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Electro/magnetoencephalographic signatures of human brain insulin resistance

Maike A Hege[1], Stephanie Kullmann[2,3,4], Martin Heni[2,3,4], Franziska Schleger[2,3,4], Katarzyna Linder[2,3,4], Andreas Fritsche[2,3,4] and Hubert Preissl[2,3,4,5]

Human insulin action influences eating behavior, peripheral metabolism and cognition. Detailed insights into the neuronal processes related to human brain insulin action can be obtained by direct measures of neuronal activity with electroencephalography and magnetoencephalography. Results of recent studies show that spontaneous, task and stimulus related neuronal activity is modulated by insulin and that several factors like increased body weight and body composition can result in brain insulin resistance. Recent technological advances even allow the investigation of human brain functions *in utero* in relation to the metabolic status of the mother and indicate an effect of the mother's insulin sensitivity on the brain function of the fetus. In conclusion, studies based on direct neuronal measurements may help to determine the developmental trajectory related to insulin action and resistance.

Addresses
[1] Institute of Medical Psychology and Behavioral Neurobiology/fMEG Center, Eberhard Karls University Tübingen, Tübingen, Germany
[2] Institute for Diabetes Research and Metabolic Diseases (IDM) of the Helmholtz Center Munich at the University of Tübingen, Tübingen, Germany
[3] German Center for Diabetes Research (DZD), Neuherberg, Germany
[4] Department of Internal Medicine, Division of Endocrinology, Diabetology, Angiology, Nephrology and Clinical Chemistry, Eberhard Karls University, Tübingen, Germany
[5] Department Pharmacy and Biochemistry, Faculty of Science, University of Tübingen, Tübingen, Germany

Corresponding author: Preissl, Hubert (hubert.preissl@helmholtz-muenchen.de)

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Introduction

The ingestion of nutrients is essential for survival. The present excessive availability and ingestion especially of food high in fat and carbohydrates, however, has contributed to an epidemic increase in obesity in most parts of the world. According to the World Health Organization, more than 1.9 billion adult people are overweight and about 500 million people are obese [1]. Excessive body weight is associated with various diseases, particularly cardiovascular diseases [2], diabetes mellitus type 2 [3] and certain types of cancer [4]. The causes for this increase in obesity are multifactorial and certainly include a strong gene–environment interaction. However, common gene variants that were found to increase obesity-risk in genome wide association studies (GWAS) show only small effect sizes. For example, the per-allele effect size on body weight ranges between 100 g and 1.5 kg for such polymorphisms. This makes evolutionary based hypotheses, as the selection of the thrifty phenotype through evolution, untenable [5]. Nonetheless, most of the genes that harbor obesity-associated risk variants are highly expressed in the human brain and not only in homeostatic areas like the hypothalamus but also in cortical areas. In addition, obesity is associated with a large number of hormonal alterations, in particular peripheral insulin resistance. In this context, it was shown that despite the observation that glucose utilization in the brain seems to be independent of insulin signaling [6], the brain also contains a large number of insulin receptors. The receptor density is highest in the hypothalamus and olfactory bulb, but insulin receptors are expressed all over in the brain [7].

These concurrent findings, namely that obesity related genes and insulin receptors are expressed in the brain, led to a growing interest to investigate the functional significance of insulin action in the brain. In this review, we will focus on human studies on insulin resistance in the brain over the lifespan and discuss possible future application.

Measuring neuronal activity in the human brain

In this review, we will further focus on studies that implemented electroencephalography (EEG) and magnetoencephalography (MEG) to assess neuronal electrical activity. EEG and MEG are the only non-invasive methods in human research that measure neuronal activity directly and do not rely on proxies like cerebral blood flow or similar quantities. Synaptic activity, mainly in the dendritic tree of pyramidal neurons in the cortex, leads to a current flow in and volume currents outside of the neurons. When an ensemble of neurons (estimates 10,000–100,000) is activated simultaneously, the small

volume currents add up and lead to a potential change. This change can be recorded with electrodes attached to the head (EEG) and the dendritic currents result in a corresponding magnetic field change which can be measured by magnetic sensors (MEG). Current MEG systems use low temperature (4 K) superconducting sensors (between 250 and 300) located in a helmet covering the whole head. EEG recordings can be performed with variable numbers of electrodes, however, current neuroscientific research is performed mainly with high density recordings that is 64–256 electrodes distributed over the whole head (for a detailed description of EEG use [8] and the current state of MEG is described in [9]).

During a study, the time traces of the electric or magnetic signals are recorded and can be analyzed in the time or frequency domain. Time domain analysis is mainly performed with event-related designs. An event can be an external uni-modal or multi-modal stimulation in different sensory systems, for example auditory, visual, somatosensory, or reactions such as motor executions or specific tasks. Based on the low signal to noise ratio elicited by a single event the responses are determined by time locked averaging. This means that single responses are averaged in relation to the event. These averages exhibit specific components (event-related potentials) defined by distinct activity changes that occur at a particular latency after the event. Based on the EEG literature, components are named by their polarity (N: negative, P: positive) and the latency of their occurrence after the event. Components with latencies up to 100 ms are regarded as exogenous components, which are generated mainly by a stimulus (these are also called evoked components). For example, visual stimulation generates a prominent negative component with a latency around 100 ms and is called N100 or N1 (in the following we indicate the component by the short name). Components with latencies above 300 ms are regarded as endogenous components generated by feedforward and feedback loops between different cortical processes. A well-established component is the P3 which can be recorded for example during decision processes and represents the evaluation of the stimuli. Latencies between these values often bear the signatures of both categories. An example is the P2 which is related to perceptual processes but is also modulated by attention. In the MEG field similar components can be described, however, they are often named as magnetic counterparts of the EEG components, for example M1. Frequency domain analysis is based on the fact that EEG and MEG signals can be regarded as a mixture of different frequency components. Frequency analysis of EEG/MEG reveals that specific frequency ranges are associated with certain tasks or conditions. EEG/MEG activity is divided into the following frequency bands: delta (<4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz) and gamma (30–200 Hz). Theta activity is for example related to memory processes and gamma activity is often associated with diverse cognitive processes.

In addition to the analysis at the sensor level, EEG and MEG facilitate the investigation of the brain sources generating the observed sensor activity. However, the source reconstruction does not provide a unique solution (inverse problem) but depends on certain model assumptions. In addition, due to the strong dependency of the source localization accuracy on the signal to noise ratio, EEG and MEG source reconstruction is largely limited to the investigation of cortical sources as the sensitivity for localization of activity in deep structures such as the hypothalamus is very limited.

1. Insulin action in the brain

It is now well established that peripheral insulin can cross the blood brain barrier by a receptor mediated transport process [10] and affects neuronal processes in a large number of brain regions including hypothalamus and higher cortical areas like the prefrontal cortex [11]. Brüning et al. [12] showed that the brain-specific insulin receptor knockout in mice leads to an obese phenotype [11,13,14].

In general, hormones form a complex interacting network, making it difficult to determine the isolated effect of a single hormone. To investigate specific insulin action in the brain, mainly three approaches are established. One of them is the oral glucose tolerance test (OGTT), which leads to a rise in circulating glucose and to a physiologic increase in plasma insulin concentrations after a challenge with a drink containing 75 g glucose. For the delivery of exogenous insulin, two different approaches are established. Intravenous infusion of insulin while keeping blood glucose levels stable during a hyperinsulinemic euglycemic glucose clamp not only allows for a detailed measurement of peripheral insulin sensitivity but also delivers significant amounts of insulin to the brain. As an elegant alternative, insulin can be administered as a nasal spray [15]. Intranasal insulin delivery elevates insulin levels in the brain without a major effect on peripheral insulin concentrations [16,17].

The first studies in humans related to insulin action were performed with event-related potential EEG measures. Whereas visual event-related potentials (N1) were not altered during application of a hyperinsulinemic euglygemic glucose clamp [18,19], auditory-event-related responses and neuronal activation in a memory task showed reduction of early and late components (100–300 ms after stimulus, N1, P3) after intranasal and intravenous insulin administration (clamp technique) [6,20]. Further, intravenous insulin injection led to a rapid (~7 min after application) negative shift in frontal direct current potentials, a measure of general excitability of the human cortex [21].

The first study on human brain insulin resistance was performed by investigating spontaneous brain activity during a hyperinsulinemic euglycemic glucose clamp [22]. Spontaneous activity is recorded without stimulation

or a specific task for the subject. This spontaneous activity is characterized by a rather stable network structure, which comprises local activity and associated functional connectivity within the network (resting state networks). During the hyperinsulinemic euglycemic clamp, we observed increased insulin level specific changes in the theta and beta band [22]. Whereas lean subjects showed increases in theta and beta band with increased insulin levels, this effect was absent in obese subjects. The observed changes in these frequency bands were correlated with body mass index, percent body fat and insulin sensitivity. In addition, stimulus event-related fields were affected. During increased insulin levels, lean subjects showed an increased auditory mismatch response compared to obese subjects. Besides body weight, additional factors that might influence brain insulin resistance should be considered. In particular, peripheral insulin sensitivity decreases with age, although this effect is mainly driven by body composition changes and weight gain. In Tschritter et al. [23], it was shown that brain insulin sensitivity in the beta range was correlated with age independent of body weight. These results indicate that there are age related effects on brain insulin sensitivity independent of body composition, which might be a link of brain insulin action on cognitive changes that are associated with aging. In addition, it was shown that certain genetic risk factors for obesity and/or type 2 diabetes are associated with impaired brain insulin sensitivity [24–26]. Further, results of an initial study suggest that it might be possible to overcome brain insulin resistance in humans and mice by the application of the long lasting insulin analog detemir [27]. In addition, detemir also leads to increased cortical activity in mice and in humans to a stronger EEG direct current change [28,29]. In conclusion, these studies clearly indicate that obese humans express brain insulin resistance, which can be reliably measured using MEG. This also raises the issue of possible impacts of human brain insulin resistance. After a lifestyle intervention of 9 months, we were able to show that insulin-stimulated cerebrocortical theta activity before the intervention correlated with a reduction in total adipose tissue and visceral adipose tissue. Brain insulin resistant participants benefited markedly less from the intervention program [30]. This indicates that brain insulin resistance should be considered as a possible target in relation to obesity development and treatment.

MEG is also specifically suited to investigate the dynamics of brain networks, which can be quantified by network based metrics. We investigated the effect of intranasal insulin on the small world dynamics of resting state magnetoencephalographic brain activity. Stingl et al. [31] observed insulin induced subject specific changes of the weighted path length in the theta band. This change again showed a statistically significant positive correlation with the body mass index of individual subjects, which supports the hypothesis of cerebral insulin resistance in obese individuals. Weighted path length is a measure of the global interconnectedness of a network and its global efficiency. These observations confirmed the assumption that insulin is a strong modulator of global communication of brain networks.

Visual processing and categorization

The before mentioned studies were not specifically related to eating processes. An effective way to investigate basic eating related processes is the application of visual stimulation by food pictures. Visual stimulation results in a hierarchically organized processing in different areas of the human cortex. The initial processing is located in the primary visual cortex, which is mainly related to the processing of the physical properties of the visual stimuli. The perception and categorization of pictures mainly involves the ventral occipito-temporal pathway [32]. In general, categorization involves the recognition of objects on the basis of common properties independently of their physical differences.

In humans, visual categorization leads to specific neuronal activities as early as 80 and 200 ms after stimulus onset [33]. As a matter of fact, food is an ill-posed category due to very inhomogeneous visual properties and large variations of food pictures regarding structure, color and cultural background. Nevertheless, food versus non-food pictures result in significantly different cortical activations already 120 ms after stimulus onset and localized to the primary visual cortex [34,35,36]. Later differences at around 160 ms post-stimulus can be observed in the inferior-occipital region and are probably related to the categorization of the objects. These studies showed that already early visual bottom-up processing is influenced by the characteristics of external cues. However, early processes can also be modulated by intrinsic top-down motivational states [37•]. Intranasal insulin modulated the event-related component at around 160–170 ms during a visual recognition task in lean volunteers [38]. Of notice, this modulation was specific for food pictures and not present when watching non-food stimuli. In obese individuals the modulation of the magnetic event-related components was absent, providing additional support for the hypothesis of cerebral insulin resistance in obese individuals. In conclusion, insulin affects perceptual and cognitive processes like categorization differently in lean and obese subjects.

Developmental aspects of brain insulin resistance

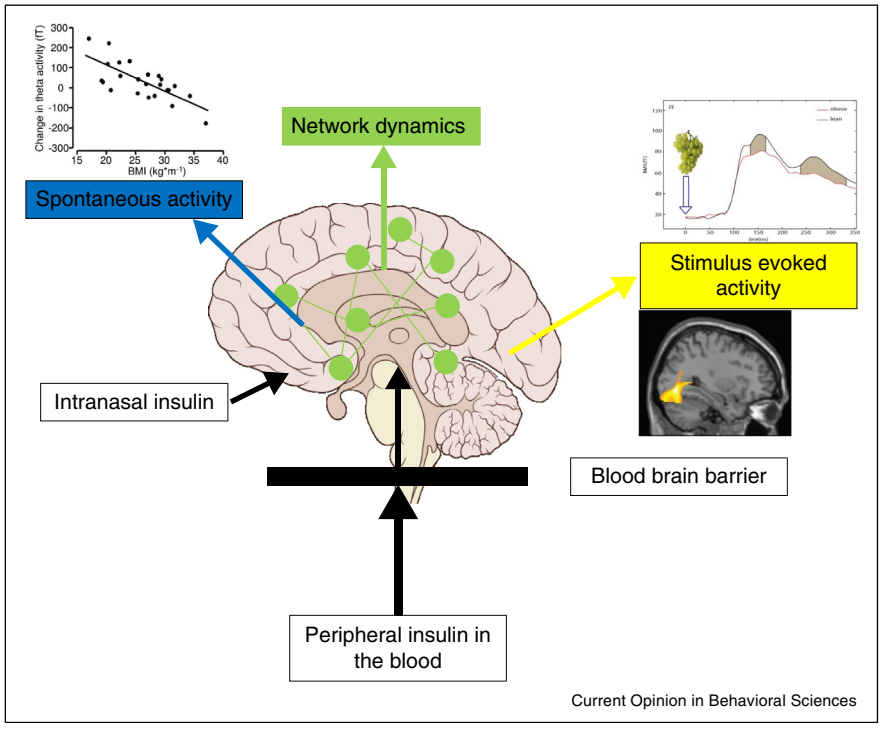
Most current studies related to insulin resistance in the brain were performed in adults. The development of new imaging techniques, nowadays even allow non-invasive investigation of brain activation in human fetuses. The fetal MEG is a specific device designed for the recording of biomagnetic signals originating from the fetus. Fetal brain signals, specifically event-related fields elicited by auditory or visual stimuli, can be reliably recorded during

the last trimester. Several studies clearly showed that the latency of auditory event-related fields decreases over gestation and can be used as a neurodevelopmental parameter (for review see [39]). To assess neurodevelopmental changes in fetuses in relation to the metabolic status of the mother, we performed an OGTT in healthy pregnant women and measured fetal brain responses to auditory stimuli before, 60 and 120 minutes after glucose ingestion. While maternal insulin does not pass the placenta, the increasing blood sugar of the mother does. This causes a rise in fetal glucose levels, which in turn stimulates insulin secretion from the fetus' pancreas. 60 minutes after the pregnant mother ingested the glucose, a significant latency decrease of the biomagnetic signal originating from the fetal brain was revealed. Baseline levels were reached again after 120 minutes. A median split of the group based on the insulin sensitivity of the mother assessed by HOMA-IR showed that the decrease in latency was attenuated for mothers with decreased insulin sensitivity [40]. In a subsequent study, we included pregnant women with gestational diabetes, which is an insulin resistance occurring during gestation characterized by a hyperglycemic, hyperinsulinemic state. Under baseline condition, that is before glucose ingestion, the fetal brain responses of mothers with and without gestational diabetes did not show any differences [41••]. However, 60 minutes after glucose ingestion, fetuses of women without gestational diabetes again showed a decrease in latency compared to baseline, while this was not observable for fetuses of women with gestational diabetes. This indicates that the dearrangment of neuronal processes is a dynamic factor depending on postprandial metabolic parameters like glucose and insulin.

Discussion

Although EEG/MEG are the only non-invasive methods in human research that measure neuronal activity directly, recent brain imaging research is largely dominated by functional magnetic resonance imaging (fMRI). The major advantage of this method is that it has an improved spatial resolution and allows the investigation of deep brain structures like the hypothalamus or basal ganglia. For example Kullman et al. [42] showed that the insulin action in the hypothalamus depends on the visceral fat mass. In addition, it was shown that different regions of the hypothalamus are tightly connected to cortical areas in the human brain [43]. Then again, this method uses only proxies for neuronal activity like cerebral blood flow. These proxies have intrinsically a time resolution in the second range. EEG and MEG will be crucial to improve

Figure 1



Effect of insulin on neuronal activity in humans. Insulin can be delivered to the brain either by peripheral insulin which is transported to the brain or direct application to the brain by intranasal delivery. Insulin affects spontaneous activity, network dynamics and stimulus event-related responses. Insulin induced spontaneous activity is reduced with increasing body mass index (adapted from [22]). Activity in the visual cortex elicited by food pictures is different for lean and obese subjects and modulated by insulin in lean subjects but not obese (adapted from [49] and [38]). The network dynamics is described by certain indices quantifying the interconnections and functional integration and separation of the brain. The insulin sensitivity of the brain is modulated by factors including body mass index, body composition and genetic background.

the description of cortical process with higher temporal resolution to address functional interaction of cortical processes. In addition, these methods are highly valuable for special subject groups that are not accessible by other means. This is especially relevant for fetal brain development studies which can be performed completely non-invasive by fMEG. Further, EEG can be used in natural settings and can also be applied in specific subject groups like extremely adipose subjects which often have to be excluded in fMRI or MEG studies based on weight restrictions and accessibility of these systems.

In regard of future research in this area, we believe that it might benefit from more tailor-made research questions that exploit to a larger extent the specific advantages of the respective methods. This especially relates to our increased understanding of the functional significance of the different event-related components. For example, the N2 and P3 are commonly elicited by task relevant events in general, and have been linked to cognitive processes of stimulus identification, novelty, distinction and memory-updating processes [44]. Another very promising avenue is the usage of electrophysiological measures for the investigation of decision related processes [45], in particular how insulin and/or obesity may influence food related decision processes. Further, EEG and MEG research could largely benefit from the establishment of a stronger consensus between researchers concerning data analysis strategies. An important step in this direction has been made with the setup of several open source attempts [46] to improve data analysis and provide data analysis pipelines (for example see [47,48]).

Conclusion and future directions

Human brain imaging based on neuronal measurements clearly shows that the human brain is an insulin sensitive organ and that insulin action in the brain is modulated by various factors. Furthermore, obese subjects exhibit brain insulin resistance in spontaneous, stimulated and task studies (see Figure 1). This brain insulin resistance also seems to affect capabilities for improving metabolic health. The developmental trajectory of brain insulin resistance is, however, still largely unknown. Initial studies with brain imaging in human fetuses suggest that brain insulin resistance may already develop *in utero*. This fetal programming can indicate that brain insulin resistance is probably the cause of metabolic diseases instead of a consequence. But this remains open to debate and should be investigated further in future studies.

Conflict of interest

Nothing declared.

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