# Neurotransmitters & networks

# Valorization

## Relevance

Thousands of MR studies have been performed to investigate functional brain networks and neurotransmitter concentrations. These studies are primarily performed in the fields of neurology, neurosciences and psychology. Two different aims can be distinguished in these studies: firstly, to increase the understanding of healthy or diseased brain functioning; and secondly, to detect biomarkers that might be used for diagnosis, to predict disease progression or treatment effects [1–3].

In this thesis, we focused on brain connectivity in epilepsy, and its relation to cognition. In the Netherlands, there are approximately 120,000 patients with epilepsy, and six-thousand new patients are diagnosed every year [4]. Epilepsy is often accompanied with cognitive problems, such as impaired memory, concentration, or slowed information processing speed [5]. These cognitive problems may be caused by the epilepsy itself, the underlying etiology, or as side effect of antiepileptic drug (AED) treatment. At this moment, neurologists have no objective means to predict who will develop adverse side effects or not.

We mainly focused on the effects AED treatment in this thesis. Cognitive side effects are among the least tolerated side effects for patients with epilepsy [6], and are an important reason to halt or change the AED treatment [7]. Besides a large burden for the patients, cognitive side effects are also accompanied with economic costs, including increased health care costs, productivity losses, and patients and family costs. The total societal costs of cognitive side effects are estimated to be around 7,000 € per patient per year in the Netherlands [8]. Better understanding of the relation between epilepsy, AED treatment, and cognition might help during clinical decision-making and ultimately improve treatment of patients with epilepsy.



## Main findings

In the first part of this thesis, clinical studies are presented that assessed associations between AED use, cognition, and MR markers. We observed associations between decreased information processing speed and lower glutamate concentrations. These glutamate concentrations were also associated with AED use. The second part of this thesis described methodological studies to neurotransmitter

measurements. We compared two methods to measure *in vivo* glutamate concentrations using MR spectroscopy: PRESS and MEGA-PRESS. This study showed a good accuracy for both methods, although the repeatability was better in PRESS than MEGA-PRESS. Finally, we developed a method to assess 'neurotransmitter networks', and showed an increased glutamate and GABA connectivity in patients with epilepsy.

## Target groups

First of all, the findings of this study are relevant for patients with epilepsy, as the findings might, in future, improve pharmacological treatment in epilepsy. This is also of interest for their neurologist, who might be better able to select proper treatment, and the pharmaceutical industry. Pharmaceutical applications of MRI are starting to develop, and MR markers might be beneficial to capture cognitive side effects or treatment efficacy in an early state, or to explore proper dose ranges [9].

The methodological part is mostly relevant for other researchers in the field of neurology, neurosciences and psychology, as it might aid new studies of the involvement of neurotransmitter levels in different neurological, psychological and psychiatric diseases. Therefore, other patients suffering from these diseases might benefit from these studies as well.

## Innovation and future directions

The studies presented in this thesis should be considered as explorations on the interplay of MR methods and epilepsy, AED treatment, and cognition. While advanced MR imaging of epilepsy and its consequences is an emerging field, MR studies to study AED effects are relatively scarce and to our knowledge, the studies in this thesis are the first that associate AED use and cognitive functioning to respectively neurotransmitter levels and functional brain organization. The observed associations between glutamate levels and cognitive function might be useful as biomarker to predict which patient will suffer from cognitive side effects, and who will not. However, it is currently not known whether the differences in glutamate levels precede the cognitive problems or coincide with these problems. Therefore, longitudinal studies to this topic are required.

The main objective of the comparison between PRESS and MEGA-PRESS was to aid future clinical studies aiming to measure glutamate concentrations. In our study, we applied both PRESS, to measure glutamate concentrations, and MEGA-PRESS, to measure GABA concentrations. We showed that the glutamate

concentration could also be measured with MEGA-PRESS; comparable studies might therefore choose to only apply a MEGA-PRESS scan, and thereby shortening the scanning time.

Neurotransmitter networks, described in Chapter 6, are a newly introduced concept and might provide new possibilities to study brain function. Future studies should aim at a further evaluation of this concept. Optimization is still possible at the acquisition and the analysis stage of the data. Furthermore, the concept should be tested in larger groups and in different populations, such as children or elderly, or in different brain diseases.

## References

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