Review

Metabolic and functional MR biomarkers of antiepileptic drug effectiveness: A review

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A R T I C L E   I N F O

Article history:
Received 4 March 2015
Received in revised form 7 October 2015
Accepted 12 October 2015
Available online 22 October 2015

Keywords:
Cognitive side effects
Treatment failure
Anticonvulsant
MR spectroscopy
Functional MRI

A B S T R A C T

As a large number of patients with epilepsy do not respond favorably to antiepileptic drugs (AEDs), a better understanding of treatment failure and the cause of adverse side effects is required. The working mechanisms of AEDs also alter neurotransmitter concentrations and brain activity, which can be measured using MR spectroscopy and functional MR imaging, respectively. This review presents an overview of clinical research of MR spectroscopy and functional MR imaging studies to the effects of AEDs on the brain. Despite the scarcity of studies associating MR findings to the effectiveness of AEDs, the current research shows clear potential regarding this matter. Several GABAergic AEDs have been shown to increase the GABA concentration, which was related to seizure reductions, while language problems due to topiramate have been associated with altered activation patterns measured with functional MR imaging. MR spectroscopy and functional MR imaging provide biomarkers that may predict individual treatment outcomes, and enable the assessment of mechanisms of treatment failure and cognitive side effects.

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1. Introduction

Despite the introduction of several antiepileptic drugs (AEDs) in recent decades, a large number of patients with epilepsy do not respond favorably to AEDs. Ideally, AED usage results in complete seizure freedom, without any unwanted side effects. However,
20–30% of the patients are drug resistant (or, synonymous, medically refractory), i.e. they do not reach seizure freedom after two adequately chosen, dosed and tolerated AEDs (Loscher et al., 2013). Furthermore, many patients suffer from unwanted side effects, even though the newer generation AEDs is suggested by pharmaceutical companies to have a more beneficial tolerability profile. Today, approximately 10–40% of the patients with epilepsy report side effects spontaneously or in (unstructured) interviews, while 60–90% of patients have been reported to suffer from side effects using validated screening methods (Perucca and Gilliam, 2012). The low effectiveness, i.e. the low combined efficacy and tolerability, results in early treatment discontinuation, high disease burden, and increased health care costs (Perucca and Gilliam, 2012; Toledoano and Gil-Nagel, 2008). Considering the need for improvement of the effectiveness, a better understanding of the mechanisms of drug resistance and the cause of side effects is highly desired. This knowledge might, in future, aid the realization of an objective, tailored choice of a specific AED in the individual patient.

Knowledge of the in vivo working mechanisms of AEDs is essential to understand drug resistance and side effects. Currently, most AEDs are discovered using animal screening models, in which the anticonvulsant effect of a compound is tested, prior to the exploration of the precise mechanisms of action (Loscher et al., 2013; Rogawski, 2006). Animal models are used to test for efficacy (Loscher et al., 2013) and side effects (Sankar and Holmes, 2004). The molecular mechanisms of action are assessed at a later stage using in vitro research, including studies in neuronal cell cultures, patch-clamp measurements, and biochemistry (Dichter and Pollard, 2006). These studies have resulted in some basic understanding of the different molecular mechanisms of the available AEDs. However, it still remains difficult to relate these mechanisms of action to the anticonvulsant effect of an AED in patients, mainly because the anticonvulsant effect is also influenced by the pharmacokinetic properties of the compound, such as its ability to cross the blood brain barrier or its metabolism (Brodie et al., 2011; Rogawski, 2006). Furthermore, the complexity of the brain limits a straightforward translation of in vitro effects of isolated neuronal cells to in vivo effects. Finally, in vitro or animal studies cannot completely assess potential side effects on cognition, which can only present themselves after administration in human subjects. Therefore, there is a need for alternative techniques that can assess the effects of AEDs on human brains.

Clinically, magnetic resonance imaging (MRI) is commonly used to provide anatomical information. These anatomical scans are also applied to assess effects of AEDs on for instance brain volume or cortical thickness (De Marco et al., 2003; Pardoe et al., 2013). However, there are also MR techniques available that provide information beyond the anatomy, such as metabolism and function, which expectedly are more sensitive to AED treatment. MR spectroscopy (MRS) enables in vivo measurements of neurotransmitter and other brain metabolite concentrations, and can therefore be employed to gather insight in the metabolism of AEDs (Puts and Edden, 2012; Ross and Sachdev, 2004). Another technique is functional MRI (fMRI), which can provide a measure of drug effects on brain activity (Wise and Tracey, 2006). These MRI assessments are noninvasive, which makes them suitable for repeated measurements, as no contrast agents or ionizing radiation are necessary, in contrast to other imaging techniques such as computed tomography (CT) or positron emission tomography (PET).

An overview of the previous MRS and fMRI studies to the effects of AEDs on the brain is presented in this review. These MR techniques are sensitive to brain metabolism and function, respectively, which are both directly related to the AED mechanisms of action. Special attention is paid to the possible relation of MR measures with drug resistance and central nervous system (CNS) mediated side effects of AEDs.

### Table 1
Molecular targets of anti-epileptic drugs (Fisher, 2011; Kwan et al., 2001; Rogawski and Loscher, 2004; Stephen and Brodie, 2011; White et al., 2007).

<table>
<thead>
<tr>
<th>AEDs</th>
<th>Voltage-gated ion channels</th>
<th>Neurotransmitter systems</th>
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<tbody>
<tr>
<td>Benzodiazepines:</td>
<td>GABA system</td>
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<tr>
<td>Clonazepam</td>
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<td>Midazolam</td>
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<td>Carbamazepine</td>
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<tr>
<td>Ethosuximide</td>
<td>Na+, (Na+), Ca2+</td>
<td>GABA system, glutamate receptors</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Na+, Ca2+</td>
<td>GABA system, glutamate receptors</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>(Na+), (Ca2+)</td>
<td>GABA system, glutamate receptors</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>(Na+)</td>
<td>Glutamate receptors</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Na+, (Ca2+)</td>
<td>(GABA system, glutamate receptors)</td>
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<td>Levetiracetam</td>
<td>(Ca2+)</td>
<td>(GABA system, glutamate receptors)</td>
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<tr>
<td>Oxcarbazepine</td>
<td>Na+, (Ca2+, K+)</td>
<td>GABA system, (glutamate receptors)</td>
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<td>Phenytoin</td>
<td>Na+</td>
<td>GABA system, (glutamate receptors)</td>
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<td>Pregabalin</td>
<td>Ca2+</td>
<td>GABA system</td>
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<td>Retigabine</td>
<td>K+</td>
<td>GABA system</td>
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<td>Stiripentol</td>
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<td>GABA system</td>
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<td>Tiagabine</td>
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<td>GABA system</td>
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<tr>
<td>Topiramate</td>
<td>Na+, Ca2+</td>
<td>GABA system, glutamate receptors</td>
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<tr>
<td>Valproate</td>
<td>(Na+, Ca2+)</td>
<td>GABA system, (glutamate receptors)</td>
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<tr>
<td>Vigabatrin</td>
<td>Na+, Ca2+</td>
<td>GABA system</td>
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*Not all molecular mechanisms are well understood; possible molecular targets are displayed between parentheses.*

2. Methods

A literature study was performed in Medline/PubMed on August 7, 2015, using the Medical Subject Headings (MeSH) ‘anti-convulsants’, ‘Magnetic Resonance Spectroscopy’ and the terms ‘functional MRI’ or ‘fMRI’ and ‘treatment failure’. Additionally, separate searches were performed per individual AED (the considered AEDs are listed in Table 1). Furthermore, relevant references from the reviewed articles are included. Only articles written in English and performed in human subjects are considered. The abstracts of the resulting articles were screened to select only the relevant articles, i.e. articles describing effects of AEDs detectable with MRI, or relating MRI outcomes to seizure reduction or side effects. Studies describing the effects of AEDs in patients with other types of disorders than epilepsy were omitted, because of potential differences in working mechanisms in different diseases, and unknown effects of comorbidities. Studies comparing patients with epilepsy using AEDs to healthy controls not using these AEDs were also omitted, because the effect of the epilepsy itself and drug use cannot be distinguished in these studies.

3. Pharmacodynamic and pharmacokinetic mechanisms of action

Epileptic seizures are characterized by excessive, synchronal neuronal activity in the brain. AEDs, ideally, suppress this activity via several distinct mechanisms, which can be divided into three main categories: (1) Modulation of the voltage-gated ion channels, i.e. of the sodium or calcium channels, and, less common, of the potassium channels. This modulation can result in a more stable membrane potential, reduced release of neurotransmitters, and a reduction in seizure spread. The exact effects of this modulation depend on the specific channel type. (2) Elevation of the seizure threshold by targeting the γ-aminobutyric acid (GABA) system. The
GABA system can be affected by two mechanisms: by increasing the sensitivity of the GABA_A receptors or by augmenting the GABA concentration. (3) Reduction of the excitatory neurotransmitter. AEDs with the latter mechanism function as antagonists of the glutamate receptors (Rogawski and Loscher, 2004; White et al., 2007). Several AEDs combine different mechanisms, and the mechanisms are not completely understood for all AEDs (Table 1).

In addition to these pharmacodynamic mechanisms, pharmacokinetic properties contribute to the positive and negative effects of AEDs. Pharmacokinetic properties include the absorption, distribution, metabolism, and excretion of a compound. These factors can differ greatly among different users and with different AEDs, and complicate the prediction of the efficacy and the tolerability in individual patients (Johannessen Landmark et al., 2012).

Unfortunately, the mechanisms that aim to suppress epileptic seizures can also affect normal brain activity. Modifying these mechanisms can also induce side effects. These CNS mediated side effects include sedation, coordination disturbances, cognitive difficulties, and behavioral problems. Although the probability and severity of these side effects depend on the AED type, several of these events are quite similar among the different AEDs (Perucca and Gilliam, 2012). Also several non-CNS mediated side effects can occur with the use of AEDs, which might result from pharmacokinetic properties, interaction effects, or effects on other organ systems and the immune system (allergic reactions) (Perucca and Gilliam, 2012; Toledo and Gil-Nagel, 2008).

Treatment failure is defined as the appearance of recurrent seizures after adequate intervention (Kwan et al., 2010). Treatment failure in previous AEDs is a strong indicator of treatment failure for new AEDs: While approximately 62% of the patients became seizure free after the first, adequately chosen AED, only 17% of the patients became seizure free after failure of two to five adequately chosen AEDs in a cohort study of 478 patients with newly administered AEDs and various epilepsy types (Schiller and Najjar, 2008). The mechanisms of treatment failure and drug resistance are also still largely unknown, and both pharmacodynamic and pharmacokinetic properties are likely to be involved in these mechanisms. Several hypotheses have been formulated which explain treatment failure in patients with epilepsy, of which the transporter and the target hypothesis are most popular. The transporter hypothesis argues that AEDs cannot sufficiently penetrate the epileptogenic brain tissue, as a result of increased expression of efflux transporters in the blood–brain barrier. According to the target hypothesis, AEDs are able to reach the ion channels or receptors, but cannot exert their function due to structural and/or functional alterations of these targets. A combination of the above listed hypotheses and other mechanisms (including inflammatory, epigenetic, and also unknown pathways) most likely cooperate in some way to drug resistance in epilepsy (Loscher et al., 2013; Schmidt and Loscher, 2005).

4. Magnetic resonance spectroscopy

AEDs exert their anticonvulsant properties by affecting the excitatory and inhibitory neurotransmitter systems. Effects on the GABA and glutamate concentrations can be measured directly in vivo using 1H MRS (proton MRS). The merit of 1H MRS is based on the shielding effect of the chemical environment of protons, which causes a small shift in resonance frequency. 1H MRS results in a spectrum with peaks at different resonance frequencies, characteristic for different molecule groups (Fig. 1). The area underneath these peaks is proportional to the concentration of the molecule. Whether it is possible to measure a particular metabolite depends on its concentration in the brain, spectral overlap with other metabolites, and spin–spin interactions, which can result in lower resonance peaks (Puts and Edden, 2012).

GABA and glutamate both are subject to spectral overlap and spin–spin interactions (Fig. 1). Special editing techniques or 2D 1H MRS are commonly used to resolve this problem (Henry et al., 2011; Puts and Edden, 2012). These techniques enable a reliable estimation of the concentration of the metabolites (Henry et al., 2011). Due to their overlapping resonances, the glutamate and glutamine concentrations are frequently combined, resulting in a so-called ‘Glx’ concentration. Other metabolites which are commonly measured using 1H MRS include N-acetyl aspartate (NAA), creatine or choline-containing compounds. The functions of these metabolites are elaborately discussed elsewhere (Govindaraju et al., 2000; Rae, 2014).

Several AEDs with a GABAergic mechanism of action have been shown to elevate GABA concentrations in the brain, including vigabatrin (VGB) (Mueller et al., 2001a; Novotny et al., 1999; Petroff et al., 1995, 1999a, 1999d; Verhoeff et al., 1999; Weber et al., 1999), topiramate (TPM) (Kuzniecky et al., 1998, 2002; Petroff et al., 1999b, 2001b) and gabapentin (GBP) (Cai et al., 2012; Kuzniecky et al., 2002; Petroff et al., 1996a, 2000) (Fig. 2). Elevated GABA concentrations were already detectable within hours after intake of a single dose and also appeared during chronic VGB, TPM and GBP use, although no effects of a single low dose GBP on the GABA concentration were found by Preuss et al. (2013). There is a linear relation between the VGB dosage and the resulting GABA concentration. However, with high VGB dosages, the GABA concentration does not increase any further and reaches a plateau (Petroff et al., 1996b). The GABA concentration was related to seizure reduction in patients with focal epilepsy with VGB (Petroff et al., 1996c) and GBP use (Petroff et al., 1996a). Moreover, a relation was found between seizure reduction and the GABA concentration before and during VGB treatment in patients with poorly controlled focal epilepsy (Mueller et al., 2001b). Patients with focal epilepsy with complete seizure control had a lower baseline GABA concentration in the epileptic hemisphere, compared with the non-epileptic hemisphere, and a significant increase of GABA. However, patients with no VGB-induced seizure reduction did not reveal concentration differences between the hemispheres or a significant increase in GABA concentration. The pretherapeutic concentration differences between the hemispheres correlated with the seizure reduction during VGB treatment (Mueller et al., 2003). These results suggest a causal relation between GABAergic mechanisms of action, the increase in GABA concentration, and seizure reduction. However, this causal link cannot be proven using these radiological techniques in human studies.

In contrast to these results, no effects of a single dose of tiagabine (TGB) on the GABA concentration were found in healthy participants by Myers et al. (2014), although TGB is an AED with a solely GABAergic mechanism of action as well. Generalizations across the different AEDs should be considered with caution, because the mechanism of action each individual AED is unique even for chemically related AEDs.

The effects of levetiracetam (LEV) on the GABA concentration are not clear. The mechanisms of action of LEV are not completely understood but according to literature it has probably multiple mechanisms of action, including a GABAergic mechanism (Rogawski and Loscher, 2004). While one study showed a significant increase in the GABA concentration after LEV use in patients with focal epilepsy who had a seizure reduction (Doelken et al., 2010), another study failed to show effects on the GABA concentration in healthy participants (Kuzniecky et al., 2008). Besides the difference in participants (patients with focal epilepsy versus healthy people), this difference might be explained by the timing of the measurements: the MRS measurements were performed before and 2–6 weeks after initiation of LEV treatment in the patients with
epilepsy, while the measurements were performed before, at 3 and
at 6 h after a single dose of LEV in the healthy participants.

The effect on the GABA concentration of AEDs without a known
GABAergic mechanism of action is rarely assessed. However, ele-
vated GABA concentrations are shown in healthy participants with
lamotrigine (LTG) use, albeit only after four weeks use and not
directly after a single dose or after 2 weeks of LTG use, imply-
ning that the GABA concentration is increased by indirect effects
of LTG (Kuzniecky et al., 2002).

Also the effects of AEDs on the homocarnosine and pyrroli-
dine metabolites were assessed. These metabolites are precursors
of GABA and have been suggested to have anticonvulsant proper-
ties themselves (Petroff, 2002). The homocarnosine and pyrroli-
dine concentrations were shown to increase with the use of TPM
(Petroff et al., 1999b, 2001b), VGB (Petroff et al., 1998, 1999a) or GBP
(Petroff et al., 2000). The authors suggested that homocarnosine
(and not GABA) is associated with seizure reduction in patients with
focal epilepsy using TPM and GBP (Petroff et al., 2006), using VGB
(Petroff et al., 1998), or in a group of patients with focal epilepsy
or juvenile myoclonic epilepsy using valproate (VPA) or LTG (Petroff
et al., 2001a).

The effects of AEDs on the glutamate concentration are also not
clear. Articles assessing the effects of GBP (Cai et al., 2012; Preuss
et al., 2013), benzodiazepines (Brambilla et al., 2002; Henry et al.,
2010), VPA (Simister et al., 2007), or TPM (Moore et al., 2006) on
the glutamate, glutamine, or Glx concentration failed to show con-
sistent results. In contrast to the GABAergic mechanisms, AEDs do
not alter the glutamate concentrations directly, but rather decrease

![Fig. 1](image_url) Fig. 1. (A) Example of magnetic resonance spectrum measured in the occipital lobe of a healthy human. The concentrations of NAA, creatine and the choline-containing compounds are relatively high in the brain, resulting in large resonance peaks. Although GABA, glutamate and glutamine are also abundant in the brain, their resonance peaks are much smaller because of spin–spin interactions. The 4CH group of GABA has approximately the same resonance frequency as the 2(CH3) group of creatine and is only measurable using advanced acquisition or analysis methods (Govindaraju et al., 2000). The same holds for glutamate and glutamine. (B) Estimations by LCModel (Provencher, 2001) of the contribution of single molecules to the spectrum displayed in (A) Cho: choline-containing compounds; Cr: creatine; GABA: γ-aminobutyric acid; Glu: glutamate; Gln: glutamine; NAA: N-acetyl-aspartate; ppm: parts per million.

![Fig. 2](image_url) Fig. 2. Graphs illustrating the effect of topiramate on the GABA concentration, as measured with MR spectroscopy. (A) Serial GABA spectra of a patient with epilepsy before and after use of topiramate. This spectrum, measured using a special editing technique, shows an increase in GABA concentration in an individual patient (Reprinted from Petroff et al., 1999b). (B) Time changes of the GABA concentrations (dashed line) and serum topiramate (TPM, solid line) levels before and during TPM use (Reprinted from Kuzniecky et al., 2002). The GABA concentration is significantly increased compared with the baseline concentration during TPM use. * p < 0.001, ** p < 0.006, *** p < 0.002, **** p < 0.005. GABA: γ-aminobutyric acid; ppm: parts per million, h: hours, w: weeks.
the sensitivity of the glutamate receptors. The glutamate concentration might be decreased through the negative modulation of the voltage-gated channels, which are affected by most of the AEDs. Indirectly, AEDs might also affect the concentrations of other metabolites. Campos et al. (2010) showed decreased NAA concentrations in patients with focal epilepsy who did not respond to their AED treatment compared with responders one to two years after initiation of AED therapy. As the NAA concentration is generally associated with neuronal density or integrity, these results suggest that treatment failure can be associated with neuronal damage. The choline concentration did not differ between these responder groups. Furthermore, patients with various types of epilepsy using VPA showed reduced myo-inositol concentrations compared with patients taking other AEDs, but similar NAA and creatine concentrations (Simister et al., 2003, 2007). The authors argue that the myo-inositol reductions are not likely to be related to the antiepileptic efficacy of VPA. In healthy participants, no changes in the NAA or choline concentrations were measured after GBP intake (Preus et al., 2013), and also lorazepam intake did not affect the NAA, creatine, myo-inositol, or trimethylamine concentrations (Brambilla et al., 2002).

Effects on neurotransmitter concentrations can also be measured in animal models. However, the results of animal studies do not always correspond to human studies. For instance, the effect of TPM on the GABA concentration was not predicted by animal models (Petroff et al., 1999b). Moreover, homocarnosine concentrations are much lower in rodents compared to humans, while homocarnosine is suggested to be involved in the anticonvulsant mechanisms (Petroff et al., 1999b). The results of Kuzniecky et al. (2002), showing long-term elevations of GABA after LTG use, illustrate that also AEDs without a known GABAergic mechanism can (indirectly) alter the GABA concentrations. This necessitates human in vivo measurements.

5. Functional MRI

fMRI uses the blood oxygen level dependent (BOLD) effect to indirectly measure brain activity. By comparing the BOLD signal of a baseline condition to a situation with a task, an activity measure for the brain areas involved in this task can be obtained (Wise and Tracey, 2006). BOLD measurements can also be performed without a certain task. This so-called resting state fMRI measures the spontaneous fluctuations of the ongoing neural signaling. The spontaneous fluctuations show correlations between several distinct brain areas, and these correlations are assumed to reflect intrinsic functional connections. Advanced analysis techniques, such as independent component analysis or graph theory, can be applied to assess the functional brain connectivity (van den Heuvel and Hulshoff Pol, 2010).

It is plausible to assume that AEDs, by suppressing the epileptiform activity, also affect normal brain activity and thereby the BOLD signal. Different brain areas might be more susceptible to AED actions compared with other regions, as AEDs exert their function on specific receptors which might be more prominent in specific brain areas than other. fMRI can be used to identify these altered activation patterns in relation to CNS-mediated side-effects or treatment failure.

Several studies employing task fMRI indeed show that AEDs have different effects on brain activation patterns in healthy participants (Aupperle et al., 2012; Del-Ben et al., 2012; Iannetti et al., 2005; Li et al., 2004; Munoz-Torres et al., 2011; Paulus et al., 2005; Ragnedhe et al., 2007) or in patients with drug-resistant temporal lobe epilepsy (Jokeit et al., 2001). These effects vary among AEDs (Li et al., 2010, 2011) and depend on the specific task performed during the measurements (Bell et al., 2005). While AEDs mainly attenuate the activation patterns, as can be expected from their mechanisms of action, also enhanced activation during AED use has been reported (Aupperle et al., 2011). This seemingly contradictory result could be an indirect effect of attenuated activation in other brain areas, or result directly from AED mechanisms, as a computer simulation showed that modulation of the sodium channels by phenytoin or carbamazepine can also lead to increased excitation (Thomas and Petroz, 2013).

Using graph analysis, a lower hubness (‘the presence of hyper-connected nodes that connect distant parts of the brain’) was found in patients with temporal lobe epilepsy using carbamazepine or oxcarbazepine compared with patients using other AEDs, implying a less efficient organization (Haneef et al., 2015). Relating these findings to anticonvulsant mechanisms or the development of CNS mediated side effects was outside the scope of these articles.

Other studies assessed associations between cognitive side effects, brain activation and TPM, which induces cognitive side effects including language disturbances (Kwan and Brodie, 2001). In a study comparing patients with cryptogenic (i.e. with unknown cause) focal drug resistant epilepsy using TPM with patients using other AEDs, several language areas appeared to be significantly underactivated during a language task in the patients using TPM (Fig. 3). Decreased activation in these areas was also correlated to the language problems (Jansen et al., 2006). Similar results were found in patients with migraine treated with TPM (De Ciantis et al., 2008). Another study found comparable differences in brain activation between patients with temporal lobe epilepsy using TPM and patients using other AEDs, although the observed differences also depended on the lateralization of the epileptic focus (Szafarski and Allendorfer, 2012). Besides effects in language areas, patients with frontal lobe epilepsy taking TPM showed a reduced deactivation of the default mode network (Yasuda et al., 2013). The default mode network consists of functionally connected brain areas which are active during rest, but deactivate during tasks. Appropriate deactivation of this network is considered necessary for correct task performance.

In contrast to TPM, LEV does not negatively affect cognitive abilities, and is even suggested to improve cognitive function (Kwan and Brodie, 2001). Patients with temporal lobe epilepsy taking LEV showed more deactivations in the ipsilateral mesial temporal structures compared with patients using other AEDs during working memory tasks (Wandschneider et al., 2014). Stronger deactivation in these structures is commonly associated with improved functioning (Wandschneider et al., 2014). Whether this reduction was also associated with better cognitive functioning in this study was not reported.
Treatment failure is hypothesized to be caused by alterations of the blood–brain barrier or the molecular targets of the AEDs (Loscher et al., 2013). Because of these alterations, AEDs cannot exert their function in the epileptogenic brain tissue. However, the location of this epileptogenic brain tissue varies largely between patients, while fMRI is mainly employed to assess the susceptibility of distinct brain areas to the effects of AEDs. In case fMRI experiments are combined with knowledge about the epileptic focus, fMRI might provide new information about mechanisms of action.

Interestingly, Kay et al. (2013) also showed associations between treatment resistance and functional connectivity. Patients with idiopathic generalized epilepsy resistant to AEDs showed a reduced connectivity in the default mode network compared with patients who did show a seizure reduction. Whether this is a consequence of the drug resistance (i.e. the continuing seizures) or is preceding the drug resistance remains unknown.

6. Limitations

The application of MR techniques in AED treatment is still in its infancy, and several research gaps need to be bridged before these techniques can prove their clinical utility. Currently, the number of MR studies assessing the effects of AEDs is limited, and only a few studies relate MR outcomes to either seizure reduction or CNS mediated side effects. Furthermore, many of the included articles have low participant numbers and have to deal with practical constraints such as polytherapy and possible confounding effects of the epilepsy itself, limiting the quality of these studies.

Beside these general study limitations, the different MR techniques also have some limitations. The interpretation of $^1$H MRS findings is currently debated (Duncan et al., 2014; Stagg et al., 2011). $^1$H MRS measures all available neurotransmitters: both synthetically and extrasynthetically (presynaptic terminals, synaptic vesicles or neurotransmitter uptake mechanisms), and it is not known where and how these neurotransmitters act precisely (Duncan et al., 2014). $^1$H MRS is also only able to measure the neurotransmitter concentrations but not the receptor sensitivity, while this sensitivity is affected by AEDs in particular and could be crucial for effectiveness. Furthermore, the neurotransmitter concentrations are usually measured in a large, single voxel located in the occipital brain regions, whereas the majority of the side effects concerns functions dependent on other brain regions. The use of smaller voxels or voxels located in those other brain areas is limited by the signal-to-noise ratio (SNR) and magnetic field inhomogeneities.

Moreover, most AEDs exert their anticonvulsant activity using several mechanisms, and the interaction between these mechanisms is largely unknown. Only analyzing the effects of the AEDs on the GABA concentration might therefore be too simplistic. Although currently not many effects of AEDs on the glutamate concentrations are shown, it is recommended to measure this concentration as well to have an indication of the balance between the main inhibitory and excitatory mechanisms.

No general conclusions can be drawn about the specific effects of AEDs on the brain activity. Most fMRI studies are performed with specific tasks, and the results of these studies are difficult to generalize because of their task-dependency. Another drawback of fMRI studies is that some AEDs might affect the blood flow and thereby the BOLD signal, irrespective of their antiepileptic effect. These effects should be considered in future fMRI studies to AEDs. For instance, fMRI studies can be combined with arterial spin labeling measurements, to measure the blood flow (Detre et al., 2012).

7. Perspectives

Despite these limitations, both MRS and fMRI results show potential promising applications in future AED research. The suggested relation between GABAergic mechanisms of action, the GABA concentration measured using MRS, and seizure reduction implies several possibilities. First, the GABA concentration can be used as a biomarker for seizure reduction, enabling an earlier indication of treatment failure than clinical evaluation. Furthermore, MRS might provide insights in the development of CNS mediated side effects. The mechanisms responsible for this development still remain largely unknown, although some studies hypothesize that GABAergic mechanisms are involved (Jansen et al., 2006; Sankar and Holmes, 2004). By providing a tool to measure the effects of these GABAergic mechanisms, MRS might indicate whether these mechanisms can indeed be associated with CNS mediated side effects. Therefore, MRS might provide valuable information for the selection of the most suitable AED, or exclusion of AEDs which are less suitable, prior to or soon after initiation of treatment. These potential utilities can only be proven after future suitable studies.

fMRI might be employed to pinpoint the neuronal substrate of the side effects. Abnormal activation patterns could possibly explain in part why some patients experience more and others less CNS mediated side effects, and might even predict this for individual patients. Furthermore, the occurrence of side effects might be predicted for new antiepileptic compounds, if it is known how AED effects on brain activity are associated with these side effects.

New studies should focus on the usefulness of these MR techniques for different types of epilepsy, especially when relating treatment failure to MR outcome. Treatment failure is more common in specific epilepsy syndromes (Ohtahara syndrome, early myoclonic encephalopathy, West syndrome, Dravet syndrome, or Lennox–Gastaut syndrome) and underlying etiologies (hippocampal sclerosis, cortical dysplasia, hemorrhage) (Beleza, 2009), and the mechanisms of drug resistance might depend on the specific brain pathology (Schmidt and Loscher, 2005). MRS and fMRI might also be employed to assess the effects of other epilepsy treatments, such as the ketogenic diet, and compare these to AED effects on brain metabolite concentrations or activation patterns (Wang et al., 2003).

Novel, and more advanced MR technologies offer new opportunities to overcome many of the current limitations. With the use of higher magnetic field strengths, the SNR of MRS can be increased. Smaller voxels, frontally located voxels, and even multivoxel MRS becomes feasible with 7 T MR studies (see for instance Pan et al., 2013). These studies can increase the knowledge of regional effects of AEDs on the neurotransmitter concentration. Besides $^1$H MRS, also $^{13}$C MRS can be employed. This method enables the assessment of neurotransmitter cycling and human brain energetics, although $^{13}$C MRS is less accessible than $^1$H MRS due to the low natural abundance of $^{13}$C and the need for labeled compounds and special hardware (Rothman et al., 2011). Furthermore, while MRS does not measure the receptor sensitivity, multimodal studies combining PET and MRS enable assessments of both receptor sensitivity and neurotransmitter concentrations (Weber et al., 1999).

Finally, contrast-enhanced MRI allows for the assessment of the blood–brain barrier integrity, which could be an important feature of treatment failure (van Vliet et al., 2014).

The advanced analysis methods for fMRI data provide opportunities to assess the functional brain connectivity. This functional brain connectivity might be more related to cognition than brain activity patterns (van den Heuvel et al., 2009), and therefore more relevant to assess especially cognitive side effects than task-related activity analysis. These methods are often employed in combination with resting state fMRI, thereby also omitting the
task-dependence of the results (van den Heuvel and Hulshoff Pol, 2010).

To conclude, MR techniques provide several unique possibilities to assess neuronal substrates of the effectiveness of AEDs, which might be employed for future individualized patients care. These possibilities are supported by the technological improvements of the last decade, which open new possibilities to apply fMRI and MRS to assess AED mechanisms and effects. However, future studies are still necessary to investigate the potential of the different MR techniques to provide biomarkers, to predict treatment outcome or to assess the mechanisms of treatment failure and side effects.

References


