Morphological and functional Magnetic Resonance Imaging at ultra-high field

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Main findings

Following the title of this thesis ("Morphological and functional Magnetic Resonance Imaging at ultra-high field: Clinical research applications in preeclampsia and epilepsy"), the main findings can be divided into observations related to two disorders, e.g. preeclampsia and epilepsy.

Preeclampsia is a pregnancy-related hypertensive disorder, with vascular dysfunction at the center of the disease. It is a major cause of maternal and fetal morbidity, that results in an increased risk of cerebrovascular disease later in life. The neurovascular unit represents the structural and functional relationship between the brain tissue and blood vessels and, therefore, could play a role in preeclampsia. In the preeclampsia cohort described in this thesis, we found that different elements related to the neurovascular unit, but not brain morphology in terms of brain volume, are altered after preeclampsia. More specifically, we found that the local, but not global, functional network organization in formerly preeclamptic women, as measured with functional MRI, was different from control women with uneventful pregnancies. After preeclampsia, we demonstrated a higher local efficiency in the prefrontal cortex and anterior cingulate cortex, while a lower local efficiency and clustering coefficient was observed in the amygdala and parahippocampal cortex. Furthermore, another aspect of the neurovascular unit that was examined was the blood-brain barrier. The blood-brain barrier is an important member of the neurovascular unit that regulates transport between the blood and brain tissue. The integrity of the blood-brain barrier can be measured with dynamic contrast-enhanced MRI. When the blood-brain barrier is disrupted, the contrast agent leaks out of the blood vessels into the brain tissue, which can be measured as changes in signal intensity with dynamic contrast-enhanced MRI. For this we developed a new dynamic contrast-enhanced MRI protocol at 7 Tesla, which we applied in preeclampsia, and can also be used to assist future research. This continuous sampling dynamic contrast-enhanced MRI protocol was proven sensitive to a large range of leakage rates obtained with healthy volunteers and patients with cerebro-vascular disease. This novel 7 Tesla protocol was used to show a globally impaired blood-brain barrier years after a preeclamptic pregnancy.

Moreover, in the epilepsy cohort used in this thesis, we investigated the volumetric and functional lateralization of the hippocampus, hippocampal subfields, and frontal and temporal lobes. First, we found that the volume and function are highly symmetric in controls. Additionally, in temporal lobe epilepsy, but not frontal lobe epilepsy, volumetric and fluctuation amplitude lateralization effects, particularly in the hippocampal regions, were observed.

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Relevance

Previous research has shown that in some situations, clinical and neuroscientific research can benefit from moving to ultra-high field MRI. These benefits include the use of 7 Tesla MRI when small effects or changes are expected, such as after preeclampsia, or when concise delineation of brain structures, such as before surgery in patients with epilepsy, is needed. By moving to higher field strengths, images with greater detail and/or contrast can be acquired. This is related to the theoretical increase in signal-to-noise and contrast-to-noise ratios when moving to ultra-high field strengths. To describe the relevance of ultra-high field MRI, the studies in this thesis focus on the applications of morphological and functional MRI techniques in preeclampsia and epilepsy.

Worldwide, 6 – 8% of the pregnancies are complicated by preeclampsia, with 1800 – 5400 women diagnosed in the Netherlands every year. Preeclampsia is a hypertensive disorder related to pregnancy and cerebrovascular abnormalities are thought to play a role in the pathogenesis of preeclampsia. It is also known that hypertension alters the structure of the cerebral vasculature. However, the etiology of the cerebrovascular abnormalities in preeclampsia are still poorly understood. Additionally, preeclampsia is also associated with an increased risk of cardio- and cerebrovascular complications, as well as cognitive impairment, later in life. We have now obtained evidence that there may be a long-term role for the microvasculature in the brain after preeclampsia as formerly preeclamptic women showed a global increase in blood-brain barrier disruption and local alterations in the functional brain network. As microvascular dysfunction appears to be present, this could for instance play a role in the increased risk for cerebrovascular complications and (subjective) cognitive complaints which are often reported after preeclampsia. The relationship between blood-brain barrier breakdown and cognitive decline has previously been shown in several brain disorders, and also in normal aging. However, this relationship between the blood-brain barrier integrity and cognitive impairment was not investigated in this thesis. In the future, this should be investigated after preeclampsia and could help in the development of pharmaco-logical or lifestyle interventions to reduce the cerebrovascular risks and cognitive complications after preeclampsia.

7 Tesla MRI was also used in a study with patients with epilepsy. Epilepsy is one of the most common neurological disorders characterized by unprovoked recurrent seizures. The prevalence of epilepsy is between 4 and 10 per 1000 people worldwide. Approximately 60% of patients who have focal epilepsy develop drug resistance. In these patients, surgery is an important and successful treatment

option. A well-identified location of the epileptic focus has been associated with good surgical and seizure-free outcome, but in about 30% of the focal epilepsy patients, an epileptogenic lesion cannot be detected on EEGs and structural images acquired with 3 Tesla MRI. With ultra-high field, more frequently an epileptic lesion can be observed, which could improve surgical outcome. A lateralization analysis could help with the identification of the focus, but, in the future, the direct association between the focus and lateralization should be investigated further.

Finally, in this thesis, a novel dynamic contrast-enhanced MRI method at 7 Tesla to assess the blood-brain barrier disruption was introduced. Disruption of the blood-brain barrier may lead to leakage of toxic molecules into the brain and disturb the homeostasis, which will probably lead to brain dysfunction and/or damage. Assessing the condition of the blood-brain barrier is not only relevant in preeclampsia and epilepsy, but disruption of the blood-brain barrier is expected in many brain disorders. This dynamic contrast-enhanced MRI method can reveal more about the pathophysiology and role of the blood-brain barrier in various diseases. Therefore, it could be a useful tool to obtain an overview of the cerebrovascular health and help monitoring for an increased risk for cerebrovascular complications.

In a broader perspective, the work presented in this thesis illustrates potential applications of morphological and physiological brain MRI at 7 Tesla in preeclampsia and epilepsy. The current work expands on earlier studies that demonstrated the potential of 7 Tesla MRI in both healthy subjects and various clinical populations.

Target group

The findings in this thesis are of particular interest to other researchers, for instance (clinical) neuroscientists. This thesis describes a novel dynamic contrast-enhanced MRI protocol at 7 Tesla, which can be applied in different disorders, such as epilepsy, cerebral small vessel disease, and dementia. Our findings can also be a motivation for further research to investigate the underlying long-term pathology after pre-eclampsia, particularly related to cerebrovascular changes, which could explain the previously reported increased risks for cerebrovascular disorders after preeclampsia. Moreover, the current findings should be further investigated to establish the relation between cerebrovascular and cognitive changes after preeclampsia. These changes might also be of interest for the pharmaceutical industry, that could for instance focus on treatment aimed at preserving or restoring the cerebrovascular health, and lifestyle intervention policy makers, as the new insights in this thesis combined with future studies might emphasize the importance of treatment of

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cerebrovascular risk factors. This thesis also shows the potential of identifying the lateralization of an epileptic focus, and can, therefore, also be of interest for clinicians that aim to accurately detect an epileptic lesion before surgery.

On the other hand, our results can also be important for formerly preeclamptic women. These women often report cognitive and emotional complaints and the findings in this thesis could help to receive attention, awareness and understanding for their complaints. On the long run, the results of this thesis could also result in treatment options to reduce the negative effects and risks after preeclampsia. Finally, the findings in this thesis could be important for patients with epilepsy that are eligible for surgery as a better delineation of the epileptic focus increases the success for a seizure-free outcome after surgery.

Activities

The findings in this thesis have been presented in the research community through publications and presentations at scientific conferences (Kempenhaeghe conference 2017/2018/2019, Benelux chapter of the International Society for Magnetic Resonance in Medicine 2018/2019/2020, International Society for Magnetic Resonance in Medicine 2018, European International Society for Magnetic Resonance in Medicine and Biology 2019). The work from this thesis expands on earlier studies which demonstrated the potential of 7 Tesla MRI.

Furthermore, the preeclampsia cohort is part of the "Queen of Hearts" consortium, which consists of researchers from the five academic medical centers in the Netherlands, in which the risk factors of cardio- and cerebrovascular diseases in women are investigated. With this research, the goal is to recognize risk factors for cardio- and cerebrovascular disorders at an early stage to be able to start with preventive treatment options as early as possible. The research in this thesis can in the future help in this risk management program for cerebrovascular disorders.

Future directions

In this thesis, we applied several MRI techniques at 7 Tesla to investigate morphological and vascular aspects of the brain in preeclampsia and epilepsy.

Before the results from this thesis in the preeclampsia cohort can be of clinical use, future longitudinal studies are necessary to further investigate the associations

between a previous preeclamptic pregnancy and cerebrovascular pathology. In these longitudinal studies, the temporal changes in brain volume, blood-brain barrier disruption, functional network, white matter hyperintensities and mental health should be assessed to elucidate on the complex associations and sequence of events. Gaining this knowledge will also help to identify potential markers that can be used for monitoring of cardio- and cerebrovascular risk factors and the development of treatment strategies. Additionally, in patients with epilepsy we have shown the presence of lateralization of hippocampal regions. However, lateralization does not directly relate to the location of the epileptic focus. Therefore, before successfully adding the lateralization method in epilepsy to the clinical workflow for lesion detection, the results in this thesis should in the future be replicated in larger patient cohorts with known focus to investigate if there is a direct relationship. These findings should also be validated with post-surgical histology findings.

Given the results, the dynamic contrast-enhanced MRI method used was proven feasible of detecting group and tissue differences. However, the continuous sampling, dual-time resolution protocol applied in this thesis might require further development. These developments might include decreasing the total acquisition time and further increasing the detection sensitivity of small contrast agent concentration changes. Additionally, this method for assessing the blood-brain barrier leakage is prone to noise and is currently only applied to assess group differences. Therefore, noise reduction or even further increase of the signal to noise ratio should be performed for improvement of the MRI protocol. Furthermore, the reproducibility of the dynamic contrast-enhanced MRI protocol should be investigated to support the reliability of the application.

To conclude, in this thesis we presented the potential of 7 Tesla for new clinically relevant research applications, which led to answer new research questions.

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