenterol* 2007; **42**: 432-440 [PMID: 17454852 DOI: 10.1080/00365520600973099]
- 52 **Drewes AM**, Petersen P, Rössel P, Gao C, Hansen JB, Arendt-Nielsen L. Sensitivity and distensibility of the rectum and sigmoid colon in patients with irritable bowel syndrome. *Scand J Gastroenterol* 2001; **36**: 827-832 [PMID: 11495078]
- 53 **Dimcevski G**, Staahl C, Andersen SD, Thorsgaard N, Funch-Jensen P, Arendt-Nielsen L, Drewes AM. Assessment of experimental pain from skin, muscle, and esophagus in patients with chronic pancreatitis. *Pancreas* 2007; **35**: 22-29 [PMID: 17575541 DOI: 10.1097/mpa.0b013e31805c1762]
- 54 **Frøkjær JB**, Olesen SS, Graversen C, Andresen T, Lelic D, Drewes AM. Neuroimaging of the human visceral pain system-A methodological review. *Scand J Pain* 2011; **2**: 95-104 [DOI: 10.1016/j.sjpain.2011.02.006]
- 55 **Lelic D**, Gratkowski M, Valeriani M, Arendt-Nielsen L, Drewes AM. Inverse modeling on decomposed electroencephalographic data: a way forward? *J Clin Neurophysiol* 2009; **26**: 227-235 [PMID: 19584750 DOI: 10.1097/WNP.0b013e3181aed1a1]
- 56 **Haas S**, Brock C, Krogh K, Gram M, Nissen TD, Lundby L, Laurberg S, Drewes AM. Cortical evoked potentials in response to rapid balloon distension of the rectum and anal canal. *Neurogastroenterol Motil* 2014; **26**: 862-873 [PMID: 24750321 DOI: 10.1111/nmo.12341]
- 57 **Dejgaard A**, Gade A, Larsson H, Balle V, Parving A, Parving HH. Evidence for diabetic encephalopathy. *Diabet Med* 1991; **8**: 162-167 [PMID: 1827403]
- 58 **Cooray GK**, Hyllienmark L, Brismar T. Decreased cortical connectivity and information flow in type 1 diabetes. *Clin Neurophysiol* 2011; **122**: 1943-1950 [PMID: 21474371 DOI: 10.1016/j.clinph.2011.03.007]
- 59 **Cui D**, Liu J, Bian Z, Li Q, Wang L, Li X. Cortical source multivariate EEG synchronization analysis on amnesic mild cognitive impairment in type 2 diabetes. *ScientificWorldJournal* 2014; **2014**: 523216 [PMID: 25254248 DOI: 10.1155/2014/523216]
- 60 **Fabris C**, Sparacino G, Sejling AS, Goljahani A, Duun-Henriksen J, Remvig LS, Juhl CB, Cobelli C. Hypoglycemia-related electroencephalogram changes assessed by multiscale entropy. *Diabetes Technol Ther* 2014; **16**: 688-694 [PMID: 24892361 DOI: 10.1089/dia.2013.0331]
- 61 **Lelic D**, Brock C, Simrén M, Frøkjær JB, Søfteland E, Dimcevski G, Gregersen H, Drewes AM. The brain networks encoding visceral sensation in patients with gastrointestinal symptoms due to diabetic neuropathy. *Neurogastroenterol Motil* 2014; **26**: 46-58 [PMID: 24050116 DOI: 10.1111/nmo.12222]
- 62 **Frøkjær JB**, Egsgaard LL, Graversen C, Søfteland E, Dimcevski G, Blauenfeldt RA, Drewes AM. Gastrointestinal symptoms in type-1 diabetes: is it all about brain plasticity? *Eur J Pain* 2011; **15**: 249-257 [PMID: 20813568 DOI: 10.1016/j.ejpain.2010.08.004]
- 63 **Frøkjær JB**, Søfteland E, Graversen C, Dimcevski G, Egsgaard LL, Arendt-Nielsen L, Drewes AM. Central processing of gut pain in diabetic patients with gastrointestinal symptoms. *Diabetes Care* 2009; **32**: 1274-1277 [PMID: 19366960 DOI: 10.2337/dc09-0324]
- 64 **Brock C**, Graversen C, Frøkjær JB, Søfteland E, Valeriani M, Drewes AM. Peripheral and central nervous contribution to gastrointestinal symptoms in diabetic patients with autonomic neuropathy. *Eur J Pain* 2013; **17**: 820-831 [PMID: 23239083 DOI: 10.1002/j.1532-2149.2012.00254.x]
- 65 **Blatter DD**, Bigler ED, Gale SD, Johnson SC, Anderson CV, Burnett BM, Parker N, Kurth S, Horn SD. Quantitative volumetric analysis of brain MR: normative database spanning 5 decades of life. *ANR Am J Neuroradiol* 1995; **16**: 241-251 [PMID: 7726068]
- 66 **Bigler ED**. Magnetic resonance imaging in the evaluation of cognitive function. *Pediatr Blood Cancer* 2014; **61**: 1724-1728 [PMID: 24920351 DOI: 10.1002/pbc.25110]
- 67 **Buxton RB**. The physics of functional magnetic resonance imaging (fMRI). *Rep Prog Phys* 2013; **76**: 096601 [PMID: 24006360 DOI: 10.1088/0034-4885/76/9/096601]
- 68 **Frøkjær JB**, Andersen LW, Brock C, Simrén M, Ljungberg M, Søfteland E, Dimcevski G, Yavarian Y, Gregersen H, Drewes AM. Altered brain microstructure assessed by diffusion tensor imaging in patients with diabetes and gastrointestinal symptoms. *Diabetes Care* 2013; **36**: 662-668 [PMID: 23139372 DOI: 10.2337/dc12-1131]
- 69 **Moran C**, Phan TG, Chen J, Blizzard L, Beare R, Venn A, Münch G, Wood AG, Forbes J, Greenaway TM, Pearson S, Srikanth V. Brain atrophy in type 2 diabetes: regional distribution and influence on cognition. *Diabetes Care* 2013; **36**: 4036-4042 [PMID: 23939539 DOI: 10.2337/dc13-0143]
- 70 **van Harten B**, de Leeuw FE, Weinstein HC, Scheltens P, Biessels GJ. Brain imaging in patients with diabetes: a systematic review. *Diabetes Care* 2006; **29**: 2539-2548 [PMID: 17065699 DOI: 10.2337/dc-06-1637]
- 71 **Last D**, Alsop DC, Abduljalil AM, Marquis RP, de Bazelaire C, Hu K, Cavallerano J, Novak V. Global and regional effects of type 2 diabetes on brain tissue volumes and cerebral vasoreactivity. *Diabetes Care* 2007; **30**: 1193-1199 [PMID: 17290035 DOI: 10.2337/dc06-2052]
- 72 **Jongen C**, van der Grond J, Kappelle LJ, Biessels GJ, Viergever MA, Pluim JP. Automated measurement of brain and white matter lesion volume in type 2 diabetes mellitus. *Diabetologia* 2007; **50**: 1509-1516 [PMID: 17492428 DOI: 10.1007/s00125-007-0688-y]
- 73 **Roberts RO**, Knopman DS, Przybelski SA, Mielke MM, Kantarci K, Preboske GM, Senjem ML, Pankratz VS, Geda YE, Boeve BF, Ivnik RJ, Rocca WA, Petersen RC, Jack CR. Association of type 2 diabetes with brain atrophy and cognitive impairment. *Neurology* 2014; **82**: 1132-1141 [PMID: 24647028 DOI: 10.1212/wnl.0000000000000269]

- 74 **Kamiyama K**, Wada A, Sugihara M, Kurioka S, Hayashi K, Hayashi T, Yoshisako T, Yamamoto N, Tsuchie Y, Yamaguchi S, Sugimoto T, Kitagaki H. Potential hippocampal region atrophy in diabetes mellitus type 2: a voxel-based morphometry VSRAD study. *Jpn J Radiol* 2010; **28**: 266-272 [PMID: 20512543 DOI: 10.1007/s11604-009-0416-2]
- 75 **Frøkjær JB**, Brock C, Søfteland E, Dimcevski G, Gregersen H, Simrén M, M Drewes A. Macrostructural brain changes in patients with longstanding type 1 diabetes mellitus - a cortical thickness analysis study. *Exp Clin Endocrinol Diabetes* 2013; **121**: 354-360 [PMID: 23757052 DOI: 10.1055/s-0033-1345120]
- 76 **Bak AM**, Egefjord L, Gejl M, Steffensen C, Stecher CW, Smidt K, Brock B, Rungby J. Targeting amyloid-beta by glucagon-like peptide -1 (GLP-1) in Alzheimer's disease and diabetes. *Expert Opin Ther Targets* 2011; **15**: 1153-1162 [PMID: 21749267 DOI: 10.1517/14728222.2011.600691]
- 77 **Holst JJ**, Gromada J. Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. *Am J Physiol Endocrinol Metab* 2004; **287**: E199-E206 [PMID: 15271645 DOI: 10.1152/ajpendo.00545.2003]
- 78 **Orskov C**, Holst JJ, Nielsen OV. Effect of truncated glucagon-like peptide-1 [proglucagon-(78-107) amide] on endocrine secretion from pig pancreas, antrum, and nonantral stomach. *Endocrinology* 1988; **123**: 2009-2013 [PMID: 2901341 DOI: 10.1210/endo-123-4-2009]
- 79 **Holst JJ**, Burcelin R, Nathanson E. Neuroprotective properties of GLP-1: theoretical and practical applications. *Curr Med Res Opin* 2011; **27**: 547-558 [PMID: 21222567 DOI: 10.1185/03007995.2010.549466]
- 80 **Kazakos KA**, Sarafidis PA, Yovos JG. The impact of diabetic autonomic neuropathy on the incretin effect. *Med Sci Monit* 2008; **14**: CR213-CR220 [PMID: 18376350]
- 81 **Li X**, Pan W, Yang GZ, Di YN, Zhao F, Zhu LY, Jiang ZH. Proteome analysis of differential protein expression in brain of rats with type 1 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2011; **119**: 265-270 [PMID: 21472662 DOI: 10.1055/s-0031-1271705]
- 82 **Ramos-Rodriguez JJ**, Molina-Gil S, Ortiz-Barajas O, Jimenez-Palomares M, Perdomo G, Cozar-Castellano I, Lechuga-Sancho AM, Garcia-Alloza M. Central proliferation and neurogenesis is impaired in type 2 diabetes and prediabetes animal models. *PLoS One* 2014; **9**: e89229 [PMID: 24586614 DOI: 10.1371/journal.pone.0089229]
- 83 **Kodl CT**, Franc DT, Rao JP, Anderson FS, Thomas W, Mueller BA, Lim KO, Seaquist ER. Diffusion tensor imaging identifies deficits in white matter microstructure in subjects with type 1 diabetes that correlate with reduced neurocognitive function. *Diabetes* 2008; **57**: 3083-3089 [PMID: 18694971 DOI: 10.2337/db08-0724]
- 84 **Northam EA**, Rankins D, Lin A, Wellard RM, Pell GS, Finch SJ, Werther GA, Cameron FJ. Central nervous system function in youth with type 1 diabetes 12 years after disease onset. *Diabetes Care* 2009; **32**: 445-450 [PMID: 19151204 DOI: 10.2337/dc08-1657]

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