IMAGING BIOMARKERS OF ANTI-EPILEPTIC DRUG ACTION: INSIGHTS FROM MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY

Lorenzo Caciagli[1,2], Fenglai Xiao[1,2,3], Britta Wandschneider[1,2], Matthias J. Koepp[1,2]

[1]*Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London, United Kingdom*

[2]*MRI Unit, Epilepsy Society, Chalfont St Peter, Buckinghamshire, United Kingdom*

[3] *Department of Neurology, West China Hospital, Sichuan University, Chendgu, Sichuan, People's Republic of China*

Correspondence to

Prof. Matthias Koepp, MD PhD

Department of Clinical and Experimental Epilepsy

UCL Institute of Neurology

Queen Square, London WC1N 3BG, UK

MRI Unit, National Society for Epilepsy

Chalfont St Peter, Buckinghamshire, SL9 0RJ

Tel. 01494601300

Fax 0149487464

E-mail: m.koepp@ucl.ac.uk

ABSTRACT

Background: Approximately one third of patients with epilepsy are refractory to medical treatment. Adverse effects associated with anti-epileptic drugs (AEDs) are considered to affect quality of life often more than the seizures themselves. Neuroimaging techniques, in particular magnetic resonance imaging (MRI), have proven instrumental in clinical decision making in relation to epilepsy surgery, but may also provide further insights into the mechanisms underlying treatment response and side effects associated with AEDs.

Objective and Method: We searched PubMed and Ovid Medline databases for original articles and reviews published in the last two decades, which addressed the effects of AEDs on MRI and magnetic resonance spectroscopy (MRS) measures.

Results: The majority of investigations implemented task-based fMRI, and probed the influence of widely used anti-epileptic drugs on tasks assessing language, executive functions and emotion recognition. Collectively, MRI is able to detect reproducible AED-related effects on regions and networks relevant to disease pathomechanisms, and so elucidates the anatomo-functional substrates of cognitive side effects. MRS analyses shed light on the molecular correlates of AED action, and may provide indicators of treatment response.

Conclusion: MRI and MRS have considerably improved our understanding of the effects of AEDs at a regional and network level, and provide biomarkers with potential to improve routine clinical decision making in epilepsy.

KEYWORDS

Antiepileptic drug, MRI, functional MRI, MR spectroscopy, biomarker, cognitive side effects, drug response

1. INTRODUCTION

Epilepsy is characterized by the neurobiological, cognitive, psychological, and social consequences of this condition, which are confounded by treatment. . Refractoriness to pharmacological treatment, termed as 'drug-resistance', is estimated to occur in about 30% of patients with epilepsy (Sander, 2003; Kwan *et al.*, 2010), despite significant advances in drug development over the last two decades, leading to more than twenty anti-epileptic drugs (AEDs). Moreover, AED-correlated adverse effects play a role in determining treatment failures, are associated with morbidity and mortality, and can considerably affect quality of life of people with epilepsy (Perucca and Gilliam, 2012).

Neuroimaging, in particular magnetic resonance imaging (MRI), contribute to diagnosis and clinical management (Bernasconi *et al.*, 2011; Duncan *et al.*, 2016). Advanced MRI techniques prove useful in characterising functional and structural brain networks *in vivo* (Honey *et al.*, 2007; Sporns, 2012; Bernhardt *et al.*, 2013; Caciagli *et al.*, 2014), and provide objectively measurable traits, which exhibit validity as indicators of biological processes as well as high test-retest reliability, thus fulfilling the defining criteria of a *biomarker* (??? 2001; Koepp, 2016). Given their ability to identify anatomo-functional markers of disease effects, MRI techniques have also been utilised to detect measurable responses to pharmacological interventions, with the aim to optimise medication choices at the individual level, and aid rationalisation of polytherapy strategies (van Veenendaal *et al.*, 2015; Wandschneider and Koepp, 2016). In this context, functional MRI (fMRI) investigations shed light on regional and network-level dynamics, and may prove particularly sensitive in unveiling drug-related effects (Nathan *et al.*, 2014; Beltramini *et al.*, 2015). As well as identifying markers of treatment response and dose-response relationships, fMRI also conveys the possibility to address a variety of cognitive functions via specific tasksrelevant to epilepsy, which is accompanied by cognitive comorbidities. with AEDs often causing additional cognitive side effects (Ortinski and Meador, 2004; Hermann *et al.*, 2008; Mula and Trimble, 2009).

In this review, we will summarise the most recent studies investigating the effects of common AEDs on MRI parameters. We will focus first on pharmacological fMRI (phMRI) studies, though relevant insights from other, structural MRI and magnetic resonance spectroscopy (MRS) metrics will also be discussed. to probe the neurochemical underpinnings of AED effects *in vivo*.

2. MRI BIOMARKERS OF AED ACTION: AN OVERVIEW

Ph-MRI study designs provide imaging correlates of AED effects. While structural MRI metrics evaluate the integrity of grey matter structures and of the interconnecting white matter tracts, fMRI conveys an indirect measure of neuronal activity via the Blood-Oxygen-Level-Dependent (BOLD) contrast, which arises from localised changes in the ratio between oxygenated and deoxygenated haemoglobin owing to metabolic demands driven by neuronal activity (Ogawa *et al.*, 1990; Logothetis *et al.*, 2001). Functional MRI data can be acquired while participants engage in specifically designed paradigms, which generate activation and deactivation patterns pertaining to brain regions subserving language, executive functions, episodic memory and sensory-motor processing (Rao *et al.*, 1993; Owen *et al.*, 2005; Kim, 2011; Price, 2012). In addition, "resting-state" fMRI sequences are commonly used, which specifically address spontaneous fluctuations of BOLD signal occurring during rest (i.e., *task free* conditions)(Fox and Raichle, 2007), and identify stable and reproducible sets of regions with strongly correlated signal time-courses, and high correspondence with task-implicated systems (Damoiseaux *et al.*, 2006; Biswal *et al.*, 2010).

Ph-MRI studies have thus far been conducted mostly via task-based fMRI. Here, effects associated with pharmacological agents are predominantly shown as interaction effects, whereby a comparison takes place between activation patterns in subjects on drugs against placebo, or against subjects not taking the drug (Mehta and O'Daly, 2011). Randomised, double-blind, within-subject designs have also been implemented, though predominantly for assessments targeting psychiatric populations (Hafeman *et al.*, 2012). The impact of drugs can be examined at a regional as well as at a network level, formalising connectivity properties via measures of statistical dependency between spatially separate BOLD time courses (Friston, 2011). Compared to other *in vivo* techniques, including positron emission tomography (PET), the advantage of pharmacofMRI is to potentially assess large-scale systems providing snapshots of network architecture across multiple scales and during different tasks, irrespective of the pharmacodynamic properties of a given compound (Borsook *et al.*, 2006; Nathan *et al.*, 2014). This resulted in pharmacofMRI to be used not only to investigate already marketed drugs, but also in the context of drug discovery (Nathan *et al.*, 2014).

This review summarises pharmaco-fMRI studies of the most frequently prescribed AEDs. Where appropriate, analyses investigating the impact of AEDs on structural MRI metrics are also considered. (Hafeman *et al.*, 2012).

2.1 TOPIRAMATE AND ZONISAMIDE

Topiramate (TPM) is currently approved for the treatment of epilepsy, in monotherapy as well as an add-on compound, and is additionally licensed for migraine prophylaxis (Bootsma *et al.*, 2004; Mula, 2012). Despite the efficacy of TPM across disease entities, there appears to be an association between its usage and neurocognitive impairment, both in healthy volunteers as well as patients with epilepsy and migraine disorders. Dysfunction appears to affect several domains, including sustained attention, psychomotor speed, working-memory, as well as expressive language skills, addressed by verbal fluency tasks (Martin *et al.*, 1999; Thompson *et al.*, 2000; Lee *et al.*, 2003; Mula *et al.*, 2003; Meador *et al.*, 2005).

The frequent incidence of cognitive impairment accompanying TPM treatment has prompted investigations into its pathophysiological underpinnings via cognitive functional MRI paradigms. TPM is the most frequently studied drug by pharmaco-fMRI, though in the majority with small participant samples (Beltramini *et al.*, 2015; Wandschneider and Koepp, 2016). Given the impact on language skills, several studies utilised expressive language fMRI tasks, such as *verbal fluency* tasks, during which participants are usually required to generate words starting with specific letters (phonemic fluency). As these paradigms often alternate active with baseline blocks of low-demand information processing (e.g., cross-hair fixation), the activation maps generally reveal areas involved in speech production (dominant inferior frontal cortex) along with regions more broadly subserving attention, task execution and working memory, including dorso-lateral frontal, medial frontal and posterior parietal cortices. Implementing a verbal fluency task, Jansen and collaborators first revealed disrupted activation of inferior frontal and medial prefrontal cortices in five patients with focal epilepsy taking TPM against ten subjects with epilepsy not on TPM, along with variable reconfiguration of occipito-parietal activations (Jansen *et al.*, 2006). Another verbal fluency study analysed ten patients on TPM for migraine prophylaxis, five of whom subjectively reported cognitive dysfunction. Compared with controls, attenuated activation of task-related frontal language areas was demonstrated in the subgroup with subjective cognitive difficulties, whereas subjects on TPM without cognitive deficits showed increased activation of language areas, interpreted by the authors as a potential

compensatory mechanism (De Ciantis *et al.*, 2008). A subsequent verbal fluency fMRI study on patients with epilepsy implemented a cross-sectional and a longitudinal component. For the cross-sectional arm, Yasuda et al. recruited patients with frontal lobe epilepsy (FLE) and demonstrated impaired task-related deactivation of midline fronto-parietal default mode areas, required for effective performance of cognitive tasks (Weissman *et al.*, 2006; Sonuga-Barke and Castellanos, 2007), in patients on TPM compared to patients not taking TPM and healthy controls (Yasuda *et al.*, 2013). This imaging trait interestingly displayed a highly significant positive correlation with drug dose. In the longitudinal component of the study, one TPM-off and one TPM-on task runs were compared for four FLE patients and two healthy volunteers, corroborating cross-sectional evidence of task-related failure to deactivate default mode areas during the TPM-on condition. In addition, qualitatively reduced activation of frontal language areas was also documented on TPM. Additional evidence of impaired deactivation of default mode areas during expressive language came from a subsequent study utilising a verb generation paradigm, asking participants to view concrete nouns and generate semantically-correlated verbs (Tang *et al.*, 2016). The investigators recruited a mixed group of 12 patients with focal epilepsy taking TPM as add-on therapy, six of whom subsequently discontinued it on clinical grounds. Overall, patients on TPM showed reduced task-related deactivation within anterior and posterior default mode areas compared with controls. In those who discontinued TPM, analysis of task-related maps post-withdrawal unveiled increased activation of right middle frontal and left superior occipital gyrus, as well as enhanced deactivation of left parahippocampal gyrus and bilateral posterior cingulate cortex.

While the above detailed studies addressed expressive language, Szaflarski and collaborators implemented a semantic decision/tone decision fMRI task (Szaflarski and Allendorfer, 2012) to map the speech comprehension system, which extends to a considerable proportion of the prefrontal cortex, temporal areas (lateral and ventral, not reliably activated by verbal fluency tasks), as well as angular and posterior cingulate gyrus (Binder *et al.*, 2008). Distinct activation patterns emerged when comparing left TLE patients on- versus off-TPM, and right TLE on- and off-TPM. Among patients with left-sided foci, those on TPM exhibited reduced activation of the left superior temporal gyrus and hyperactivation of the left anterior cingulate cortex compared with those off TPM. Right TLE patients on TPM presented with decreased activation of the inferior frontal gyrus and enhanced recruitment of bilateral superior frontal and left temporo-occipital areas. Further, greater prevalence of atypical language representation was noticed for both TLE patients on TPM than those off -TPM (Szaflarski and Allendorfer, 2012).

In summary, fMRI studies addressing the impact of TPM on language networks utilised a variety of tests, examined different and heterogeneous subject categories, and generally relied on small sample sizes. Nonetheless, converging evidence across investigations points to disrupted activation of task-relevant fronto-temporal cortices, as well as impaired de-activation of task-negative regions, predominantly represented by the default mode network. The potential mechanisms leading to such effects have been speculated upon. The presence of a sulphonamide functional group provides TPM with carbonic anhydrase inhibition properties (Leniger *et al.*, 2004), which may influence the regional BOLD contrast measured by fMRI. This was demonstrated for acetazolamide, a widely utilised carbon anhydrase inhibitor, shown to induce increases in cerebral perfusion while not affecting oxygen consumption (Bruhn *et al.*, 1994). Thus, an altered ratio between rest and activation BOLD contrast may take place, represented by an attenuated signal change in response to an increase in activity of a certain area, as shown for the visual cortex during photic stimulation (Bruhn *et al.*, 1994). While this phenomenon may prominently occur in brain areas recruited during a task, and might explain the attenuated activation of task-positive areas observed by fMRI studies, an elucidation of its influence on task-related deactivations and their spatial distribution appears less intuitive. Moreover, TPM is about 10 to 100 times less potent as carbon anhydrase inhibitor than acetazolamide (Shank *et al.*, 1994) and exhibits multifaceted pharmacodynamic properties, including blockade of voltage-gated sodium channels, L-type calcium channels, AMPA/kainate subtypes of glutamate receptors as well as potentiation of $GABA_A$-mediated neurotransmission (Perucca, 1997; Mula, 2012), whose effect on fMRI activation patterns also needs to be taken into account during data interpretation.

Valuable insights may come from investigations addressing zonisamide, an AED utilised to treat focal and generalised epilepsies and associated with a profile of cognitive side effects which is comparable, though possibly more moderate, with that detailed for TPM (Ojemann *et al.*, 2001; Mula and Trimble, 2009). Mechanisms of action of zonisamide include blockade of voltage-sensitive sodium channels, T-type calcium channels, modulation of dopaminergic and serotoninergic transmission as well as a neuroprotective effect from free-radical damage (Leppik, 2004; Patsalos, 2005). As described for TPM, zonisamide also exhibits a sulpha moiety and weak carbon anhydrase inhibition properties, estimated as 100-1000 times lower than acetazolamide (Leppik, 2004). A recent electroencephalography (EEG) study on individuals taking zonisamide for recent-onset epilepsy reported reduced current source density of beta frequencies for areas implicated in language and working memory, such as

inferior and middle frontal cortices, anterior cingulate gyri and inferior parietal lobules (Kwon and Park, 2013). In a retrospective analysis of verbal fluency fMRI, comparing patients taking Topiramate (n=32), Zonisamide (51) and Levetiracetam (62) (Wandschneider et al., 2017), we observed a similar influence of zonisamide and TPM on fronto-parietal cognitive networks in patients with focal epilepsy, as measured by verbal fluency fMRI. However, impaired task-related deactivation of default mode areas was described for the TPM group only, and not in individuals on zonisamide. These results provide evidence for medication-specific effects, substantially advancing our understanding of the impact of distinct AEDs on the architecture of cognitive networks. From a mechanistic viewpoint, it would remain to be established whether distinct effects of TPM and zonisamide may be ascribed to differences in carbonic anhydrase inhibition activity, which appears to be higher for topiramate. In this regard, characterising the influence of acetazolamide on cognitive performance and activation patterns during linguistic and executive tasks may prove useful.

2.2 CARBAMAZEPINE/OXCARBAZEPINE

Carbamazepine (CBZ) represents one of the first-generation AEDs and, along with its derivative oxcarbazepine (OXC), mainly owes its seizure suppressant activity to the inhibition of voltage-dependent sodium channels (Ambrosio *et al.*, 2002). Interaction with potassium and L-type calcium channels, $GABA_A$ receptors as well as adenosine binding sites are also reported (Liu *et al.*, 2006). CBZ represents the first drug to be investigated within an fMRI study setting. Jokeit and colleagues analysed a visuo-spatial memory retrieval task to activate mesiotemporal structures via mental navigation through a familiar route, in 21 individuals with drug-resistant TLE. An inverse correlation was detected between fMRI activations within mesiotemporal lobes and CBZ serum levels, with no additional influence exerted by lateralisation of epilepsy nor further contribution of CBZ-epoxide serum level to data explanation (Jokeit *et al.*, 2001). This provides evidence for a CBZ-related attenuation of mesiotemporal activations with a linear dose-response relationship. More recently, a resting-state fMRI analysis on patients with TLE compared a subgroup treated with CBZ/OXC against participants taking other AEDs (Haneef *et al.*, 2015), and characterised the organisational properties of functional networks via a graph-theoretical approach (Bullmore and Sporns, 2009). Patients treated with OXC/CBZ differed from those on other AEDs with respect to ‘betweenness centrality”, a metric utilised to identify ‘hubs’, nodes exhibiting high connectional weighs within the architecture of a

network, and prominent roles in ensuring connectivity between distant brain areas. The authors detected variations of betweenness centrality in several nodes, including decreases in mesiotemporal and orbitofrontal areas, anterior cingulate cortices, angular gyrus, thalamus and putamen, co-existing with increases in posterior cingulate, insular, lateral temporal, posterior parietal and temporo-occipital cortices (Haneef *et al.*, 2015). On balance, these results may indicate redistribution of hub properties with more marked shifts from limbic to lateral cortical areas in TLE treated with CBZ/OXC. Interestingly, recent evidence from graph theoretical analyses on structural and functional MRI datasets from patients with TLEpoints to disrupted nodal topology of limbic subnetworks (Liao *et al.*, 2010; Chiang *et al.*, 2014; Bernhardt *et al.*, 2015), along with major rearrangements of whole-brain network hubs, particularly involving para-limbic and lateral temporal cortices (Wang *et al.*, 2014). Thus, CBZ/OXC may be influencing the topological properties of subnetworks specifically involved in disease pathomechanisms.

2.3 LEVETIRACETAM

Levetiracetam (LEV) is one of the most widely used AEDs, and received approval in numerous countries as monotherapy as well as add-on treatment for focal and generalised epilepsies. LEV binds to the synaptic vesicle protein SV2A, probably modulating synaptic neurotransmitter release (Lynch *et al.*, 2004). In contrast to other AEDs, LEV has been repeatedly shown not to exert a detrimental impact on cognition, oror even amelioration of neuropsychological performance (Piazzini *et al.*, 2006; Helmstaedter and Witt, 2008), depicting a more favourable profile than for other AEDs, including carbamazepine (Mecarelli *et al.*, 2004; Meador *et al.*, 2007; Helmstaedter and Witt, 2010). A recent EEG study provided evidence for multi-domain cognitive improvement along with accelerated background frequencies in drug-naïve epilepsy patients after treatment with LEV (Cho *et al.*, 2012).

To characterise the imaging underpinnings of the effect of LEV on cognition, we utilised both a verbal and a visuo-spatial fMRI working memory task in a large cohort of 106 patients with TLE, 59 of whom treated with LEV, and with no between-group divergences regarding TPM or zonisamide co-medication. Compared with individuals not treated with LEV, patients on LEV exhibited increased task-related deactivations in the affected temporal lobe, namely in the left middle temporal gyrus in left TLE during the verbal working memory paradigm, and in the right hippocampus in right TLE during the visuo-spatial task. The latter effects occurred in a

dose-dependent fashion, and were not evidenced when comparing patients treated with or without CBZ, or with and without lamotrigine (Wandschneider *et al.*, 2014). Previous investigations characterising the functional architecture of working memory networks illustrated the association between attenuated activation of mesiotemporal structures and effective task performance (Dolcos and McCarthy, 2006; Cousijn *et al.*, 2012). This may occur as part of a resource redistribution process from task-irrelevant to task-relevant regions, aiming to minimise interference (Anticevic *et al.*, 2010; Cousijn *et al.*, 2012). Interestingly, studies addressing the fMRI correlates of working memory in TLE detected failure to deactivate the hippocampus ipsilateral to the seizure focus compared with healthy controls (Stretton *et al.*, 2012), in the context of morpho-functional connectivity derangements pointing to a disrupted segregation between task-negative (mesiotemporal) and task-positive (parietal) areas (Stretton *et al.*, 2013). Consequently, the influence of LEV on working memory networks in TLE, described by Wandschneider and colleagues, can be interpreted as a restoration of fMRI activation patterns described for healthy controls and, therefore, regarded as favourable.

Further evidence of a normalising effect of LEV on mesiotemporal activation comes from functional imaging studies conducted on subjects with amnestic mild cognitive impairment (aMCI) (Bakker *et al.*, 2015), in whom augmented task-related activations in mesiotemporal structures were documented during memory encoding tasks (Dickerson *et al.*, 2004; Celone *et al.*, 2006). Comparing a short treatment course with low-dose LEV versus placebo, Bakker and collaborators elegantly demonstrated a reversal of the aberrant activation patterns of dentate gyrus/CA3 hippocampal sub-regions and entorhinal cortex to levels normally observed in healthy controls, accompanied by a significant improvement in task performance (Bakker *et al.*, 2012; Bakker *et al.*, 2015).

A recent analysis on patients with benign epilepsy with centro-temporal spikes (BCETS) documented an effect of LEV on the regional homogeneity (ReHo) of fMRI resting-state signal, which addresses the local synchronisation of fMRI time-series across a set of neighbouring voxels (Zang *et al.*, 2004). As different from drug-naïve individuals, reduced ReHo was detected in patients on LEV in areas implicated in the generation of interictal epileptic spikes, such as fronto-centro-temporal cortices, basal ganglia and thalamus. Contrasting ReHo patterns in patients on LEV against those treated with sodium valproate (discussed below) revealed spatial specificity of drug effects, with LEV affecting more prominently fronto-temporal cortices and caudate nuclei while exerting a less pronounced influence on thalamic activity. LEV also exerted dissociating effects on the covariance of

thalamic and centro-temporal local fMRI metrics, shown instead as significantly correlated in drug-naïve patients and subjects treated with valproate (Zhang *et al.*, 2016). Unfortunately, the absence of a healthy control cohort in the above study impedes establishing whether regional homogeneity patterns in LEV-treated patients may indicate a reversal to normal baseline values.

Collectively, evidence across different disorders suggests a disease-specific distribution of the effects of LEV, with predominant influence on subnetworks relevant to disease pathomechanisms. Its effects may further exhibit beneficial implications for cognitive performance, as demonstrated for conditions with impact on mesiotemporal function.

2.4 SODIUM VALPROATE

Sodium valproate (VPA) is a well-established broad-spectrum AED with efficacy to treat a multiplicity of focal and generalised epilepsy syndromes, is utilised as mood stabiliser for the treatment of bipolar disorder, and is also licenced for migraine prophylaxis (Perucca, 2002; Nalivaeva *et al.*, 2009). VPA has long been regarded as a compound with diverse and complex mechanisms of action, which go beyond the potentiation of GABAergic neurotransmission and include attenuation of NMDA glutamate receptor activity, blockade of voltage-sensitive sodium channels, and modulation of dopaminergic and serotoninergic transmission (Loscher, 2002; Perucca, 2002). Furthermore, VPA exposure leads to extensive modifications of gene expression, with downstream influence on transcription regulation, signal transduction and cellular homeostasis, probably underlain by its histone deacetylase (HDAC) pan-inhibition properties (Rosenberg, 2007; Nalivaeva *et al.*, 2009; Rosenzweig *et al.*, 2012). There is also evidence of potential neuroprotective effects brought about by VPA through the modulation of signalling cascades involved in neuronal apoptosis, formation of neurofibrillary tangles and amyloid plaques (Tariot *et al.*, 2002).

The effects of a two-week long VPA course on the activation patterns of spatial attention, working memory and verbal fluency tasks were recently addressed by an fMRI study on healthy volunteers. Analysing the magnitude of BOLD signal change pre- and post-intervention across task-specific maps, Bell and collaborators observed attenuated activations for the spatial attention and word generation tasks in the VPA-treated cohort compared to subjects receiving placebo. ROI-based *post-hoc* analysis revealed changes to occur in the left

lingual gyrus during the attention task, and to encompass the supplementary motor area for the verbal fluency task. On the other hand, individuals on two-week course of lithium presented with significantly reduced activations within working memory and verbal fluency maps, but not during the attention task (Bell *et al.*, 2005). These findings may reflect a differential effect of VPA and lithium on cognitive fMRI activations, and point to the influence of VPA on expressive language and attention networks, with relative sparing of working memory. As neurobehavioral correlates were not provided, it remains undetermined whether such reconfigured patterns may be accompanied by performance changes. The above findings, however, may be in line with evidence from neuropsychological studies, collectively indicating a mild impact of VPA on measures of attention, psychomotor speed and executive functions (Thompson and Trimble, 1981; Meador *et al.*, 2003; Mula and Trimble, 2009).

Variable results were obtained in pharmaco-fMRI studies probing VPA-related effects in disease entities. In a small sample of children with mood dysregulation and familial history of bipolar disorder, no significant activation changes during an emotion attribution task were detected after three months of treatment with VPA, compared to baseline pre-treatment data. (Chang *et al.*, 2009). Investigations on patients with epilepsy, on the other hand, may suggest beneficial effects of VPA on fMRI activation maps.

Focusing on patients with juvenile myoclonic epilepsy (JME) and their un-affected siblings, we detected co-activation of motor and cognitive areas during a visuo-spatial working memory task in patients with JME and their siblings compared with controls, which may represent an imaging trait underlying the highly prevalent cognitively-triggered jerks (Wandschneider *et al.*, 2012; Wolf *et al.*, 2015; Koepp *et al.*, 2016). In JME patients, we observed an inverse relationship between VPA dose and motor cortex activation, which is indicative of a "normalising effect" of VPA on the aberrant activation patterns documented for motor areas in JME (Vollmar *et al.*, 2011). Structural and functional connectivity was augmented between motor areas and prefrontal cognitive networks (Vollmar *et al.*, 2012), In line with the above, evidence of an influence of VPA on the excitability of the motor system was also provided by analyses implementing interleaved fMRI/transcranial magnetic stimulation (TMS). During classical stimulation of the motor hotspot, diffuse attenuation of TMS-correlated BOLD response was observed within several areas belonging to the motor system after a single dose of VPA compared with placebo (Li *et al.*, 2010), along with reduction of effective connectivity between primary motor cortex and both premotor and supplementary motor areas (Li *et al.*, 2011).

In subjects affected by BCETS, regional homogeneity of fMRI time courses was attenuated in regions demonstrated to be implicated in epileptic spike generation, including fronto-centro-temporal cortices as well as thalamus, in subjects treated with VPA compared with drug-naïve individuals. Attenuation of centro-temporal regional homogeneity also appeared dose-dependent. Compared with LEV, the impact of VPA was more pronounced on thalamic activity and less evident for cortical regions. Further, subjects on VPA displayed preserved covariance of fMRI metrics between thalamus and centro-temporal cortices, possibly suggesting a balanced effect on both cortical and subcortical structures associated with VPA (Zhang *et al.*, 2016).

Imaging correlates of VPA use have also been sought for by structural MRI studies, possibly following early case reports of reversible VPA-associated pseudoatrophy and neurobehavioral deterioration (Papazian *et al.*, 1995; Guerrini *et al.*, 1998). In small samples of young individuals with subsyndromal bipolar disorder and matched controls, Chang and colleagues described no evidence of changes in total brain or amygdala volume after a three-month course of VPA (Chang *et al.*, 2009). Moreover, VPA-treated adult patients with bipolar disorder were shown to present with greater volumes of anterior and posterior cingulate cortices, which exhibited a trend-level negative correlation with symptom severity (Atmaca *et al.*, 2007). On the other hand, recent longitudinal clinical trials evaluating the effectiveness of VPA for the treatment of agitation and psychosis in Alzheimer's disease observed accelerated rates of whole-brain and hippocampal volume loss, along with more rapid ventricular expansion compared to the placebo cohort (Fleisher *et al.*, 2011; Tariot *et al.*, 2011). These changes were also paralleled by faster cognitive decline over the first treatment year, as measured by the Mini-Mental State Examination (Fleisher *et al.*, 2011). In young children (age 6-8) incurred in prenatal exposure to VPA, an analysis revealed augmented cortical thickness of the pars opercularis of the left inferior frontal gyrus and of the left medial occipital cortex, with loss of the expected right-to-left thickness asymmetry within inferior frontal cortices. Further, a trend towards a negative correlation was observed between left fronto-opercular thickness and a composite measure of verbal comprehension (Wood *et al.*, 2014). This study provides an imaging correlate of neurobehavioral findings detailed by multiple investigations, linking *in utero* exposure to VPA with poorer cognitive outcomes across several domains, particularly verbal abilities (Adab *et al.*, 2004; Gaily *et al.*, 2004; Meador *et al.*, 2009; Meador *et al.*, 2013), along with increased likelihood of atypical language lateralisation (Meador *et al.*, 2011; Nadebaum *et al.*, 2011). A study by Pardoe and colleagues identifiedreductions in total whole

brain volume, white matter volume as well as parietal lobe thickness in subjects treated with VPA compared with healthy controls and patients not on VPA. These findings were documented in two separate cohorts, one represented by subjects with drug-resistant focal epilepsy and another consisting of patients with childhood-onset seizures. Effects associated with VPA were thought to be reversible, as no differences could be detected between previous VPA users and patients who were never prescribed the drug (Pardoe *et al.*, 2013). The biological meaning of reductions in parietal lobe thickness could not be inferred, owing to the clinical heterogeneity of the analysed subjects, the absence of direct correlations with cognitive measures and of details regarding potential differences in seizure control among patient groups. Regarding decreases in white matter volume, however, experimental and human studies point to an impact of VPA on late-differentiating oligodendrocytes, due to its action as histone deacetylase pan-inhibitor (Shen *et al.*, 2008; Rosenzweig *et al.*, 2012). This effect may influence myelination/re-myelination efficiency, leading to derangements in white matter architecture and particularly affecting later-myelinating plastic circuits, which play crucial roles in multi-modal associative processing, cognitive control and goal-directed behaviour (Rosenzweig *et al.*, 2012).

On balance, recent investigations have considerably advanced our understanding of the functional and structural MRI correlates of VPA usage. Overall, results of the above detailed studies appear multifaceted. While some fMRI studies may suggest a beneficial influence of VPA, with reverberation on disease-specific subnetworks, morphometry analyses concordantly report detrimental effects correlated with VPA use across diverse conditions, each of which tapping into different life spans. Proved heterogeneity in the analysed cohorts, study design and confounding factors may be accounted for the wide spectrum of findings. It is also possible, however, that the pleiotropic pharmacodynamic of VPA might lead to unique phenotypes arising from specific interactions between disease- and drug-related effects, ultimately justifying marked variability of imaging features condition per condition.

2.5 LAMOTRIGINE

Lamotrigine (LTG) is a drug with broad spectrum efficacy, spanning from focal to generalised epilepsy syndromes and including bipolar disorder, owing to its mood stabilisation properties. Its principal mechanism of action is represented by the use- and voltage-dependent blockade of sodium channels (Cheung *et al.*, 1992; Coulter, 1997), possibly accompanied by inhibition

of voltage-sensitive calcium currents, anti-glutamatergic and neuroprotective effects (Ketter *et al.*, 2003).

Though a variety of research groups set out to investigate LTG-associated functional imaging markers, no studies at present recruited patients with epilepsy. Li and collaborators carried out a series of investigations aiming to establish the influence of LTG on fMRI activation patterns during motor and prefrontal TMS in healthy volunteers. As previously detailed for VPA, LTG was also shown to diffusely attenuate TMS-induced BOLD response over several areas of the motor system (Li *et al.*, 2004; Li *et al.*, 2010), and to impact effective connectivity between primary motor cortex and both premotor and supplementary motor areas (Li *et al.*, 2011) compared with placebo. LTG-specific effects, however, emerged during prefrontal TMS, which generally elicits the activation of medial prefrontal as well as primary sensory areas. TMS-correlated fMRI activations for the LTG condition encompassed broader areas, with significantly increased recruitment of ipsilateral hippocampus, medial frontal, anterior cingulate and orbitofrontal cortices compared to placebo (Li *et al.*, 2004; Li *et al.*, 2010). This pattern was not detected for VPA, which caused attenuated activation of all target regions of prefrontal TMS when compared against placebo, and also of the above mentioned limbic areas, when directly compared with LTG (Li *et al.*, 2010). Moreover, LTG was associated with increases in TMS-correlated effective connectivity between ipsilateral dorsolateral prefrontal and anterior cingulate cortex, while the same findings could not be detailed for VPA (Li *et al.*, 2011). As limbic hyperactivation, frontal hypoactivation and dysfunctional fronto-cingulate connectivity have been implicated in the pathophysiology of major depression and bipolar disorder (Schlosser *et al.*, 2008; Sheline *et al.*, 2010; Kupferschmidt and Zakzanis, 2011; Pizzagalli, 2011; Strakowski *et al.*, 2012), these findings provide support to the view that LTG may influence activity and connectional properties of brain areas relevant to disease pathophysiology. Indeed, several analyses focused on verbal working memory and facial emotion recognition fMRI in individuals with bipolar disorders. Haldane and colleagues report increased recruitment of task-relevant areas, such as dorso-lateral prefrontal, medial frontal and anterior cingulate cortices, after a six-week course of LTG (Haldane *et al.*, 2008). In paediatric patients, reduced activation of the right amygdala during negative facial emotion recognition was detected after 8 weeks of treatment with LTG, and was positively related to improvements in depressive symptoms (Chang *et al.*, 2008). Additional evidence of attenuated temporal activations during emotion recognition was documented for adults after 12 weeks of LTG monotherapy (Jogia *et al.*, 2008). Once again in subjects with bipolar disorder, Pavluri and

colleagues detailed augmented activation of lateral temporal, medial frontal, left inferior and middle frontal cortices during a response inhibition task after 14 weeks of initial anti-psychotic treatment followed by LTG monotherapy. These findings corresponded to a normalisation of task-related activations, which correlated with symptom amelioration (Pavuluri *et al.*, 2010).

There is also evidence that LTG may contribute to revert the fMRI correlates associated with ketamine, a well-known antagonist of NMDA glutamate receptors. After administration of ketamine, an investigation reported reduced activation of orbitofrontal and sub-genual cingulate cortices and hyperactivation of posterior cingulate, lateral temporal cortices and thalamus. Interestingly, pre-treatment with LTG led to the suppression of several of the former changes (Deakin *et al.*, 2008).

In summary, several investigations conducted on adolescent and adult patients with mood disorders documented the effect of LTG on disease-relevant regions, largely part of fronto-limbic circuits involved in the regulation of emotional responses and/or implicated in response inhibition and task execution. Collectively, such influence was shown to contribute to the restoration of activation patterns described for healthy controls, and hence can be defined as "normalising".

2.6 GABAPENTIN AND PREGABALIN

Both gabapentin (GBP) and pregabalin (PGB) selectively bind to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, leading to enhanced GABA-mediated inhibition and diminished release of neurotransmitters such as glutamate, serotonin, noradrenaline and substance P (Gee *et al.*, 1996; Fink *et al.*, 2002; Dooley *et al.*, 2007). Their clinical indications are particularly broad, ranging from the treatment of focal epilepsy syndromes to neuropathic pain conditions for both compounds, and encompassing generalized anxiety disorder for PGB only (Feltner *et al.*, 2003; Gilron *et al.*, 2005; French *et al.*, 2016). At present, no studies have been conducted to image the action of GBP or PGB in patients with epilepsy. A small number of functional imaging studies, however, addressed the effects of these two drugs in healthy volunteers, investigating brain activity related to pain processing, emotional anticipation and response to emotional faces. With a pharmacological fMRI study design, Iannetti and colleagues elucidated the modulatory effects of a single GBP dose on brain activation during nociceptive mechanical stimulation and experimentally-induced secondary hyperalgesia, the latter being a proxy for

central sensitization. Although no significant changes were evidenced by pain/hyperalgesia-related ratings, GBP-correlated imaging features included attenuated activation of operculo-insular cortices in both conditions. During central sensitization, reduced activations were additionally noticed in the brainstem, along with a reduction of stimulus-correlated deactivations during central sensitization only (Iannetti *et al.*, 2005). These findings provided quantitative traits for GBP-correlated effects, suggesting its specific influence on well-established pain-processing regions, particularly in the context of central sensitisation. After acute administration of PGB to healthy volunteers, an fMRI paradigm addressing the anticipation responses to positive and negative emotional images reported decreased activation of left amygdala and anterior insula as well as hyperactivation of the anterior cingulate cortex compared with placebo (Aupperle *et al.*, 2011). Moreover, an analysis of emotional face processing in the same study cohort revealed attenuated activation of the left amygdala in relation to fearful face processing, of the left insula specifically for angry faces, and of the fusiform gyrus for stimulus types (Aupperle *et al.*, 2012). Interestingly, reduction of amygdalar activation was also reported in other functional imaging studies addressing the influence of benzodiazepines (Paulus *et al.*, 2005) and selective serotonin reuptake inhibitors during emotional face processing (Arce *et al.*, 2008; Windischberger *et al.*, 2010), while the insula has long been regarded as a key hub for interoception and elaboration of emotional responses (Craig, 2009; Singer *et al.*, 2009). In this context, PGB may be exhibit a similar neural target to other compounds with anxiolytic properties, and exert its effects through a modulation of the activity of limbic and para-limbic circuits with salient roles in regulating responses to emotional stimuli.

3. INSIGHTS FROM MAGNETIC RESONANCE SPECTROSCOPY

Proton magnetic resonance spectroscopy (^{1}H-MRS) represents a non-invasive technique with the ability to provide quantitative measurements of specific chemical entities in determined volumes of interest. Owing to shifts in resonance frequencies induced by the local proton environment (referring to atoms within and surrounding a given molecule), ^{1}H-MRS produces a spectrum with several peaks at distinct frequencies, each one specific to a given molecular compound, and whereby the area underlying each peak relates to the concentration of the corresponding molecule (De Graaf, 2013). AEDs are presumed to exert their seizure suppression activity either via potentiating inhibition mechanisms or via an attenuation of

excitatory neurotransmission (Rogawski and Loscher, 2004), and this represented the underlying rationale of several investigations aiming to determine concentrations of GABA and glutamate (often indistinguishable from glutamine, resulting in a "Glx" composite metric) in patients with epilepsy, and to correlate the former with treatment administration as well as clinical response (Petroff *et al.*, 2000; Mueller *et al.*, 2001; Mueller *et al.*, 2003; Simister *et al.*, 2009). This topic has been elegantly reviewed by Van Veenendaal and collaborators (van Veenendaal *et al.*, 2015), who highlighted the potential of MRS to provide biomarkers predicting AED-related treatment outcomes, and to shed light into the mechanistic underpinnings of treatment failures and cognitive side effects.

AEDs with direct impact on GABAergic neurotransmission represent by far the most frequently investigated by MRS studies. There is a considerable body of evidence indicating enhanced GABA concentrations after acute and chronic administration of vigabatrin (VGB) (Petroff *et al.*, 1996b; Novotny *et al.*, 1999; Petroff *et al.*, 1999; Weber *et al.*, 1999; Mueller *et al.*, 2001; Mueller *et al.*, 2003), an irreversible inhibitor of GABA transaminase, GBP (Petroff *et al.*, 1996c; Kuzniecky *et al.*, 2002; Cai *et al.*, 2012), which increases GABA availability via the modulation of voltage-dependent calcium channels, and TPM (Petroff *et al.*, 2001; Kuzniecky *et al.*, 2002), which potentiates $GABA_A$-mediated neurotransmission. After treatment initiation with both VGB and GBP, GABA concentrations were shown to correlate with seizure reduction in patients with focal epilepsy (Petroff *et al.*, 1996a; Petroff *et al.*, 1996c). Moreover, VGB doses were shown to correlate linearly with GABA concentrations until dosages of 3g/die, exhibiting a plateau for additional dose increases (Petroff *et al.*, 1996d). Mueller and collaborators sought for MRS biomarkers of treatment response in subjects exposed to VGB, and emphasized the relevance of low pre-VGB GABA levels, followed by sharper increases of the latter after treatment start, as a potential response-associated trait in individuals with refractory focal epilepsy (Mueller *et al.*, 2001). Moreover, the difference in GABA concentrations between the epileptogenic and non-epileptogenic hemisphere before VGB treatment was demonstrated to relate to improved seizure control under VGB therapy, regardless of the proximity of data sampling to the epileptogenic focus (Mueller *et al.*, 2003). The above findings are collectively indicative of meaningful correlations between AED administration, modulation of GABA concentrations and clinical improvements. However, such level of detail is available for VGB only, which has unfortunately incurred in marked usage restrictions owing to the risk of potentially irreversible peripheral visual field deficits (Lawden *et al.*, 1999). Exposure-response relationships have not been documented for TPM and GBP, despite evidence of increased GABA concentrations associated with these AEDs. In

addition, a study investigating the effects of tiagabine, an AED with GABA reuptake inhibition properties, detected no influence on GABA levels after a single-dose administration (Myers *et al.*, 2014), suggesting of complex and potentially marked compound-specific relationships between drug administration and neurotransmitter effects.

Other MRS studies analysed GABA concentrations associated with AEDs not exhibiting a clearly documented influence on GABAergic neurotransmission. As for LTG, GABA concentrations were not elevated after acute administration nor after 2 weeks of LTG administration, but were shown as enhanced after 4 weeks (Kuzniecky *et al.*, 2002). Similar results were obtained for LEV. A study on healthy volunteers reported no effects on GABA concentrations after three and six hours following a single dose of LEV (Kuzniecky *et al.*, 2008), but subsequent evidence of increased GABA levels 2-6 weeks after initiation of LEV therapy was gathered for the responder subgroup of patients with focal epilepsy (Doelken *et al.*, 2010). Overall, these findings may suggest that augmented GABAergic neurotransmission be an indirect effect associated with chronic administration of AEDs with non-GABAergic mechanisms of action, and might correlate with response to treatment.

In contrast with the abundance of evidence on GABA levels, there are fewer reports on AED-correlated effects on glutamate/glutamine concentrations. Single doses of GBP administered to healthy subjects did not produce measurable glutamate changes (Cai *et al.*, 2012; Preuss *et al.*, 2013), and no modifications of Glx concentrations were detected by a longitudinal study assessing patients with epilepsy treated with VPA (Simister *et al.*, 2007). On the other hand, a study analysing the effects of acute TPM administration in healthy controls, and separately modelling glutamate and glutamine, detected increased glutamine within a sampling voxel located in the anterior cingulate cortex, but no modifications of occipital glutamine and no variations in both anterior cingulate and occipital glutamate (Moore *et al.*, 2006). On balance, no comprehensive inferences can be drawn regarding the influence of various AEDs on excitatory neurotransmission, arguably due to variability in study design and lack of longitudinal assessments.

Other metabolites measured via ^{1}H-MRS include N-acetylaspartate (NAA), a widely accepted marker of neuronal integrity (Rigotti *et al.*, 2007), as well as myoinositol, which is a glial marker exhibiting a critical role in the regulation of osmotic balance and, as a precursor of membrane phospholipids and phosphoinositides, is required for cell membrane and myelin integrity (Brand *et al.*, 1993; Haris *et al.*, 2011). In patients with TLE, assessed after one to two years from initiation of AED therapy, lower NAA concentrations within the ipsi- and

contralateral mesiotemporal sampling voxel were detected in those failing to respond to their first AED compared with those reporting seizure freedom (Campos *et al.*, 2010). These findings may represent a biomarker of AED response, potentially indicating higher levels of neuronal damage in subjects with less favourable profiles of drug-responsiveness. As various AEDs were implicated, however, compound-specific effects could not be established. In a longitudinal study on a mixed epilepsy cohort, mostly represented by idiopathic generalised epilepsy, Simister and colleagues detected reduced myoinositol levels for subjects scanned while on VPA compared with the non-VPA condition, whereas no changes were observed for other metabolites, including Glx and NAA. No correlations were identified between myoinositol levels and seizure frequency or VPA dosage (Simister *et al.*, 2007). Lower concentration of myoinositol was also detected in IGE patients treated with VPA compared with those not taking VPA (Simister *et al.*, 2003). It is tempting to speculate whether altered myoinositol levels associated with VPA exposure may be related to its putative influence on myelination efficiency (Rosenzweig *et al.*, 2012). Animal studies, however, suggest similar effects associated with lithium (O'Donnell *et al.*, 2000), and further research in humans is advocated to establish whether reduction of myoinositol may also occur in association with other AEDs.

With respect to MRS signatures of AED-related cognitive side effects, Van Veenendaal and colleagues recently conducted a cross-sectional study to address the relationship between processing speed and neurotransmitter levels in patient with focal epilepsy receiving AED therapy (van Veenendaal *et al.*, 2016). Across all participants, glutamate concentrations were positively related to processing speed. In individuals taking TPM, deemed as 'high-risk' for cognitive dysfunction, lower glutamate levels and lower processing speed scores were detected compared with patients under LEV and LTG ('low-risk' category). Lower glutamate levels but no differences in processing speed, on the other hand, were observed in the 'intermediate risk' category, grouping VPA, CBZ/OXC and phenytoin, compared to low-risk individuals. Thus, these finding may suggest a potential contribution of AED-associated lower glutamate levels to suboptimal cognitive functioning in patients with epilepsy. However, no correlations were found between GABA levels, cognitive performance and AED-associated risk category. Occipital data sampling might have partially obscured GABA-related effects, in view of previous evidence linking GABA concentrations with motor decision speed in prefrontal, but not occipital areas (Sumner *et al.*, 2010).

In summary, studies implementing MRS rely on a variety of markers addressing complementary features of brain function, have remarkably shed light on the molecular underpinnings of AED effects, and might provide useful indicators to monitor treatment response and associated side effects.

4. CONCLUSION

Collectively, this review of pharmcao-fMRI and MRS studies strongly supports the potential of imaging investigations to provide MRI biomarkers of AED-correlated effects, which can be characterised within regions and networks implicated in disease pathomechanisms.

The observed effects may not always specific to a given AED in an individual disease entity, given the considerable variability in participant inclusion criteria, study design andspecifics of the implemented paradigms,. A series of highly meaningful patterns however emerge, suggesting the influence of some AEDs on brain targets implicated in disease pathophysiology, or potentially involved in the emergence of drug-related adverse effects:

- TPM has been mostly investigated due to its adverse impact on expressive language and executive functions, and cognitive fMRI studies overall revealed its negative influence on the activation of language areas, accompanied by attenuations of task-correlated deactivations.
- CBZ attenuated activation of mesiotemporal activations with a linear dose-response relationship
- LEV favourably influenced the activity in dysfunctional mesiotemporal areas both in TLE and mild cognitive impairment, overall leading to a restoration of normal function.
- VPA’s widely variable and often diverging effects warrant further multi-modal MRI analyses on well-characterised cohorts of patients and control subjects, which may allow to better disentangle anatomo-functional trajectories correlated with its usage.
- LTG seems instead to be primarily exerting an effect on fronto-temporo-limbic circuitry involved in the regulation of emotional responses.
- GBP and PGB have been shown to affect areas with prominent roles in nociception and emotion regulation, respectively, in line with their clinical indications.
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It remains to be shown to which extent drugs with distinct pharmacodynamic properties may ultimately influence common final pathways, giving rise to overlapping MRI correlates. This may be the case, for instance, of PGB and other compounds exhibiting anxiolytic properties, such as benzodiazepines and selective serotonin reuptake inhibitors (Aupperle *et al.*, 2011; Aupperle *et al.*, 2012). Further studies are required to understand whether this might also occur for different AEDs in people with epilepsy. A further complicating factor is represented by the intrinsic features of the BOLD contrast utilised in fMRI, which offers an indirect measure of neural activity. As shown for TPM and ZNS, a compound can concurrently exert an influence on both the neuronal and vascular compartments, potentially confounding any mechanistic interpretation of the fMRI correlates of pharmacological interventions. Strategies to disentangle vascular from neuronal effects include the implementation of perfusion MRI sequences such as arterial spin labelling (Borsook *et al.*, 2013), which has been already pursued in some of the above discussed analyses (Aupperle *et al.*, 2011; Aupperle *et al.*, 2012).

While most MRI studies discussed above have either enrolled healthy volunteers, or sought to establish functional markers of drug effects on cognitive networks in patient populations, there is relative scarcity of MRI investigations aiming to establish imaging correlates of drug response, such as seizure-freedom for epilepsy. The latter issue may be more thoroughly addressed via longitudinal imaging studies comparing responders with non-responders and recruiting patients at different time points of their disease course. In this context, multi-modal complementary approaches may undoubtedly represent an asset. As discussed in the previous paragraph, an excellent example is represented by the added value of MRS, which has repeatedly proven useful in establishing the neurochemical underpinnings of the administrations of numerous AEDs, with some reports of correlations between clinical variables and neurotransmitter quantifications. As for any modality, MRS also suffers from limitations, mostly pertaining to data sampling, which is limited to large regions of interest, oftentimes in the occipital lobes only, and does not currently allow distinguishing synaptic from extra-synaptic neurotransmitter pools (Duncan *et al.*, 2014; van Veenendaal *et al.*, 2015). Further insights may come from investigating both imaging and neurophysiological techniques simultaneously, including EEG, TMS, or TMS-EEG, which offer complementary windows into the complex patterns of brain function and have demonstrated considerable potential to provide biomarkers of AED effects (Badawy *et al.*, 2010; Cho *et al.*, 2012; Badawy *et al.*, 2014; Ziemann *et al.*, 2015; Premoli *et al.*, 2016).

Lastly, the identification of biomarkers associated with pharmacological interventions has gained considerable attention in the context of personalised medicine, whereby inferences pertaining to drug effects should be drawn to tailor clinical decisions to the individual patient. All studies in this review, however, detailed findings obtained at the group level. Whether the above discussed AED-related effects may be utilised for individually customised clinical decision making remains to be shown. To this end, remarkable advancements may be brought about by initiatives aiming to develop personalised brain network models, such as the "Virtual Epileptic Patient" recently proposed by Jirsa and collaborators (Jirsa *et al.*, 2017).

In conclusion, MRI studies have improved our understanding of the impact of AEDs on single regions and complex brain networks, and provide biomarkers of clinical relevance, with encouraging prospects for improving the clinical management of epilepsy.

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