From DEPARTMENT OF CLINICAL NEUROSCIENCE
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EFFECT OF DIABETES MELLITUS ON HUMAN BRAIN FUNCTION

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Stockholm 2010

Published by Karolinska Institutet. Printed by Universitetsservice AB.

ISBN 978-91-7457-086-1

To my Family

ABSTRACT

The following thesis contains four clinical studies. Study I, II and IV were based on a cross sectional investigation on subjects with type 1 diabetes (T1DM) studying the effect of the disease on CNS function through electrophysiological parameters coupled with neuropsychological tests. Study III was an interventional study investigating the effect of strict glycaemic control on subjects with type 2 diabetes (T2DM). Several new techniques were applied to the study of EEG in both studies giving a deeper understanding of the effect of diabetes on the brain.

Paper I, II & IV: A cross-sectional study was performed in adult patients (N=150) with T1DM. Factors that are important for cognitive impairment in T1DM were identified. Furthermore, the effects of T1DM on auditory event-related potentials (ERP), spectral properties of resting EEG, connectivity between cortical regions and flow of information across the scalp of resting EEG were studied on a subgroup of 119 patients and compared to healthy controls (N=61). The strongest predictor of cognitive decline was found to be long diabetes duration and young age of diabetes onset, however, body mass index (BMI), height, age and compound muscle action potential (CMAP) were also found to predict cognitive decline. Moreover, patients had a significant decrease in auditory N100 amplitude, which correlated with a decrease in psychomotor speed. Furthermore, connectivity and information flow were reduced for patients as was EEG power. There were no significant correlations between the spectral, connectivity and information flow parameters and cognition. The influence of diabetes duration, BMI, height, age and CMAP may suggest that loss of the neuroprotective effects of insulin or insulin-like growth factors plays a role in the decline of cognitive function. Furthermore, the decline in ERP, connectivity and information flow may suggest conduction defects in the white matter and in the cortex. As the above mentioned parameters only had a partial relationship with each other we conclude that the tests measure different functions and are complementary to the cognitive tests and that several tests need to be performed to monitor the effect of T1DM on brain function.

Paper III: The mild cognitive decline associated with T2DM has been suggested to be reversible with improved glycaemic control. In order to characterise this cognitive decline and study the effects of improved glycaemic control patients with T2DM (N=28) and healthy control subjects (N=21) were studied. One group of patients with diabetes (N=15) were given a 2-month treatment of intensified glycaemic control, whereas the other group (N=13) maintained their regular treatment. Cognitive function and electrophysiological variables were studied in the two groups of patients and in healthy control subjects before and after the 2-month trial period. There were significant differences at baseline and the change between 1st and 2nd investigation was significantly different in the three groups where patients receiving intensified treatment had an improvement of HbA1c and cerebral function. In conclusion, T2DM had a similar type of effect on brain function as T1DM and intensified therapy improved the function, suggesting that the negative effect of T2DM on the brain is partly reversible.

Key words: diabetes mellitus, brain, cognition, EEG, ERP, encephalopathy, human

LIST OF PUBLICATIONS

I. Predictors of cognitive impairment in type 1 diabetes; Tom Brismar, Liselotte Maurex, Gerald Cooray, Lisa Juni-Berggren, Per Lindström, Karin Ekberg, Nils Adner, Sten Andersson; Psychoneuroendocrinology, 2007, 32, 1041-1051.

II. Cognitive impairment correlates to low auditory event-related potential amplitudes in type 1 diabetes; Gerald Cooray, Liselotte Maurex, Tom Brismar; Psychoneuroendocrinology, 2008, 33, 942-950.

III. Effects of intensified metabolic control on CNS function in type 2 diabetes; Gerald Cooray, Erik Nilsson, Åke Wahlin, Erika J. Laukka, Kerstin Brismar, Tom Brismar; Psychoneuroendocrinology, 2010 Jul 23. [Epub ahead of print].

IV. Decreased cortical connectivity and information flow in type 1 diabetes. Gerald Cooray, Lars Hyllienmark, Tom Brismar; Manuscript; Submitted

CONTENTS

LIST OF ABBREVIATIONS

BMI	body mass index
CMAP	compound muscle action potential
CN	cochlear nucleus
CNS	central nervous system
CSD	current source derivation
DM	diabetes mellitus
EEG	electroencephalogram
ERP	event related potential
IC	inferior colliculus
MGN	medial geniculate nucleus
MRI	magnetic resonance imaging
N100	negative peak 100 ms post stimulus
P300	positive peak ca. 300 ms post stimulus
PC	phase coherence
PLI	phase lag index
PSI	phase slope index
SL	synchronization likelihood
SON	superior olivary nucleus
T1DM	type 1 diabetes
T2DM	type 2 diabetes

1 INTRODUCTION

1.1 DIABETES MELLITUS

Diabetes Mellitus (DM) is a group of diseases with metabolic impairment leading to hyperglycaemia (Fauci and Harrison, 2008). It is classified into type 1 diabetes (T1DM) and type 2 diabetes (T2DM) where T1DM results from complete loss of insulin production (Eisenbarth, 2007) and T2DM from variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production (Stumvoll et al., 2005). In T1DM the insulin producing beta cells are destroyed by autoimmune pathology. The disease manifests when approximately 80% of the beta cells are destroyed. It is related to a multiple of genes, the most important ones are located in the HLA region on chromosome 6 (Eisenbarth, 2007). T2DM is polygenic and multifactorial as environmental factors such as obesity, nutrition and physical activity modulate the phenotype (Stumvoll et al., 2005). The global prevalence of T1DM and T2DM was 2.2% in 2000 and is estimated to be 4.4% in 2030 (Wild et al., 2004). It is the leading cause of end stage renal disease and adult blindness in the developed world and is a major risk factor for cardiovascular disease. T2DM will be a major cause of morbidity and mortality in the foreseeable future. There are several acute and long term complications of DM. The acute complications are diabetic ketoacidosis, hyperglycemic hyperosmolar state and hypoglycaemic coma (Kitabchi et al., 2009). These conditions require immediate attention and treatment to prevent serious injury or fatality. Hypoglycaemic coma is caused by excessive levels of insulin in comparison to blood glucose. This is a potential cause of brain damage in T1DM (see below 1.3). The chronic complications of DM constitute the majority of the morbidity and mortality associated with the disease. They can be classified into vascular and non-vascular complications, where the vascular complications can be further categorized as microvascular (retinopathy, neuropathy and nephropathy) and macrovascular disease (coronary artery disease, peripheral arterial disease and cerebrovascular disease) (Fauci and Harrison, 2008).

1.2 DIABETES NEUROPATHY

Diabetic neuropathy includes focal neuropathies, diffuse neuropathy and autonomic neuropathy (Vinik et al., 2000). Several pathophysiological mechanisms have been suggested to cause diabetic neuropathy, including microvascular insufficiency, adverse metabolic effects and autoimmune activity (Vinik et al., 2000). Demyelination, axonal atrophy and loss and atrophy of ganglia all contribute to the neuropathy (Zochodne, 1999). Diabetic neuropathy is strongly related to glycaemic control and diabetes duration (The Diabetes Trial Research Group, 1995). The disease progresses with a reduction in nerve conduction velocity of approximately 0.5 m/s/year (Hyllienmark et al., 2001). Common symptoms of peripheral neuropathy are allodynia, reduced thermal sensation, defective autonomic innervation, depressed tendon reflexes, reduced proprioception and sensory ataxia. The most serious consequence of peripheral neuropathy is foot ulceration followed by gangrene.

1.3 DIABETIC ENCEPHALOPATHY

Careful study of cognition has revealed that DM may also affect cerebral function. T1DM causes deficits in speed of information processing (Ryan et al., 2003, Brands et al., 2006), psychomotor efficiency (Weinger et al., 2008), attention (Wessels et al., 2007), mental flexibility and visual perception (Northam et al., 1998, Kodl and Seaquist, 2008). In patients with T2DM, an increase in memory deficits (Perlmuter et al., 1984, Messier, 2005, Munshi et al., 2006), a reduction in psychomotor speed (Gregg et al., 2000), processing speed (Messier, 2005), attention (Fontbonne et al., 2001) and reduced frontal lobe/executive function (Munshi et al., 2006) have been identified (see also review by Kodl and Seaquist, 2008). For T2DM cognitive decline may be detected even with crude measures of cognitive function such as the Mini Mental Test (Alencar et al., 2010). Furthermore, there are several electrophysiological abnormalities in DM. Evoked responses for visual (Pozzessere et al., 1988) and auditory (Martini et al., 1987, Dejgaard et al., 1991, Kurita et al., 1996, Kramer et al., 1998) stimuli have shown reduced amplitude and increased latency. Several of these electrophysiological alterations have been shown to be strongly related to cognition (Kurita et al., 1996). Resting EEG was shown to be affected by diabetes with a slowing of fast activity (Howorka et al., 2000, Brismar et al., 2002, Hyllienmark et al., 2005). Moreover, structural alterations have also been detected in DM. Magnetic resonance imaging (MRI) of subjects with T1DM has shown the presence of both cortical atrophy (Longstreth et al., 2000, Schmidt et al., 2004, Musen et al., 2006, van Harten et al., 2006, Wessels et al., 2006, Northam et al., 2009) and white matter lesions (WML) (Dejgaard et al., 1991, Ferguson et al., 2003, van Harten et al., 2006, Jongen et al., 2007, Kodl et al., 2008, Northam et al., 2009). Conclusively, there is neuropsychological, electrophysiological and neuroradiological evidence for the presence of diabetic encephalopathy.

Several causes for the pathogenesis of the diabetic encephalopathy have been suggested. Hyperglycaemia (Ryan et al., 1993, Kaufman et al., 1999, Cox et al., 2005, Jacobson et al., 2007), hypoglycaemia (Hershey et al., 1997, Rovet and Alvarez, 1997, Hershey et al., 1999, Warren et al., 2007), microvascular, macrovascular disease and insulin resistance (Kodl and Seaquist, 2008) are some of the suggested causes. As the pathologies causing T1DM and T2DM are different the causes of cognitive dysfunction may be different for the two diseases. Moreover, improved control of hyperglycaemia seems to be associated with less cognitive dysfunction in T2DM (Gradman et al., 1993, Meneilly et al., 1993) suggesting hyperglycaemia to be a cause of cognitive dysfunction. Insulin receptors are present in several parts of the brain, with particularly high density in the olfactory bulb and regions of the striatum and cerebral cortex (Schulingkamp et al., 2000). However, the uneven distribution of insulin receptors in the brain and the fact that neuronal glucose uptake is independent of insulin (Hasselbalch et al., 1999, Seaquist et al., 2001) suggest other actions of insulin in the brain. Neuromodulatory effects of insulin have been demonstrated in the mammalian CNS where insulin modulates monoamine uptake allowing insulin to modulate neural signalling via specific neuronal insulin receptors (Boyd and Raizada, 1983, Boyd et al., 1985).

1.4 NEUROPSYCHOLOGICAL ASSESSMENT

Cognition refers to information processing and can be assessed using neuropsychological tests. These test scores are estimates of cognition and should be given under standardised test situations to minimize the effect of measurement errors. Moreover, the neuropsychological tests are validated to reliably assess cognitive function over time and test situations. A group of tests may be combined in order to score the function in a defined cognitive domain, and some tests may be included in more than one domain. Commonly, several cognitive domains are investigated to give an overall measure of a subject's cognitive state. Attention, memory, executive function, visuospatial ability, verbal ability and psychomotor speed are examples of cognitive domains often assessed.

1.4.1 Attention

Attention is assessed as this is of importance if the evaluation of other cognitive domains is to be valid. Attention could be assessed with *Digit Span Forwards and Backwards* from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) test battery (The Psychological Corporation, 1991) and *Paced Auditory Serial Attention Test* (PASAT) (Gronwall, 1977, Lezak, 1995, Diehr et al., 1998). *Digit Span Forwards and Backwards* consists of a list of random digits presented at a rate of approximately one new digit every second. Thereafter the subject is asked to recite these digits either in the order they were presented or in the reverse order. PASAT consists of single digits presented at a rapid rate where the patient must add each new digit to the one immediately prior to it.

1.4.2 Memory

Memory functions are often assessed with tests evaluating the different aspects of memory including short and long term memory. Memory can be assessed using *Claeson—Dahl's Test of Learning and Memory* (Psykologiförlaget, 1998), *Rey Complex Figure Test* (RCFT) with immediate recall, delayed recall and recognition (Psychological Assessment Resources, 1995) or *Digit Symbol Coding* (The Psychological Corporation, 1991). For *Claeson—Dahl's Test of Learning and Memory* subjects are required to remember presented words and are thereafter instructed to choose the words from a longer list of words with distractors. Moreover, the subjects are tested if they can remember the order in which the words were presented. RCFT is composed of a copy trial with an immediate and a delayed recall trial, as well as a recognition trial which assesses memory. For *Digit Symbol Coding* subjects are presented digit symbol pairs followed by a list of digits. The subject is instructed to write down the corresponding symbols with maximum speed.

1.4.3 Visual-spatial ability

Visual-spatial ability is a measure of the ability to construct and perceive spatial relations. It can be assessed using the *Block Design Test* from the WAIS-R test battery and the RCFT copy trial. Subjects are required to choose blocks that have white sides, red sides, and those with both red and white sides and arrange them according to a pattern while performing the block test.

1.4.4 Verbal ability

Verbal ability is tested using vocabulary and naming tasks, such as *Vocabulary* from the Wechsler Adult Intelligence Scale-Revised test battery (The Psychological Corporation, 1981) and *Controlled Oral Word Association FAS* (Fernaeus and Almkvist, 1998, The Psychological Corporation, 2001) where subjects are instructed to produce as many words as possible starting with a given letter. *Vocabulary* consists of 35 words which the subjects are asked to define which will give an estimate of the subjects' expressive verbal knowledge.

1.4.5 Executive function

Executive functions include all cognitive processes allowing a subject to adapt to a situation so as to complete a predetermined objective. It could be assessed using *Controlled Oral Word Association FAS* (Fernaeus and Almkvist, 1998; The Psychological Corporation, 2001), *Zoo Map Test* (Chamberlain, 2003) or the *Trail Making Test B* (Lezak, 1995a). For *Controlled Oral Word Association FAS* subjects are instructed to produce as many words as possible belonging to a certain taxonomic group. The *Zoo Map Test* involves tracing through a map that does not contravene a set of rules. Penalties are imposed for rule breaks and lack of speed. The *Trail Making Test B* consists of 25 circles including both numbers and letters. The subject is instructed to draw lines in order to connect the circles in an ascending pattern, alternating between the numbers and letters.

1.4.6 Psychomotor speed

Psychomotor speed is the relationship between cognition and movement and is often tested with the speed and dexterity with which different objectives are completed. These objectives often demonstrate fine motor skills or precision in using tools. The *Grooved Pegboard Test* (Lezak, 1995, Lafayette Instrument, 1997) is often used to score psychomotor speed. The subject must insert pegs, which have a key along one side, into holes with randomly positioned slots.

1.5 EEG

The scalp electroencephalogram (EEG) is defined as the recording of the electric potential fields elicited on the scalp over time due to neuronal activity. The cerebral generators of EEG are cortical neurons which create measurable fields when large populations of neurons (10^5 cells or more) fire in synchrony. The main sources are pyramidal cells, which lie perpendicular to the cortical surface, creating current sinks and sources producing an extracellular current loop. These currents will in turn cause potentials throughout the brain which could be measured on the scalp. Each pyramidal cell creates a dipolar potential distribution across the scalp. The direction of the dipole field depends on whether the pyramidal cells are excited or inhibited, what cortical level this excitation or inhibition occurs (Ebersole and Pedley, 2003) and also on the orientation of the cell due to the folding of the cortex. Moreover, the potentials (currents) are highly attenuated when they reach the scalp due to the distance between the scalp and cortex and the resistive layers (skin, skull and meninges) in between.

1.5.1 Resting EEG

Visual analysis of adult resting EEG reveals oscillatory activity with different frequencies in different regions of the scalp. The most obvious is the occipital alpha rhythm which ranges in frequency from 8 to 13 Hz (Berger, 1929, Adrian and Matthews, 1934). The alpha rhythm can also be found in central and temporal regions. The envelope of these waves increases and decreases smoothly with time. It is blocked by eye opening though the effect of other conditions on the rhythm could be variable. Mental concentration can in some instances block the alpha rhythm; however, in a group of young adults no such blocking was observed (Maulsby et al., 1968). The alpha rhythm is considered to be generated by thalamic neurons and further to be affected by intra-cortical connections leading to the reactivity and spreading of the waves (Lopes da Silva, 1991) (Fig. 1). Several studies have simulated lumped-parameter models of alpha rhythms with thalamic and cortical networks producing results close to that observed in EEG (Lopes da Silva et al., 1974, Robinson et al., 2002, David and Friston, 2003). It was further shown that manipulation of the parameters of a model could create a close approximation of the full power spectrum of resting EEG (Robinson et al., 2002).

It has been suggested that alpha waves are resonances of neural noise in the cortex. Neural signals can travel between cortical regions with speeds of approximately 6-9 m/s. These moving signals or waves will cause standing waves due to the size and spherical shape of the cortex (the cortex of each hemisphere is homomorphic to a sphere) with a frequency of approximately 10 Hz. (Nunez and Srinivasan, 2006). This theory predicts that increased propagation speed of signals along intracortical tracts would increase the peak frequency of the alpha waves. During development, axon diameter and myelination increase which causes an increase in the propagation speed, in agreement with the observation that the peak frequency of alpha waves increases during childhood (Nunez, 2010). However, the inverse relationship between head size (cortical area) and peak frequency has so far not been shown (Valdes-Hernandez et al., 2010).

Slower waves (theta) are prominent in children and young adults of frequency between 4-7 Hz in the frontal and frontal-central regions. These waves are generally of lower voltage (*ca.* 15μV), and increase in amplitude with increasing drowsiness (Ebersole and Pedley, 2003). Moreover, oscillatory activity of frequency above the alpha band is present in the EEG of healthy subjects. Most common is the activity between 13 and 25 Hz (beta). It is present mainly over the pre- and post-rolandic cortex. Computer simulations of a complex model of the cortex and thalamic nuclei have shown presence of beta activity in regions corresponding to the pre- and post rolandic cortex. However, this model had identical networks for all regions of the cortex which implies that the beta activity is centered in the above mentioned regions due to anisotropy of white matter tracts (Izhikevich and Edelman, 2008).

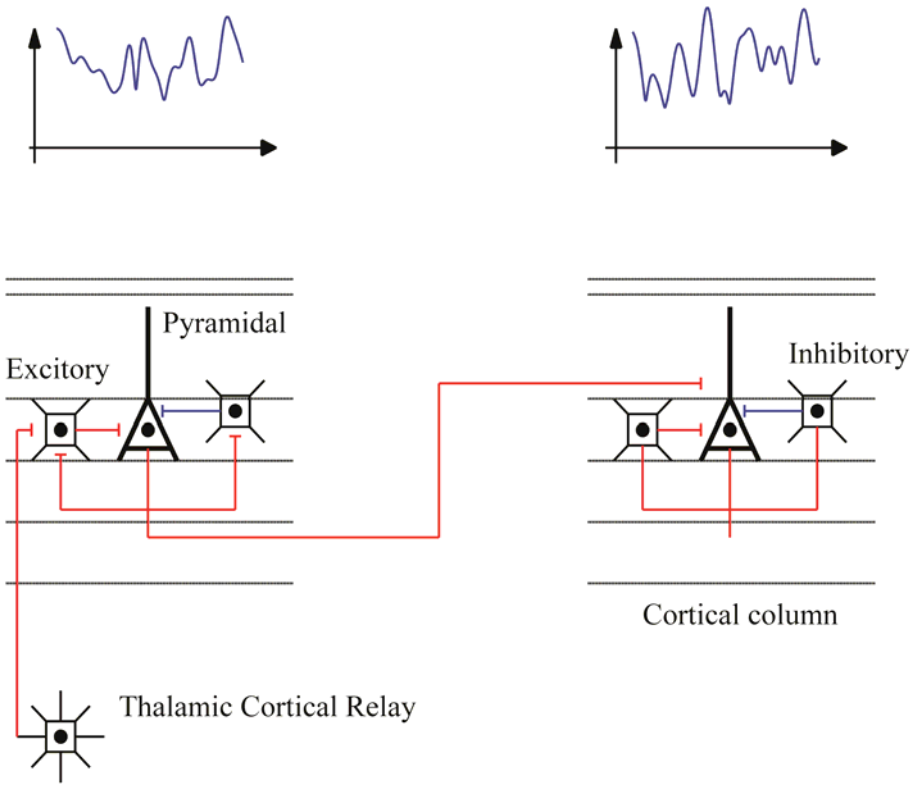

Figure 1. Cortical network creating the alpha rhythm. Two cortical columns are depicted with afferent connections through the thalamo-cortical relay neurons and also with pyramidal intra-cortical connections. Furthermore, there are excitory and inhibitory connections to the pyramidal cells within each column. Above each macro column the resultant EEG signal with the alpha rhythm is depicted.

1.5.2 Reference electrode and CSD

A potential cannot be measured without a point of reference. There are two main goals in the choice of reference: 1) to maximize the signal of interest and 2) to minimize other signals, especially artefacts. If the active electrode and the reference are equally affected by cardiac (EKG) and other external fields (*e.g.* eye movements, blinks), these signals are cancelled out. This is achieved with a 'bipolar montage' registering the difference in cortical activity between two electrodes with close locations on the scalp. As an example in the 'transverse' bipolar montage the effect of blinks and vertical eye movements is neutralized as these electric fields are mainly directed along the anterior-posterior axis affecting both electrodes equally (goal 2), but the signal of interest is also to some extent neutralized. On the other hand a distant reference point such as on the nose virtually picks up no cortical activity which maximizes the signal difference relative to the active electrode on the scalp giving large signal of interest (goal 1). The draw-back is that artefacts from eye movements are much more prominent. An often used compromise between these two alternatives is 'linked mastoids' where the reference point is the average of the signal from electrodes placed on both mastoid protuberances. As long as signals from all different electrode positions have been

included in the recorded data, digital technique now makes it possible to 're-reference' the signal in the post-processing.

In most studies the potential is measured to infer knowledge of the activity of neuronal assemblies in the cortex. These sources are assumed to lie in the cortex of the brain. Due to the high resistivity of the skull the currents these sources produce will flow the shortest distance through the bone giving the current flow a radial propagation (tangential flow through the skull would only increase the resistance of the path) through the cranium. In contrast, the skin has a much lower resistance making the currents propagate along the surface of the head. The surface of the scalp would then have current sources and sinks located above the areas of cortical activation. The presence of current sources and sinks in the scalp can be estimated from the scalp potential independently of the reference point of potential. Let the scalp be modelled by a 2-dimensional isotropic conducting medium. Denote the current density (current crossing a unit length of distance) with $\vec{j}$. The density of current sources/sinks is denoted *s* and is given by the divergence ($\nabla \cdot$) of $\vec{j}$,

(1) $$\nabla \cdot \vec{j} = s$$

$\vec{j}$ is calculated from Ohm's law where σ is conductivity and $\vec{E}$ is electric field.

(2) $$\vec{j} = \sigma \vec{E}$$

$\vec{E}$ is the negative gradient (∇ , in one dimension equivalent to the derivative) of the potential, ϕ ,

(3) $$\vec{E} = -\nabla \phi$$

Putting equation 2 and 3 into 1 gives a relation between the potential and the current source density,

(4) $$\sigma \nabla^2 \phi = -s$$

Thus the density of sources and sinks is proportional to the laplacian (sum of 2nd derivatives) of the potential. Even though the potential cannot be measured accurately due to the difficulty in assigning a point of reference, the laplacian can be calculated independently of this reference. This value is also related to the activity of the current sources on the cortex which is the quantity that is desired. Thus calculating the laplacian gives a better estimate of neuronal activity. Several methods have been described to estimate the laplacian. Calculation of the laplacian gives an estimate of the current source density (CSD).

1.5.3 Nearest neighbour laplacian

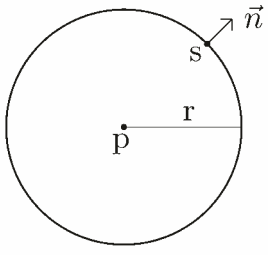

Figure 2

Nearest neighbour laplacian was first proposed by Hjorth in 1975 (Hjorth, 1975). In this paper the laplacian at each point of measurement (electrode) was estimated as the difference in potential between the electrode and the average of the potentials measured at neighbouring electrodes. This result can be derived in a few steps. Let *p* denote the electrode at which the laplacian is to be estimated. Around this electrode imagine a small circle of radius *r*. Let $\vec{n}$ denote the unit outward normal of the circle (Fig. 2).

The following relation holds by Gauss law:

$$\int \nabla\phi \cdot d\vec{n} = \iint \nabla^2 \phi dA \tag{5}$$

$\nabla\phi \cdot d\vec{n}$ can be estimated by the following:

$$\nabla\phi \cdot d\vec{n} \approx \frac{\phi(s) - \phi(p)}{r} ds \tag{6}$$

Putting equation 6 into the left hand side of equation 5 will give:

$$\int \nabla\phi \cdot d\vec{n} \approx \int \frac{\phi(s) - \phi(p)}{r} ds = 2\pi \cdot \left(\langle \phi(s) \rangle - \phi(p) \right) \tag{7}$$

Note that the average of the potential is taken over the circle in the first term on the right hand side. The right hand side of eq. 5 can be approximated:

$$\iint \nabla^2 \phi \cdot dA \approx 2\pi r^2 \nabla^2 \phi \Big|_p \tag{8}$$

Eq. 7 and 8 will give:

$$-\nabla^2 \phi \Big|_p \approx \frac{\phi(p) - \langle \phi(s) \rangle}{r^2} \tag{9}$$

This approximation will depend on the size of r and how well the average potential along the circle can be approximated. Thus the laplacian of the potential at an electrode can be approximated as the difference between the potential at that electrode and the average of the surrounding electrodes. If the 10-20 system is used with standard 21 scalp electrodes this will usually result in 4 electrodes placed along the circle and a fixed interelectrode distance (r).The method described by Hjorth allows for the calculation of CSD, although at electrodes placed at the border of the montage there will be a lack of neighbouring electrodes which gives a bad approximation of CSD. Other more complex methods have been described for a better estimation of CSD at any place on the scalp. These methods start with an estimation of the "global" potential over all points of the scalp.

1.5.4 Thin plate spline interpolation of CSD

The CSD is again estimated using equation 4. The first part of the calculation of CSD is estimating the potential at all points across the scalp. This is done with thin plate spline interpolation (Perrin et al., 1987) which is often used to interpolate between data values positioned along a flat surface. Its effect can be illustrated as bending a thin metallic plate minimally so it passes through each of the measured data values. As the plate does not kink a smooth surface is obtained between the data points which further does not have any unnecessary bends. The surface spline U which interpolates the measured potential values, denoted ϕ_i at position (x_i, y_i), is given by

$$U(x,y) = \alpha_{n+3}x + \alpha_{n+2}y + \alpha_{n+1} + \sum_i \alpha_i \Phi(\vec{x}, \vec{x}_i) \tag{10}$$

The radial basis function ($\Phi(\vec{x}, \vec{x}_i)$) is given by,

$$\Phi(\vec{x}, \vec{x}_i) = \|\vec{x} - \vec{x}_i\|^2 \log\left(\|\vec{x} - \vec{x}_i\|^2 + w^2\right) \tag{11}$$

Entering the coordinates (x_i, y_i) of the electrodes and assigning $U(x_i, y_i) = \phi_i$ results in *n* equations (corresponding to *n* electrodes) linear in the *n*+3 coefficients. This results in a solution space of maximum 3 dimensions. The solution $\vec{\alpha}$ minimizing the "bending" or energy of the surface is chosen:

$$\vec{\alpha} = \arg\min_{\vec{\alpha}} \left[\int \left(\frac{\partial^2 U}{\partial x^2} \right)^2 + \left(\frac{\partial^2 U}{\partial x \partial y} \right)^2 + \left(\frac{\partial^2 U}{\partial y^2} \right)^2 \right] \tag{12}$$

The potential can be calculated at all points of the surface when the coefficients defining *U* are known (Fig.3). As the potential is described as a smooth function the laplacian can be calculated using eq. 4. The locations of the electrodes, (x_i, y_i), are calculated by projecting them from the spherical surface of the head to a plane using a suitable method. The thin plate method of assessing CSD has several advantages as compared to the nearest neighbour method described above as it allows for the estimation of CSD at points between electrodes and also for electrodes placed at the border of the montage (Fig.4).

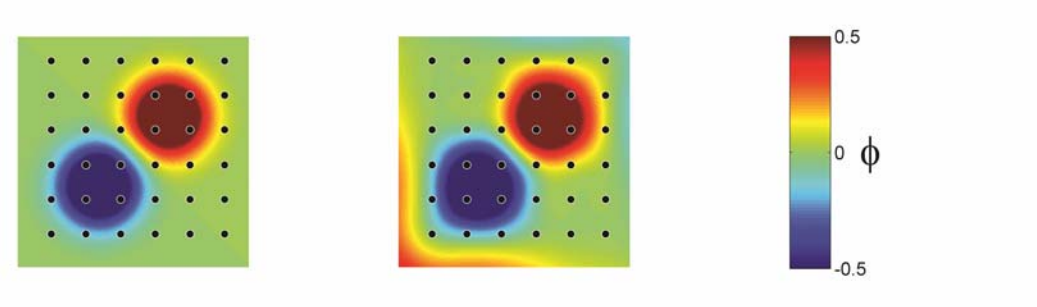

Figure 3. Left: Simulated potential (sum of two gaussian curves) sampled at electrodes (black symbols). Right: Potential interpolated from potential values at electrode positions using a thin plate spline. Positive values are coded in red and negative values in blue as indicated by colour bar.

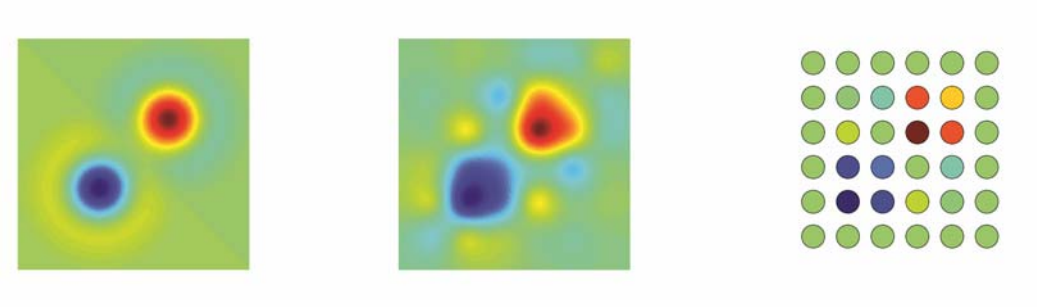

Figure 4. Left: Current source density (CSD) calculated from simulated potential in Fig. 3. Middle: CSD estimated by thin plate spline interpolation. Right: CSD estimated at electrode locations using nearest neighbour laplacian (Hjorth method).

1.5.5 Connectivity analysis of EEG

Cognitive function of the brain is considered to be based on interactions between different neural assemblies. These interactions could be investigated by studying different statistical relationships between the electrical signals created by the neural assemblies assessing the connectivity between them. Several techniques have been used to assess connectivity. Four nonlinear measures were used in the thesis, phase coherence (PC) (Mormann et al., 2000), phase lag index (PLI) (Stam et al., 2007), synchronisation likelihood (SL) (Stam and van Dijk, 2002, Montez et al., 2006) and phase slope index (PSI) (Nolte et al., 2008). Scripts for calculating PC, PLI and SL are presented in the Appendix. Linear methods use estimators that can only capture the linear properties of the relationship between time series (Wendling et al., 2009). Nonlinear measures can detect both linear and nonlinear interactions.

1.5.5.1 Phase Coherence

The mathematical definition of phase coherence is explained in paper IV. For a given signal a phase (angle) can be defined mathematically at every time. Phase coherence is defined as the circular average of the phase differences between two signals. The absolute value of the circular average of the phase difference over time is a number

between 0 and 1. PC =1 when the phase difference between the two signals is constant and PC = 0 if the phase difference is distributed randomly over the circle (Fig. 5.)

1.5.5.2 Phase Lag Index

Phase Lag Index (PLI) is a modification of PC and was constructed to be less sensitive to volume conduction than PC (Stam et al., 2007). In EEG recordings each electrode detects potentials from several sources. However, it can be assumed that signals in different sensors originating from the same source will have the same phase. To reduce the effect of volume conduction phase differences close to zero are ignored. This is achieved by taking the difference between the number of negative and positive phase differences (Fig. 5.). The average of these numbers results in a number between -1 and 1. The absolute value is taken as PLI. If the two signals are identical or if there is equal number of phase differences that are negative and positive PLI will be 0

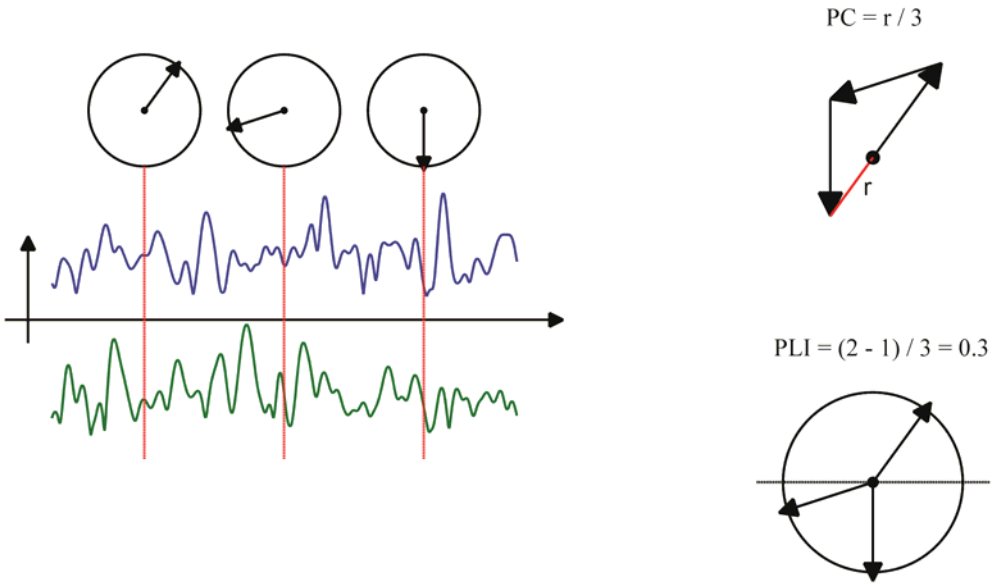

Figure 5. Left: Phase coherence and phase lag index calculated at three time points for two EEG signals. The phase difference between the two signals is represented as a vector in the unit circle. Upper right: Phase coherence is the resultant (r) of these vectors. Lower right: phase lag index is the difference in the number of negative (two arrows pointing downward) and positive (one arrow pointing upward) phase difference vectors.

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1.5.5.3 Synchronisation Likelihood

The mathematical definition of synchronisation likelihood (SL) is given in paper IV. SL measures synchronous activity between two time signals. For a given time a defined number of events in one signal are compared to the same number of events in the other signal. The ratio of simultaneous occurrences is calculated at all time points and averaged giving an approximate value of SL (Fig.6).

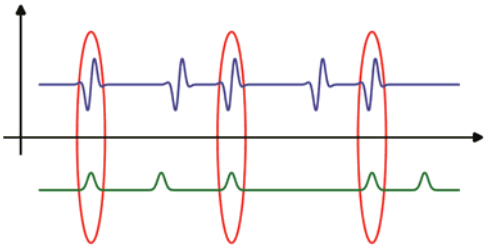

Figure 6. Estimation of SL of two EEG signals. Five similar events are examined for each signal. There are three simultaneous occurrences giving a SL a value of 3/5.

1.5.5.4 Phase Slope Index

Phase Slope index (PSI) (Nolte et al., 2008) is related to the slope of the phase of the cross spectra between two signals, the exact definition of PSI is given in paper IV. It is assumed that there is a temporal delay between two signals that are strongly connected. This delay in time will cause a non-zero phase of the cross-spectra dependent on frequency. PSI is the weighted sum of the phase slope of the cross-spectra. However, in contrast to the other measures PSI also indicates the direction of information flow across the cortex.

1.5.6 Connectivity, volume conduction and reference electrode

When estimating neuronal connectivity between different cortical regions there are several factors which could result in false assessment of connectivity. Connectivity between signals measured at electrodes is measured to assess the functional connectivity between cortical sources. However, activity from any given cortical area is often projected to several electrodes, *i.e.* volume conduction. This common activity increases the resemblance between the time signals at the electrodes and results in a false connectivity (Nunez et al., 1997). The reference electrode contributes to both of the compared signals which falsely give a high similarity (connectivity) between the active electrodes (Guevara et al., 2005). Several methods have been developed to reduce the above effects, *e.g.* estimating CSD using the laplacian of the potential. The effect of volume conduction can be compensated for by noting that any volume conducted signal will have a zero phase difference, thus a measure of connectivity sensitive only to non-zero phase differences would not be affected by volume conduction. As mentioned above PLI was designed to reduce the effect of volume conduction (Stam et al., 2007). The effect of non-neural noise on the measured

connectivity is difficult to compensate for. A decrease in signal to noise ratio due to artefactual noise results in a 'drowning' of the synchronized signals with falsely low values of connectivity. This effect should be avoided by high standards of measurement with high signal to noise ratio.

1.6 EVENT RELATED POTENTIALS

Event related potential (ERP) is the time locked potential appearing in EEG after visual, auditory or sensory stimulus, overlaid on the background EEG. They are often observed after taking averages of EEG recordings time locked to the evoking stimulus. There are three main models of how these potentials are created.

- ERP is created by a set of silent neurons activated by the stimulus resulting in a potential locked in time to the stimuli appearing together with the background EEG (Shah et al., 2004, Makinen et al., 2005, Mazaheri and Jensen, 2006). The evoked model has a long tradition and is well established (Sauseng et al., 2007).
- ERP is created by a set of neurons previously oscillatory active undergoing a sudden transition to a specific phase, *i.e.* resetting, due to the stimulus. This activity appears together with the activity of neurons unaffected by the stimulus (Sayers et al., 1974, Makeig et al., 2002, Hanslmayr et al., 2007). Phase resetting has been supported by several studies (Brandt, 1997, Basar, 1999, Makeig et al., 2002).
- ERP is created by low frequency activity, termed baseline shifts. These baseline shifts are correlated to the amplitude of high frequency oscillations which are further affected by stimulus. When the EEG signals are averaged the high frequency components cancel leaving the baseline shifts (Nikulin et al., 2007).

There is no general consensus on the generation of ERP. However, several recent studies have suggested (Fell et al., 2004, Mazaheri and Picton, 2005) that ERPs are created by a mixture of phase synchronisation and activation of silent neurons. A critical discussion has been written by Sauseng (Sauseng et al., 2007) describing the current knowledge.

1.6.1 Auditory pathway

Auditory ERP is created at the scalp after stimulation of the auditory pathway. This pathway consists of two physiological parts, the peripheral auditory system consisting of the ear and primary auditory nerves and the central auditory system. The sound waves are converted into electrical impulses by the hair-cells in the cochlea. These impulses travel along the 8^{th} cranial nerve to the brainstem. In the brainstem the nerve bifurcates into the dorsal and ventral cochlear nucleus (CN). A large proportion of the cells in the nuclei terminate ipsi- and contralaterally in the superior olivary nucleus (SON), inferior colliculus (IC) and the nucleus of the lateral lemniscus. Hereafter, there is a bilateral projection to the medial geniculate nucleus (MGN) which has an ipsilateral projection to the primary auditory cortex located on the inner surface of the superior temporal cortex (Fig.7). In the superior temporal plane there are subsequent projections to adjacent secondary sensory areas.

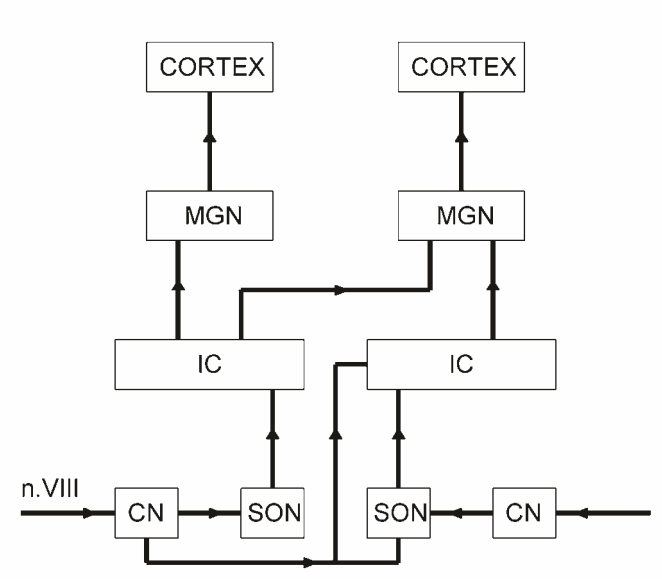

Figure 7. The auditory pathway has connections that are symmetric between left and right side. Several connections are not illustrated for clarity. Abbreviations: cochlear nucleus (CN), superior olivary nucleus (SON), inferior colliculus (IC) and medial geniculate nucleus (MGN).

1.6.2 N100 and P300

Transients in the auditory ERP with latency more than 50 ms are considered to be of cortical origin. The main components of auditory ERP are an early negative peak with delay 100 ms (N100 or N1) and a later positive peak at 300 ms (P300 or P3) (Fig. 8). N100 is influenced by features of the stimulating signal such as stimulus intensity and tonal frequency (Naatanen and Picton, 1987) and is likely to be caused by activation of primary auditory areas on the supratemporal plane, from cortico-cortico activation in surrounding association areas, and from direct thalamo-cortical projections to frontal and parietal areas (Elberling et al., 1982, Naatanen and Picton, 1987).

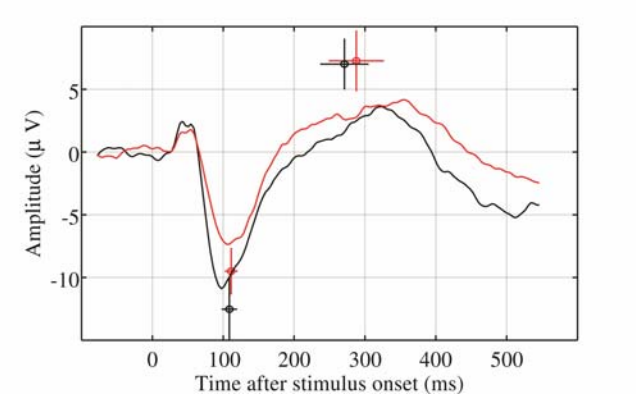

Figure 8. Auditory ERP for subjects with T2DM (red) and healthy controls (black) elicited using a choice paradigm. Symbols designate mean amplitude and latency for N100 and P300 peak.

Electrophysiological recordings and anatomical tracing in rhesus monkeys have revealed two cortico-cortico pathways originating in separate, non-primary, cochleotopic auditory fields of the superior temporal region and terminating in distinct regions of the frontal lobes (Romanski et al., 1999). The N100 topography is characterized by negative potential fields over the frontal-central scalp areas, and positive potentials around the temporal mastoid sites, this polarity reversal being typical of activities in the auditory cortex (Vaughan and Ritter, 1970). This polarity distribution leads to an augmentation of the N100 amplitude if the mastoids are used as a reference electrode.

P300 is considered to be more 'endogenous' than N100 and mainly to be affected by the cognitive processing of the stimulus (Polich and Kok, 1995). P300 is typically initiated with target stimuli, the experiment often designed as an odd-ball paradigm where target stimuli are detected in a train of non-target stimuli. The amplitude depends on target probability and discriminability of targets. Moreover, P300 is related to both attention and working memory (Linden, 2005).

2 AIMS OF THE THESIS

2.1 GENERAL AIM

The overall aim was to identify how diabetes mellitus (both T1DM and T2DM) affects brain function and to contribute to the understanding of the underlying pathophysiology.

2.2 SPECIFIC AIMS

2.2.1 T1DM (paper I, II and IV)

- To identify predictors of cognitive decline in T1DM. To investigate the relationship between cognition as evaluated with neuropsychological tests and the clinical parameters. In particular the aim was to identify those clinical parameters that are the greatest risk factors for cognitive decline (Paper I).
- To contribute to the understanding of the pathophysiology for cognitive decline in T1DM. In particular the aim was to study the effect of T1DM on auditory ERP and how changes in different ERP parameters related to cognitive test results, demographic data and disease parameters (Paper II).
- To deepen the analysis of the mechanism for cognitive decline in T1DM. To this end we used novel methods for analysis of brain connectivity. Moreover, the aim was to study how different measures of brain function in T1DM were related (connectivity, ERP, neuropsychological, EEG power) (Paper IV).

2.2.2 T2DM (paper III)

- To investigate the effect of T2DM on cerebral function utilizing EEG, ERP and cognitive tests, and to identify similarities and differences as compared with T1DM.
- To study the effect of improved glycaemic control on cerebral function and assess if these functional abnormalities to some extent were reversible.

3 SUBJECTS AND METHODS

3.1 SUBJECTS

3.1.1 T1DM

Paper I, II and IV are based on a cross sectional investigation of subjects with T1DM (N=150) and a group of sex and age matched healthy control subjects (N=61). Only patients with diabetes duration of more than 5 years and age between 22 and 56 years were included. All subjects underwent a physical examination and neurological examination, clinical chemistry laboratory testing, nerve conduction studies and quantitative sensory tests. Occurrence of diabetic complications was evaluated from these tests and from the medical records. Presence of retinopathy, neuropathy, nephropathy and hypertension was noted together with level of long-term metabolic control and number of episodes of severe hypoglycaemia and coma. Patients were subjected to a neuropsychological test, resting EEG and auditory ERP. Blood glucose was measured in connection with these tests. Demographic and clinical data as well as exclusion criteria are detailed in Paper I.

3.1.2 T2DM

Paper III is an interventional study of subjects with T2DM (N=28) and a group of healthy control subjects (N=21). Patients between 50 and 70 years of age without diabetes complications (*i.e.* cardiovascular disease, angiopathy, microangiopathy, retinopathy or nephropathy) were eligible for the study. Patient history, bedside examination and medical records were used to assess presence of complications. Patients were separated in to two groups: one that received a 2-month period of intensified treatment for glucose control (N=15), and another that maintained the regular treatment (N=13). All participants were investigated at two occasions with an interval of 2 months, which was the period of intensified treatment. The examinations consisted of cognitive testing, EEG/ERP recordings and metabolic tests including HbA1c and plasma glucose.

3.2 NEUROPSYCHOLOGICAL ASSESSMENT

In paper I, II and IV the cognitive test included ten cognitive domains: psychomotor speed, memory, visual perception and organization, visual–spatial ability, speed of information processing, attention, working memory, verbal ability, general intelligence and executive functions. In paper III the cognitive test included four domains: verbal episodic memory, verbal fluency, semantic memory and visuospatial ability.

3.3 ELECTROPHYSIOLOGY

Resting EEG and ERP recordings were performed on all participants described in paper I-IV.

3.3.1 Resting EEG

Resting EEG was recorded with 23 electrodes placed over both hemispheres, according to the 10-20 International System (Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, O2 and both mastoids). The recording reference was

placed on the nose. Recordings were made for 8 min on subjects who were resting and awake, following a strict protocol with cycles of open eyes 5 s and closed eyes 55 s, repeated seven times. The purpose of this method was to reduce the spontaneous variability in the frequency content. The recordings were visually screened for artefacts. The entire EEG during the closed eyes conditions was included in the analysis except for segments with artefacts in order to avoid bias in the pruning of data segments (Maltez et al 2004). The spectral content was studied using a fourier transform and the difference between patients and control subjects was described as colour coded p-values in schematic maps of the scalp locations.

3.3.2 Auditory event related potentials

Auditory ERP was evoked in two experiments using a two-choice reaction test and an odd-ball paradigm. Tone signals of 100 ms duration with low or high pitch were delivered from a loudspeaker in two pre-programmed experiments. In experiment 1 (choice reaction) the subjects were given 60 tone signals of low or high pitch randomly with weight 1:1 and with a pseudorandom rate and were instructed to press the response key in the left hand hearing the low pitch signal, and the response key in the right hand hearing the high pitch signal. In experiment 2 (oddball) tone signals were given with a regular interval of 1.0 s. The signals had randomly a low or high pitch with a weight between low and high of 4:1. The subjects were instructed to press the button held in their right hand on hearing the high pitch signal (infrequent, target). Average ERP was obtained by averaging over trials with low and high pitch tones in experiment 1 and 2, respectively. N100 was defined as the negative peak in the interval 60-160ms, and P300 as the positive peak in the interval 200-500 ms. The latencies were the delay of the peaks from the beginning of the tone signal.

3.3.3 Connectivity

Connectivity between electrode sources was evaluated using three different techniques: phase coherence, phase lag index and synchronisation likelihood (see 1.5.5). The signal was re-referenced to a linked mastoid reference for the connectivity analysis. Connectivity was assessed for artefact free EEG recordings of 40 s length in the delta, theta, alpha, beta and gamma band. Connectivity was estimated at each electrode by averaging all measures of connectivity between the individual electrode and the other electrodes. Furthermore, average connectivity within inter-hemispherical electrode pairs and intra-hemispherical pairs was estimated. The information flow across the cortex was estimated using phase slope index (PSI) (see 1.5.5). PSI is a recently developed method which describes the flow of information with application on signal flow across the cortex. Moreover, connectivity data and information flow was also calculated using CSD estimates to reduce confounding effects due to the reference electrode and volume conduction (see 1.5.6).

3.4 PERIPHERAL NERVE STATUS

Sensory nerve conduction velocity (SCV) and action potential amplitude (SNAP) were measured in the sural nerves bilaterally. Motor nerve conduction velocity (MCV) and compound muscle action potential amplitude (CMAP) was measured bilaterally by stimulation of the peroneal nerve. Subjects were further examined clinically for

peripheral neural disease following a fixed examination protocol including sensory screening for touch, pin prick, vibration and temperature. The different responses were graded as normal, decreased or absent (0, 1 or 2 points, respectively) and the sum was the neurological impairment score (NIA), see paper I.

4 RESULTS AND DISCUSSION

4.1 PREDICTORS OF COGNITIVE IMPAIRMENT IN T1DM

Bivariate analysis indicated strong correlations between several cognitive domains and clinical variables. The clinical variables with the most abundant correlations to cognitive domains were disease duration and age at onset. Furthermore, the cognitive domains with the most abundant correlations to clinical variables were psychomotor speed, visual perception and visual–spatial ability. However, several of the disease variables were interrelated so a multiple forward linear regression analysis was performed in order to separate their effects. The strongest predictors for cognitive impairment were long diabetes duration and young age of diabetes onset in particular for psychomotor speed and processing speed. Furthermore, low compound muscle action potential (CMAP), old age, short stature, high BMI and hypertension were also significant predictors of cognitive decline. Hypoglycaemic events did not show any increased risk for cognitive impairment though we cannot exclude the possibility that the influence of young age of diabetes onset depends on the effect of hypoglycaemic events early in life. Presence of retinopathy or long-term metabolic control did not have any impact on cognitive function. The influence of diabetes duration, BMI, height, age and CMAP may suggest that loss of the neuroprotective action of insulin or insulin-like growth factors plays a role. BMI, body height and CMAP are correlated to circulating levels of insulin-like growth factors (IGFs) and IGF binding proteins (Chang et al., 2002, Veldhuis et al., 2005, Gram et al., 2006). Several studies have suggested that IGF-I delays age-dependent degenerative changes in the brain and cognitive impairment (de la Monte and Wands, 2005, Carro and Torres-Aleman, 2006, Okereke et al., 2006).

4.2 COGNITIVE IMPAIRMENT AND EVENT-RELATED POTENTIAL

T1DM reduced N100 amplitude but did not significantly affect N100 latency. The decrease in N100 amplitude was distributed over all scalp locations in both hemispheres with $p<4x10^{-6}$ for the difference between mean N100 amplitudes of the two study groups. Furthermore, patients had an increase in the mean P300 latency ($p<0.0004$). P300 amplitude showed only a small reduction limited to the parieto-occipital region ($p<0.05$). Psychomotor speed correlated with N100 and P300 amplitudes and even more strongly with the peak-to-peak N100-P300 amplitude. There was a correlation between N100 latency and cognitive score for psychomotor speed, visual perception-organization and processing speed. Also several correlations were found between the ERP variables and the peripheral nerve status. N100 amplitude correlated with MCV ($p<0.003$), SNAP ($p<0.01$) and negatively with the NIA score ($p<0.01$). P300 latency correlated with CMAP ($p<0.007$). After Bonferroni's correction for multiple tests of correlation it was only the correlation between MCV and N100 amplitude that remained significant among the nerve conduction variables.
A correlation has previously been reported between white matter volume and cognitive speed (which we found to correlate strongly with N100 amplitude) in T1DM (Wessels et al., 2007). Moreover, brainstem auditory evoked responses (BAER) have shown increased latency in T1DM (Fedele et al., 1984, Durmus et al., 2004). No increase in latency was found in this study for N100; however, the absence of effect on N100

latency is not a contradiction to the effect on BAER, since the increase in BAER is only fractions of a millisecond. It is hypothesized that nerve conduction defects due to diabetes cause an increased temporal dispersion of the afferent volley in the auditory pathways, leading to a loss of synchrony in cellular activation at different levels of the brain stem and in the cortex with a subsequent decrease in the amplitude of the cortical response.

4.3 CONNECTIVITY AND INFORMATION FLOW

Study IV has revealed that patients with T1DM have a decrease in connectivity, cortical information flow and EEG resting beta and gamma power. Connectivity was assessed in resting EEG with phase coherence (PC), phase lag index (PLI) and synchronisation likelihood (SL). Information flow was assessed using phase slope index (PSI). Data was correlated to demographic variables, cognitive scores and auditory ERP obtained at the same occasion. There were very strong correlations between the three measures of connectivity. PC was reduced in the theta ($p<0.0003$), lower alpha ($p<0.003$), upper alpha ($p<0.001$), beta ($p<0.0005$) and gamma band ($p<0.04$), with maximum reduction in frontal and central regions. Multivariate test on the connectivity and information flow data averaged over all frequencies and electrodes showed a difference between patients and controls both with mastoid reference ($p < 0.01$) and CSD ($p<0.04$). EEG power was reduced in the delta ($p<0.01$), theta ($p<0.01$), lower alpha ($p<0.04$), beta ($p<0.01$) and gamma band ($p<0.005$). PC had a positive correlation to power in several, but not all frequency bands. After correction for multiple comparisons PC and EEG-power neither correlated with the cognitive tests nor the clinical variables.
Thus study IV showed that patients with T1DM have a decrease in connectivity, cortical information flow and EEG resting beta and gamma power. The reduction in connectivity and information flow support our previous hypothesis that a loss of synchronization in afferent impulse flow may contribute to the decline in N100 amplitude in T1DM. Similarly, conduction defects in the white matter and in the cortex are expected to cause a decrease in connectivity and possibly power. In multiple sclerosis where WML is one of the main features (Lassmann, 2009), MEG has demonstrated a decrease in alpha band interhemispheric coherence (Cover et al., 2006). These abnormalities add to the previously described decrease in N100 amplitude found in the same study population of patients with T1DM. Our studies have indicated that there is not one main factor in the disease history that correlates with the functional abnormalities, such as seen between poor long-term metabolic control and peripheral neuropathy.

4.4 METABOLIC CONTROL AND CNS FUNCTION IN T2DM

The aim of study III was to investigate the effect of strict glycaemic control on cognition in patients with T2DM. There were significant differences at baseline ($p < 0.02$) between patients with T2DM and controls. Patients had lower scores in two cognitive domains: verbal fluency ($p < 0.01$) and visuospatial ability ($p < 0.03$). T2DM also affected ERP with a decrease in N100 amplitude ($p < 0.04$) and an increase in P300 latency ($p < 0.03$). Furthermore, resting EEG activity in the beta band (13-30Hz) was reduced ($p < 0.04$). The change between 1st and 2nd investigation was significantly different in the three groups of patients/subjects ($p < 0.03$). Patients receiving

intensified treatment for glycaemic control had an improvement of cognitive ability in visuospatial ability ($p < 0.02$) and semantic memory performance ($p < 0.04$) together with increased resting EEG activity in the alpha band (8-13 Hz, $p < 0.02$) and connectivity in the theta (4-8 Hz, $p < 0.03$) and alpha bands ($p < 0.03$) over central and lateral regions. Furthermore, there was an increase in the connectivity in the beta band ($p < 0.04$) over the central regions of the scalp. In conclusion, subjects with T2DM had a similar type of cognitive function impairment and EEG/ ERP abnormality as previously demonstrated for subjects with T1DM. Intensified therapy resulted in improvement of cognitive function and electro-physiological measures not shown for regular treatment, suggesting that the negative effect of T2DM on brain function to some extent is reversible by means of improved glycaemic control.

5 CONCLUSIONS

Conclusions from the studies on subjects with T1DM:

- Long diabetes duration and young age of diabetes onset were the strongest predictors of cognitive impairment. Hypoglycaemic events were not a predictor of cognitive impairment.
- Patients had a highly significant decrease in the auditory N100 peak amplitude which was strongly associated with a decline in psychomotor speed. This association and the comparatively smaller abnormality in P300 latency is different from those typically found in dementia associated with cortical atrophy, and suggests that the underlying defect may be located in the brainstem or the white matter.
- Patients with T1DM had a decrease in connectivity, cortical information flow and EEG resting beta and gamma power.
- No main factor was found in the disease history that correlates with the functional abnormalities, such as seen between poor long-term metabolic control and peripheral neuropathy.
- EEG and ERP abnormalities vary in their correlation with different cognitive domain function and it is likely that these tests measure different functions and are complementary to the cognitive tests.
- Several tests need to be performed in order to monitor the effect of T1DM on brain function.

Conclusions from the study on subjects with T2DM:

- There are similar ERP and EEG abnormalities in T2DM as previously found in T1DM.
- Improved glycaemic control can to some extent restore the cerebral function in T2DM.
- The difference in treatment effect on ERP *vs.* EEG and cognition may indicate that the CNS abnormalities have different pathophysiology and therefore may be restored with different time course.

6 APPENDIX

6.1 MATLAB ® SCRIPT FOR PHASE COHERENCE

```
function PC=Phase_coherence(a)

% a is a filtered multichannel signal (time x channels)
% hilbert(a) calculates analytic signal (complex valued) of each
% column of a. Phase Coherence between channel i and j averaged over
% time bins is stored in PC(i,j)

% number of channels
N=size(a,2);

PC(1:N,1:N)=0;

complex_a=hilbert(a);

for i=1:N
    for j=1:N
        if i<j

            pc = complex_a(:,i)./complex_a(:,j);

            % phase difference between signals

            n_pc = pc./abs(pc);

            % circular average of phase difference

            PC(i,j)=abs(mean(n_pc));

        end
    end
end

PC = PC + PC';

return
```

6.2 MATLAB ® SCRIPT FOR PHASE LAG INDEX

```
function PLI=Phase_lag_index(a)

% a is a filtered multichannel signal (time x channels)
% hilbert(a) calculates analytic signal (complex valued) of each
% column of a. Phase Lag Index between channel i and j averaged over
% time bins is stored in PLI(i,j)

% number of channels
N=size(a,2);

PLI(1:N,1:N)=0;

complex_a=hilbert(a);

for i=1:21

    for j=1:21

        if i<j

PLI(i,j)=abs(mean(sign(imag(complex_a(:,i)./complex_a(:,j)))));
        end

    end

end

return
```

6.3 FORTRAN 90 SCRIPT FOR SYNCHRONISATION LIKELIHOOD

```
!_________________Function SL_FUNC for 2 channels_____________________
real function SL_FUNC(x,y,freq_samp,p_ref,n_rec,l,m,w1,w2,n,t)

! define paramters
!=====================================================================
integer, intent(in)    :: l       ! time lag
integer, intent(in)    :: m       ! embedding dimension
integer, intent(in)    :: w1      ! min distance to sampling window
integer, intent(in)    :: w2      ! max distance to sampling window
integer, intent(in)    :: n       ! length of shortened time signal
integer, intent(in)    :: t       ! length of time signal
integer, intent(in)    :: n_rec   ! neighbours within critical
!distance

real, intent(in)       :: p_ref   ! % neighbours within critical
!distance
real, intent(in)       :: x(t)    ! 1st signal
real, intent(in)       :: y(t)    ! 2nd signal


real (kind=8)          :: xx(n,m) ! embedded vectors of signal x
real (kind=8)          :: xy(n,m) ! embedded vectors of signal y

!_____________________________________________________________________

real (kind=8), allocatable :: dx(:,:) ! distance between embedded
vectors
real (kind=8), allocatable :: dy(:,:) ! distance between embedded
vectors
real (kind=8), allocatable :: rx(:)   ! crit dist for embedded
!vectors
real (kind=8), allocatable :: ry(:)   ! crit dist for embedded
!vectors

!_____________________________________________________________________

real (kind=4)          :: dx0(m), dy0(m)       ! dummy variables
real (kind=4)          :: normx, normy         ! dummy variables
real (kind=4)          :: p, ss, s(n-w2)       ! dummy variables
real (kind=4)          :: r, rmin, rmax        ! dummy variables
integer                :: i,j,k,ttdx,ttdy      ! dummy variables
integer                :: tdx,tdy,n_ab         ! dummy variables


! Allocate variables
!=====================================================================
allocate(dx(n-w2,n),dy(n-w2,n))
allocate(rx(n-w2),ry(n-w2))
allocate(px(n-w2),py(n-w2))
```

```
! Embedd vectors
!=====================================================================

do i=1,n
  do j=1,m

! vectors with lag l of dimension m at each time
    xx(i,j)=x(i+(j-1)*l)
    xy(i,j)=y(i+(j-1)*l)

  enddo
enddo


! Calculate distance between embedded vectors
!=====================================================================

do i= (1+w2), (n-w2)

  do j= (i-w2), (i-w1)

! Euclidean distance between vectors

    dx0 = xx(i,:)-xx(j,:)
    dy0 = xy(i,:)-xy(j,:)
    dx(i,j) = sqrt(dot_product(dx0,dx0))
    dy(i,j) = sqrt(dot_product(dy0,dy0))

  enddo

  do j= (i+w1), (i+w2)

! Euclidean distance between vectors
    dx0 = xx(i,:)-xx(j,:)
    dy0 = xy(i,:)-xy(j,:)
    dx(i,j) = sqrt(dot_product(dx0,dx0))
    dy(i,j) = sqrt(dot_product(dy0,dy0))

  enddo

enddo
```

```
! Estimate critical distance signal x
!=====================================================================

do i= (1+w2), (n-w2)

! starting values for optimisation

  ttdx=0       ! number of close neighbours
  r=30         ! starting value for crit distance
  rmax=1000    ! max value for crit distance
  rmin=0       ! min value for crit distance

! Calculate critical distance in a maximum of 60 iterations

  do k= 1, 60

! If the number of close neighbours not equal to target value
! increases or decreases change the critical distance

    if (ttdx/=n_rec) then

    ! count close neigbours

      tdx = 0

      do  j=(i-w2),(i-w1)

        if ((r-dx(i,j))>0 ) then
          tdx = tdx + 1
        endif

      enddo

      do  j=(i+w1),(i+w2)

        if ((r-dx(i,j))>0 ) then
          tdx = tdx + 1
        endif

      enddo
```

```
      ! store number of close neighbours in ttdx

      ttdx=tdx

      ! if there too many close neighbours reduce crit distance

      if ( ttdx > n_rec) then
        rmax = r
        r=(r+rmin)/2

        ! If max iterations performed and no convergence, return

        if (k==60) then
          SL_FUNC=100
          return
        endif

      ! if there too few close neighbours increase crit distance

      elseif (ttdx < n_rec) then
        rmin = r
        r = (r+rmax)/2

        ! If max iterations performed and no convergence, return

        if (k==60) then
          SL_FUNC=100
          return
        endif

      ! if close neighbours at target value, store crit distance
      else

       rx(i)=r

      endif

    enddo

enddo
```

```
! Estimate critical distance signal y
!====================================================================

do i= (1+w2), (n-w2)

! starting values for optimisation

  ttdy=0       ! number of close neighbours
  r=30         ! starting value for crit distance
  rmay=1000    ! max value for crit distance
  rmin=0       ! min value for crit distance

! Calculate critical distance in a maximum of 60 iterations

  do k= 1, 60

! If the number of close neighbours not equal to target value
! increases or decreases change the critical distance

    if (ttdy/=n_rec) then

    ! count close neigbours

      tdy = 0

      do  j=(i-w2),(i-w1)

        if ((r-dy(i,j))>0 ) then
          tdy = tdy + 1
        endif

      enddo

      do  j=(i+w1),(i+w2)

        if ((r-dy(i,j))>0 ) then
          tdy = tdy + 1
        endif

      enddo
```

```
      ! store number of close neighbours in ttdy

      ttdy=tdy

      ! if there too many close neighbours reduce crit distance

      if ( ttdy > n_rec) then
        rmay = r
        r=(r+rmin)/2

        ! If max iterations performed and no convergence, return

        if (k==60) then
          SL_FUNC=100
          return
        endif

      ! if there too few close neighbours increase crit distance

      elseif (ttdy < n_rec) then
        rmin = r
        r = (r+rmay)/2

        ! If max iterations performed and no convergence, return

        if (k==60) then
          SL_FUNC=100
          return
        endif

      ! if close neighbours at target value, store crit distance
      else

       ry(i)=r

      endif

    enddo

enddo
```

```
! estimating simultaneous repetitions
!=====================================================================

do i=(1+w2),(n-w2)

  n_ab=0

    do  j=(i-w2),(i-w1)

      if ((rx(i)-dx(i,j))>0) then
        if ((ry(i)-dy(i,j))>0) then
          n_ab = n_ab + 1
        endif
      endif

    enddo

    do  j=(i+w1),(i+w2)

      if ((rx(i)-dx(i,j))>0) then
        if ((ry(i)-dy(i,j))>0) then
          n_ab = n_ab + 1
        endif
      endif

    enddo

! calculating SL at given time point
s(i)= (0.5*n_ab)/(p_ref*(w2-w1+1))

enddo

! sum simultaneous repetitions
ss=0
do i=1+w2,N-w2
           ss=ss+s(i)
enddo


! normalise simultaneous repetitions

ss = ss/(N-w2*2)

SL_FUNC=ss

end function SL_FUNC
```

7 ACKNOWLEDGEMENTS

I am deeply grateful to my major supervisor Prof. Tom Brismar, who introduced me to the field of neuroscience and in particular to quantitative EEG analysis. I thank Prof Tom Brismar for sharing his great knowledge on the subject and also his guidance without which this work would not have been completed.

I thank Docent Lars Hyllienmark for his advice on the clinical and electrophysiological aspects of cerebral dysfunction in diabetes mellitus and for his generous support during the course of the work

I thank Prof. S. Allen Counter for his interest and support during the course of this work.

I would like to thank Mrs Britten Winström-Nordemar for her tireless effort in recording EEG and collecting subjects for the studies.

I thank Prof Kerstin Brismar for her invaluable guidance in the clinical aspects of diabetes mellitus and also generously allowing me to access patient data at her laboratory. Furthermore, I would like to thank Dr. Erika Jonsson Laukka, Dr. Liselotte Maurex, Dr. Erik Nilsson and Prof Åke Wahlin for their guidance and help regarding aspects of neuropsychological evaluation of subjects.

I would like to give thanks to Docent Magnus Andersson for generously offering me his time for guidance and support.

I would like to thank Elisabeth Fabian for her technical assistance during the course of this work.

I thank everyone at the Department of Clinical Neurophysiology for creating a pleasant environment to work.

I would like to thank my brother and my sister in-law, Charith and Anna, for being my friends and the support they have given.

I am deeply in debt to my parents for their continuous support, guidance and involvement in my education from my early days to the present. Furthermore, I am thankful for their inspiring interest in the work.

I thank my wife Shamara for her patience and help in pursuing this work. Finally, I thank my daughter Sanduni for the happiness she brings into our life.

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