Functional Network Correlates
of
Language and Semiology in Epilepsy

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Thesis submitted to UCL for the degree of Doctor of Philosophy

London, 2022

Declaration

I, Louis André van Graan confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

The studies presented in this thesis reflect the contributions of several scientists including colleagues from the Department of Clinical and Experimental epilepsy, the ION and Welcome Centre for Neuroimaging, UCL. I have outlined my individual contribution below.

I used patient data and ictal activity marked on EEG from a previous study conducted in the UCL EEG-fMRI group to derive BOLD activations related to semiology.

In the initial phases of the cognitive fMRI studies, expertise in methods and data acquisition were provided by Dr Gloria Gonzálvez. I recruited and performed the imaging in all patients and healthy controls. Along with radiographers, I acquired the neuroimaging data, comprising conventional structural MRI, diffusion imaging data and five cognitive functional paradigms.

I participated in the development and testing of the ICN_atlas tool and adjusted output functions of the published atlas to obtain one of the metrics employed in the current studies.

I performed all psychometry in healthy controls. I created image masks for all the canonical intrinsic connectivity network areas for use in lateralisation indices.

I performed all the fMRI data analyses, statistical analyses, interpretation of results and data presentation in this thesis. Detailed clinical data concerning diagnoses and medication was obtained from a database compiled by Mrs Jane Burdett.

London, 2022 Louis André van Graan

Abstract

Epilepsy surgery is appropriate for 2-3% of all epilepsy diagnoses. The goal of the presurgical workup is to delineate the seizure network and to identify the risks associated with surgery. While interpretation of functional MRI and results in EEG-fMRI studies have largely focused on anatomical parameters, the focus of this thesis was to investigate canonical intrinsic connectivity networks in language function and seizure semiology. Epilepsy surgery aims to remove brain areas that generate seizures. Language dysfunction is frequently observed after anterior temporal lobe resection (ATLR), and the presurgical workup seeks to identify the risks associated with surgical outcome. The principal aim of experimental studies was to elaborate understanding of language function as expressed in the recruitment of relevant connectivity networks and to evaluate whether it has value in the prediction of language decline after anterior temporal lobe resection. Using cognitive fMRI, we assessed brain areas defined by parameters of anatomy and canonical intrinsic connectivity networks (ICN) that are involved in language function, specifically word retrieval as expressed in naming and fluency. fMRI data was quantified by lateralisation indices and by ICN_atlas metrics in a priori defined ICN and anatomical regions of interest. Reliability of language ICN recruitment was studied in 59 patients and 30 healthy controls who were included in our language experiments. New and established language fMRI paradigms were employed on a three Tesla scanner, while intellectual ability, language performance and emotional status were established for all subjects with standard psychometric assessment. Patients who had surgery were reinvestigated at an early postoperative stage of four months after anterior temporal lobe resection. A major part of the work sought to elucidate the association between fMRI patterns and disease characteristics including features of anxiety and depression, and prediction of postoperative language outcome. We studied the efficiency of reorganisation of language function associated with disease features prior to and following

surgery. A further aim of experimental work was to use EEG-fMRI data to investigate the relationship between canonical intrinsic connectivity networks and seizure semiology, potentially providing an avenue for characterising the seizure network in the presurgical workup. The association of clinical signs with the EEG-fMRI informed activation patterns were studied using the data from eighteen patients' whose seizures and simultaneous EEG-fMRI activations were reported in a previous study.

The accuracy of ICN_atlas was validated and the ICN construct upheld in the language maps of TLE patients. The ICN construct was not evident in ictal fMRI maps and simulated ICN_atlas data. Intrinsic connectivity network recruitment was stable between sessions in controls. Amodal linguistic processing and the relevance of temporal intrinsic connectivity networks for naming and that of frontal intrinsic connectivity networks for word retrieval in the context of fluency was evident in intrinsic connectivity networks regions. The relevance of intrinsic connectivity networks in the study of language was further reiterated by significant association between some disease features and language performance, and disease features and activation in intrinsic connectivity networks. However, the anterior temporal lobe (ATL) showed significantly greater activation compared to intrinsic connectivity networks – a result which indicated that ATL functional language networks are better studied in the context of the anatomically demarked ATL, rather than its functionally connected intrinsic connectivity networks. Activation in temporal lobe networks served as a predictor for naming and fluency impairment after ATLR and an increasing likelihood of significant decline with greater magnitude of left lateralisation.

Impairment of awareness served as a significant classifying feature of clinical expression and was significantly associated with the inhibition of normal brain functions. Canonical intrinsic connectivity networks including the default mode network were recruited along an anterior-posterior anatomical axis and were not significantly associated with clinical signs.

Impact Statement

Functional MRI and EEG are non-invasive and cost-effective methods that can evaluate the neural basis of a wide range of physiological and psychological events. Behavioural characteristics have been attributed to neural population activity, specifically large-scale networks (ICNs). The work presented in this thesis contributes to insight into the role of these networks in language function and clinical ictal semiology.

This thesis also lends support for the validity and role of a dedicated tool (ICN_atlas) that provide fMRI BOLD map analyses with its standardised objective metrics being potentially advantageous in clinical and research settings. This software augments the radiologist's expertise in evaluating fMRI BOLD maps with many potential applications beyond the field of epilepsy.

My research showed that strong *spatial* similarity between rest and task derived connectivity networks as represented in the ICN_atlas do not equate to correspondence in language activation. This has significant implication for the design of studies that rely on results of resting state fMRI to predict task derived connectivity.

This thesis elaborates evidence that features of disease can impact significantly on intensity of BOLD activations and task performance. Descriptive data presented in this thesis suggest that specific configurations of disease burden and reorganisation of language function confer risk of language decline after ATL. The potential utility of these indices calls for further study.

Analyses of groups of subjects that represented homogenous fMRI patterns showed that disease features were not associated with group level haemodynamic patterns and reiterates the need for comprehensive patient specific profiles beyond imaging studies to predict language outcomes following surgical interventions.

My results show that fMRI activations of a priori defined intrinsic connectivity networks and anatomical ROIs can predict clinically significant language dysfunction following ATLR, with greater magnitude of activation associated with increasing likelihood of decline. This thesis provides further support for the utility of *naming* paradigms and prominence of activation in temporal lobe networks in predicting post-surgical naming decline; task specific predictive value in relation to post-surgical decline was also shown for *phonetic fluency*, and novel evidence was presented for *semantic fluency*. Given potential for further recovery the results also provide data as to plasticity at four months post-surgery. These findings are directly applicable to clinical practice: Specifically, it helps to identify the risk of significant language difficulties and serves to inform and guide clinicians and patients as to the impact on social and occupational function beyond the acute stage of recovery.

This thesis shows that EEG-fMRI and anatomical atlasing can delineate semiology networks across cortical and subcortical structures. The findings do not support a role for normal connectivity as reflected in ICNs, in relation to clinical signs but reflect anatomical organisation and evolution of the seizure discharge. The results showed that each sign is associated with a transient network that comprise varying degrees of activation, deactivation and idiosyncratic connectivity across cortical and subcortical areas. It calls for a greater research focus on the relationship between seizure semiology, electrophysiology, functional correlates of haemodynamic deactivation and seizure mechanisms at a cellular level.

I provide novel evidence for the utility of impairment of awareness as a diagnostic classifier in epilepsy and show that neural inhibition across multiple structures, rather than any one ROI, serve as the basis for impairment of awareness. The methods, data and novel results are likely to inform further research in epileptology.

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List of Abbreviations

AED	Antiepileptic drug
AN	Auditory naming
ANOVA	Analysis of variance
ATLR	Anterior temporal lobe resection
BG	Basal ganglia
BOLD	Blood oxygenation level dependent
CG	Cingulate gyrus
CSM	Cortical stimulation mapping
CTR	Controls
DMN	Default mode network
EEG	Electroencephalography
FC	Functional connectivity
FF	Free fluency
FLE	Frontal lobe epilepsy
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
GLM	General linear model
GSWD	Generalised spike and wave discharge
HRF	Haemodynamic response function
IAT	Intracarotid amytal test
ICA	Independent component analysis
IED	Interictal epileptiform discharges
IFG	Inferior frontal gyrus
IGE	Idiopathic generalised epilepsy
ILAE	International League against Epilepsy
IQ	Intelligent quotient
LFP	Local field potential
LI	Lateralisation index
MEG	Magnetencephalography
MFG	Middle frontal gyrus
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging

MTG	Middle temporal gyrus
MTL	Medial temporal lobe
PFC	Prefrontal cortex
PPV	Positive predictive value
NPV	Negative predictive value
RCI	Reliable change index
PN	Picture naming
ROI	Region of interest
SCP	Slow cortical potential
rsFC	Resting state functional connectivity
SF	Semantic fluency
SFG	Superior frontal gyrus
SPc	Scrambled pictures
SPM	Statistical Parametric Mapping
TLE	Temporal lobe epilepsy
VF	Verbal fluency

Publications Associated with this Thesis

Review Articles as First Author

van Graan, L., Lemieux, L., & Chaudhary, U. (2013a). *Neurology & Neurophysiology Scalp and Intracranial EEG-fMRI in Epilepsy*. *4*(3). https://doi.org/10.4172/2155-9562.1000156

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Kozák, L.R., van Graan, L.A., Chaudhary, U., Szabó, A., Lemieux, L. (2014, June 11). Describing epilepsy-related BOLD changes in the framework of resting state functional networks. [Poster session]: Organisation of Human Brain Mapping; Hamburg, Germany.

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Wandschneider, B., van Graan, A., Koepp, M. (2015, December 6). Effect of seizures and AEDs on task-related networks. Neuroimaging: Advanced Network Analysis Methods: Are They Clinically Useful? [Conference presentation]. Special Interest Group Meeting of the American Epilepsy Society. 69th Annual Meeting. Philadelphia. USA.

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van Graan, LA., Kozák, L.R., Chaudhary, U.J., Szabó, A., Lemieux, L. (2015, August 3). Intrinsic Connectivity Network – Based Quantification of the BOLD Changes associated with Epileptiform Activity. [Poster session]: 7th International workshop on seizure prediction. Melbourne. Australia.

Charalambous, M., van Graan, L.A., Liston, A., Lemieux, L. (2016, September 16). Application of a Functional Brain Atlas to Interpret Human Epileptic Seizure-Related fMRI Maps and Considerations for Application in Animals. [Poster session]. The European Society and College of Veterinary Neurology. 29th Symposium. Edinburgh. Scotland.

Awards

Runner-up, 14th Queens Square Symposium. icEEG-fMRI in Humans, UCL Institute of Neurology; May 10, 2013; London, England.

Scientific investigator's 1st prize award for clinical research. *Intrinsic Connectivity Network–Based Quantification of the BOLD Changes associated with Epileptiform Activity*. 7th International workshop on seizure prediction. August 3, 2015, Melbourne. Australia.

Acknowledgements

I learned a great deal at UCL and found my time at the MRI unit in Chalfont particularly rewarding and formative. I enjoyed the company of many people who have supported me in completing this thesis: The work presented here would not have been possible without the help and guidance of Professor John Duncan who has been inspirational. A word of thanks to Professor Xavier Golay who introduced me to the study of brain networks. I am grateful for the input and support of Professor Louis Lemieux who conceived the idea of an atlasing tool and its application to the study of ictal semiology. I am grateful to Dr Beate Diehl for discussion and ideas. I received valuable input from Dr Aileen McGonigal and co-workers in the Marseille research group and thank Dr Bernard Giusiano for sharing data and code that served to inform my methods.

A special word of thanks to Dr Lajos Kozak who programmed the atlas script and who shared the expertise. He provided valuable practical input in relation to image processing. I am grateful to Dr Umair Chaudhary for sharing the ictal dataset and to Dr Jacopo Fantini who reviewed patient's clinical history to establish frequency of typical seizure semiology. I thank Dr Pam Thompson for sharing patient test scores.

I am indebted to Professor Mathias Koepp for his personal support and encouragement to research drug effects on cognition and for facilitating financial support from the Henry Smith Charity.

I fondly remember the scientific input, fun and friendship from other fellows and researchers - Gloria Gonzales, Karin Trimmel, Anja Haag, He Chi, Britta Wandschneider, Maria Centeno, Mark Nowell, Lorenzo Caciagli, Lucy Townsend, Sjoerd Vos, Lucas Franca, and the support from Roman Rodionov and David Carmichael.

I thoroughly enjoyed working time in the scanner area and benefiting from the expertise of radiographers Philippa Bartlett, Jane Burdett, Andrea Hill at the Epilepsy Society MRI Unit.

I thank Peter Gilford for his help with computers. I am grateful to all the volunteers and patients who participated in the study and to Xandra Harman who made the MRI Unit, a friendly and welcoming environment.

With this I remember my parents who valued academia and I thank my family for their encouragement and support for the entire PhD.

Chapter 1

Epilepsy

The essence of this thesis is focal refractory epilepsy. In this chapter I provide a descriptive overview of epilepsy with an emphasis on specific investigations in the presurgical workup. I cite definitions and introduce causes, epidemiology, and the classification of epilepsy disorders. Insofar experimental studies in this thesis focus on language fMRI and semiology, the pre-surgical work-up is reviewed with amplification of, the value of semiology in providing insights into the seizure network, and the role of language fMRI in predicting cognitive impairment in surgical outcome.

Definitions

The International League Against Epilepsy (ILAE) Commission for Classification and Terminology (Fisher et al., 2017) cites a definition of "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain."
The formal definition proposed by the ILAE in 2005 required the occurrence of at least one epileptic seizure' (Fisher et al., 2005), but it was later advised that epilepsy, in practice be defined as a person having two or more unprovoked seizures occurring at least 24 hours apart. A person is considered to have active epilepsy when they are currently in treatment or if their most recent seizure has occurred within the previous two to five years (Thurman et al., 2011).

Causes

Cause' in epilepsy is often multifactorial and can result from genetic and acquired factors. While a medical model has categorised the known causes of epilepsy it has been noted that, being epileptic is far more than just having seizures; that is, the interpersonal, social, domestic, occupational and cultural connotations of epilepsy can often be far more important than the occurrence of seizures (Shorvon et al., 2019).

Epidemiology

The National Institute for Health and Care Excellence (2012) estimated the prevalence of active epilepsy in the United Kingdom to be around 5–10 cases per 1000 whereas the incidence is around 50 per 100 000. Epilepsy is well controlled with anti-epileptic drugs (AEDs) in two-thirds of patients. A somewhat higher prevalence of epilepsy is evident in poorer countries (Kotsopoulos et al., 2002) commensurate with indications that socio economic deprivation is positively correlated with a greater risk of developing epilepsy (Heaney et al., 2008).

Classification of epilepsy disorders

There have been developments in a range of fields including neuroimaging (Duncan et al., 2016; Duncan, 2009, 2010) that not only helped management but have prompted multiple revisions in terminology and classification by the ILAE over the last few decades (Berg et al., 2010). The ILAE 2017 classification proposes three levels of description, namely seizure type, epilepsy type, and that of epilepsy syndrome (Chang et al., 2017). Epilepsy is conceived of as a curable disease. It is said to be resolved when there has been a seizure-free period of ten years with the last five years spent without medications, or the patient is no longer at risk for age-related epilepsy syndrome (Fisher & Bonner, 2018).

The classification is relevant for adult and paediatric seizures as well as epilepsies, except for neonatal seizures, that are classified separately (Falco-Walter et al., 2018): Seizures in the neonatal period, are often provoked seizures with an acute cause and may be electrographic-only. It may not readily fit into the classification schemes for seizures that have been developed for other age groups (Pressler et al., 2021).

Seizure type

The first level is seizure type: Seizures are defined as transient symptoms and signs due to abnormal excessive or simultaneous neuronal activity of a population of neuronal cells

in the brain, and are divided into those of focal, generalised, (meaning of focal or generalised onset), unknown onset, with subcategories of motor, nonmotor, with retained or impaired awareness for focal seizures (Fisher et al., 2017). Some patients, may have both generalised and focal seizures, more often seen in some of the early-onset, drug-resistant epilepsies such as Lennox-Gastaut syndrome or Dravet syndrome (Wirrell, 2022a). Where, the seizure onset is missed or obscured, the seizure is of unknown onset.

For neonates, the ILAE classification emphasizes the key role of electroencephalography (EEG) for the diagnosis of seizures. Seizures can occur with or without clinical manifestations. As seizures are focal, classification in this group, makes no provision for generalised onset. Seizure type is determined by descriptors that are divided into motor, non-motor, and sequential as represented by the predominant clinical feature (Pressler et al., 2021).

Structure of the classification. Focal epilepsies may be unifocal, multifocal or hemispheric (ILAE 2017) and can be characterised as focal to bilateral tonic clonic. Classification according to onset has an anatomic basis, so that a focal onset seizure could be characterised by hemispheric lateralisation and or lobar localisation – that is, frontal, temporal, parietal, or occipital. Insofar the earliest (anatomic) indicator or classifier may not the most significant behavioural feature of a seizure, description of the ensuing features are encouraged to aid classification (Fisher et al., 2017).

Seizures could be depicted by specified onset feature (impaired awareness, motor and nonmotor signs). Thus, focal aware or impaired awareness seizures may optionally be further characterised by one of the listed motor or nonmotor onset symptoms, reflecting the first and earliest prominent sign or symptom in the seizure. Both methods of classification – that is, by anatomical onset and by behavioural features are available and can be used in concert (Fisher et al., 2017). The classification of seizures is depicted in Table 1.1

Table 1.1

ILAE 2017 Classification of seizures

FOCAL ONSET		GENERALISED ONSET	UNKNOWN ONSET
Aware	**Impaired Awareness**	**Motor Onset**	**Motor**
Motor Onset		tonic-clonic	tonic-clonic
automatisms		clonic	tonic-clonic
atonic		tonic	**Nonmotor**
clonic		myoclonic	behaviour arrest
Epileptic spasm		myoclonic-tonic-clonic	
hyperkinetic		myoclonic-atonic	**Unclassified**
myoclonic		atonic	
tonic		epileptic spasms	
Nonmotor Onset		**Nonmotor Onset**	
autonomic		typical	
behaviour arrest		atypical	
cognitive		myoclonic	
emotional		eyelid myoclonia	
sensory			
Focal to bilateral tonic-clonic			

Note. Adapted from Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi 19.1111/epi.13671.

The structure of the seizure classification is not hierarchical so that levels can be skipped. The classification of an individual seizure can stop at any level: For example, a

"focal onset" or "generalised onset" seizure, with no other elaboration, or a "focal sensory seizure," "focal motor seizure," "focal tonic seizure," or "focal automatism seizure," and so on. The use of additional classifiers are encouraged (Fisher et al., 2017).

Epilepsy type

After diagnosis of the seizure type, the next level is diagnosis of epilepsy type. Epilepsy is defined as a chronic disorder of the brain characterised by an enduring disposition towards recurrent unprovoked seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. (Sarmast et al., 2020). Epilepsy types are as follows: (1) focal, (2) generalised, (3) combination of focal and generalised, and (4) unknown (Falco-Walter, 2020). The categorisation of an epilepsy type is based on its type of seizure. Thus, a focal epilepsy describes focal seizures, and a generalised epilepsy describes generalised seizures. A combined generalised and focal epilepsy has both focal and generalised seizures. The 'unknown' epilepsy type refers to seizures that at the time of diagnosis are of unknown onset (Chang 2017). All seizure types a patient has must be defined to determine the epilepsy type: If a patient has focal aware cognitive to bilateral tonic clonic seizures which arise from the left and right temporal lobes, they have focal epilepsy. If they have both focal as well as generalised seizures (as in Lennox–Gastaut syndrome, for example), they have combined focal and generalised epilepsy (Falco-Walter, 2020). Accordingly, 'different practical definitions may be formed and used for various specific purposes' (Scheffer et al. 2017).

Aetiology

The classification encourages consideration of aetiology and comorbidities at each level (Zuberi & Brunklaus, 2018). Thus, once the epilepsy type has been defined, then the aetiology should be determined. The categories defined for epilepsy aetiologies are (1) structural, (2) genetic, (3) infectious, (4) metabolic, (5) immune, and (6) unknown (Falco-

Walter, 2020). A patient may have more than one aetiologic category (Scheffer et al. 2017). The six groups of aetiologies are available and incorporated at each of the three levels (i.e., seizure type, epilepsy type, epilepsy syndrome) given its potential implications for treatment (see Figure 1.1).

Epilepsy syndrome

The third level of classification is that of epilepsy syndrome. It refers to "a cluster of features incorporating seizure types, EEG, and imaging features that tend to occur together. It often has age-dependent features such as age at onset and remission (where applicable), seizure triggers, diurnal variation, and sometimes prognosis. It may also have distinctive comorbidities such as intellectual and psychiatric dysfunction, together with specific findings on EEG and imaging studies. It may have associated etiologic, prognostic, and treatment implications" (Scheffer et al., 2017). Epilepsy syndromes is less frequent in adults but thought to be possible in approximately one-quarter of epilepsy cases beginning in infancy and childhood (Wirrell, 2022a) and have been recognized for more than 50 years, as distinct electroclinical phenotypes with therapeutic and prognostic implications (such as childhood absence epilepsy, West and Dravet syndromes). The ILAE 2017-2021 Nosology and Definitions Task Force, have provided formal definitions of epilepsy syndromes (Wirrell et al., 2022), that divide into three groups as per age of onset together with a separate group called idiopathic generalised epilepsies (see below).

In addition to the typical age at onset, syndromes are further characterised by seizure and epilepsy types as well as association with developmental and/or epileptic encephalopathy or progressive neurological deterioration (Wirrell et al., 2022). Syndromes are defined as those with onset in: neonates and infants (up to age two years) (Riney et al., 2022), childhood (Specchio et al., 2022), and at a variable age (that is, in both paediatric and adult patients) (Riney et al., 2022). For each syndrome, diagnostic electroclinical criteria, as well

as expected results of other investigations (imaging, genetics), frequent co-morbidities, and natural history are provided.

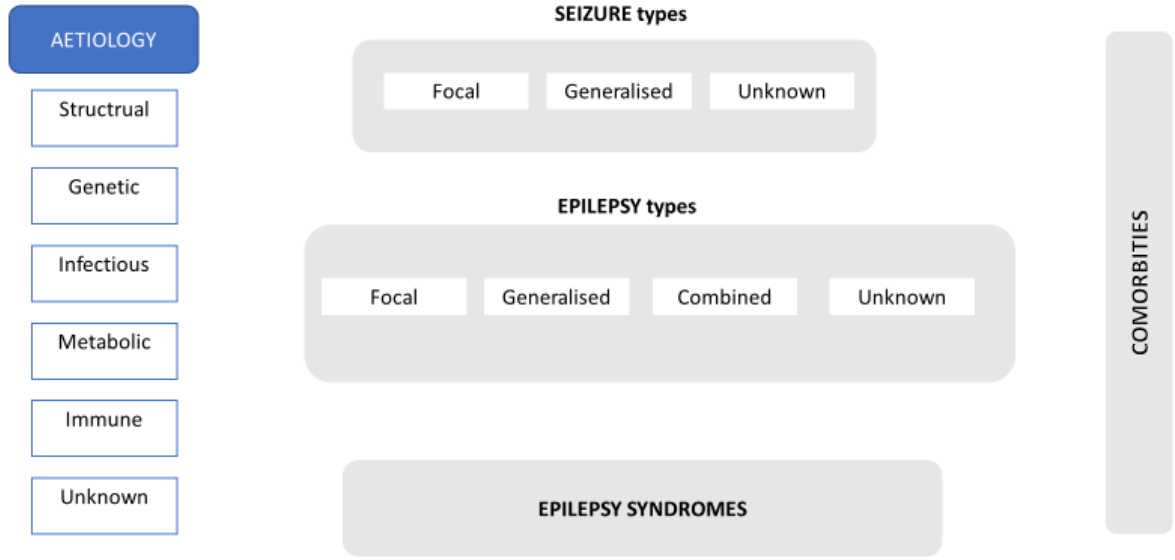
The syndromes are further subdivided into generalised, focal, or generalised and focal, based on seizure type(s) (Wirrell et al., 2022). Within the syndromes specifically the "genetic generalised epilepsies", the ILAE has, as noted above, retained the term "idiopathic generalised epilepsies" (Scheffer et al., 2017) - clinically useful insofar their classification carry prognostic and therapeutic implications (Hirsch et al., 2022). It comprises a group of four syndromes (childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and generalised tonic-clonic seizures) that typically affect developmentally normal children and young adults.

This thesis employs terminology proposed in the current ILAE (Scheffer et al. 2017) classification. The focus of this work falls in the category of focal epilepsies: The focal epilepsies that are relevant include reflex epilepsy which is characterised by seizures that have a specific mode of precipitation, as well as frontal lobe epilepsy (FLE), parietal lobe epilepsy (PLE) and temporal lobe epilepsy (TLE).

Language studies in this thesis were conducted in patients with TLE: Two main types of temporal lobe epilepsy, mesial temporal lobe epilepsy, arising in the hippocampus, the para hippocampal gyrus and the amygdala which are located in the inner (medial) aspect of the temporal lobe, and lateral temporal lobe epilepsy (LTLE), the rarer type, arising in the neocortex at the outer (lateral) surface of the temporal lobe have been recognised (Nayak & Bandyopadhyay, 2022). Based on the ILAE 2017 classification, patients with TLE are likely to be classified as having focal epilepsy, that manifest as focal onset seizures with or without impaired awareness (Nayak & Bandyopadhyay, 2022).

Figure 1. 1.

Schematic of ILAE Epilepsy Classification (2017)



The role of surgery in the management of epilepsy

Drug resistant epilepsy is defined as the failure of two appropriate and tolerated antiepileptic drugs to achieve seizure freedom (Kwan et al., 2010). In the 30% of patients with epilepsy who are pharmaco resistant (Verrotti et al., 2020), surgical treatment may be considered. The viability of surgery for patients with medial temporal lobe epilepsy was reflected in five year seizure-freedom rates of 57% achieved for anterior temporal resection and 63% for those with hippocampal sclerosis (de Tisi et al., 2011). The extratemporal epilepsies in contrast present with a wide range of potential aetiologies and neuroanatomical regions which making identification of the epileptogenic zone more difficult (Roper, 2009).

While the main purpose of epilepsy surgery is to remove the cause of seizures, surgical outcome in practise relates to a broader reality. It encompasses a spectrum of consequences within physical, psychological and social spheres, so that an extensive

evaluation and consideration for the dynamic interplay of factors in predicting outcome and guide decisions is required during pre-surgical evaluation (Duncan, 2011).

The pre-surgical workup

Patient selection typically evolves heuristically along a wide range of available investigations geared to provide optimal convergence of idiosyncratic information for guiding the physician and patient into a decision in relation to surgery (Duncan, 2011). Accordingly, elucidation of information is aimed at yielding indicators as to overall outcome and includes a detailed clinical status as well as history to inform as to the physical suitability for surgery. Such history is further informed by separate EEG and EEG video telemetry that respectively provide information on any localisation related or spread of abnormal rhythms as well as typical features related to seizure events. Neuropsychology provides baseline assessment of ability and may indicate other focal deficits. The crucial contribution of imaging is undergirded by the International League Against Epilepsy (ILAE) encouraging all patients to have a high-quality MRI (Duncan, 1997). Quantitative and computational MRI can make a significant contribution to the detection of subtle lesions that may underlie seizure generation (Duncan et al., 2016; Duncan, 2010). These investigations may be elaborated with functional data derived from fluorodeoxyglucose positron emission tomography, ictal single-photon emission computed tomography, magnetoencephalography (MEG) or from placement of intracranial EEG electrodes that attempt to localise the area of seizure onset (Duncan, 2011).

The diagnostic investigations outlined above, aim at identifying several critical cortical areas that inform the surgical perspective. It includes the symptomatogenic zone, which is the area of cortex where an epileptiform discharge produces the ictal symptoms. It is determined by an analysis of seizure semiology both on video and clinical history (Rosenow et al., 2001). The irritative zone is cortical tissue that generates interictal electrographic spikes that can be considered as ‘mini seizures’ (Rosenow et al., 2001). The

seizure onset zone is the area where clinical seizures are generated, which is distinguished from the epileptogenic zone, which is "the area of the cortex that is indispensable for the generation of epileptic seizures." The epileptogenic zone can be more extensive than the seizure onset zone and its location must be inferred indirectly by defining the other zones discussed above. The epileptogenic lesion is the cause of the epileptic seizures and is identified by high-resolution MRI (Rosenow et al., 2001). The identification of these cortical areas are elaborated in the context of the wider purpose of the pre-surgical work up with neuropsychiatric and psychological consultation as well as consideration of nursing and social care needs in the context of mental health and social vulnerabilities (Duncan, 2011).

The complete removal or disconnection of the epileptogenic zone in surgery is confounded by the risk of affecting eloquent cortex and consequentially new deficits. The possible loss of function should at least be predictable so as to inform decision about surgery and whether there are net gains from surgery (Rosenow et al., 2001).

Where resection risks eloquent cortex, the likelihood of post-surgical functional deficit is reduced by functional MRI (fMRI) that can predict the effects of temporal lobe resection on memory, lateralise language as well as localise primary motor, somatosensory and visual function (Duncan et al., 2016; Duncan, 2010, 2011).

Predicting cognitive impairment

Language deficits that can be distressing to patients and families are common in the immediate post-surgical period. While patients rapidly recover to baseline language ability, persistent language deficits are often seen at two months in a group with the most significant language deficits immediately following dominant hemisphere resection (Morrison et al., 2006). Actuarial data is required to guide physicians in relation to potential language deficits and rates of recovery (Morrison et al., 2006). In this regard language fMRI can be used to determine expressive language dominance, help in the interpretation of seizure semiology and

indicate the likelihood of language dysfunction after anterior temporal lobe resection (ATLR) (Duncan, 2010).

In a wider sense prediction of post-surgical complications is compounded by the possibility of atypical language organisation, which may influence the organisation and also compound prediction of lateralisation and localisation of other functions, such as memory or visual-spatial functions (Loring, Meador, & Lee, 1990). Given a plethora of factors that may affect language lateralisation, inferences about location and lateralisation based on neuropsychometry (Loring, 2001) cannot be relied upon in patients with mixed or right hemisphere language. Therefore, converging information is sought from the range of investigations including functional neuroimaging and electrocortical stimulation to map language functions (Duncan, 2009, 2011).

The diagnostic value of semiology

Until the introduction of the electroencephalogram by Berger, localisation in epilepsy surgery was based primarily on identifying the symptomatogenic zone (Rosenow et al., 2001). Careful analysis of semiology still compliments video/EEG monitoring, structural neuroimaging, functional mapping, and indices from neuropsychometry and forms an important component of the pre-surgical evaluation of epilepsy surgery candidates: It aids identification of the symptomatogenic zone and to localise the seizure (Foldvary-Schaefer & Unnwongse, 2011; Loddenkemper & Kotagal, 2005; Noachtar & Peters, 2009).

Summary

This chapter identified challenges in the pre-surgical workup: Specifically, that of 1) ascertaining the seizure network as reflected by ictal semiology and 2) the risk of surgery to language function. In the following Chapters, I review literature to provide a background for the focus of this thesis which is the utility of employing large scale canonical brain networks in 1) investigating and understanding the semiology/seizure network as well as 2)

understanding and predicting language impairment after epilepsy surgery. Large-scale brain networks are described: It provides a unifying theoretical framework that encapsulate understanding across levels of single neurons, neuroanatomy, neurophysiology, and neuroimaging, to neuropsychology and behaviour (Deco 2008), and may capture neural dynamics inherent in language function and ictal signs. In the experimental chapters it is employed as a systematic approach to the study of language function and ictal semiology.

Chapter 2

Language fMRI

Cognitive impairment, that is, a significant decrement or decline in function relative to expectation, is a significant comorbidity of epilepsy. Cognitive performance is impacted by cerebral lesions, interictal activity, seizures and medication with the decline of cognitive ability resulting from a range of factors that include the aetiology of the epilepsy, location and extent of the lesion, seizure frequency, and age of onset. In this chapter I provide a scoping overview of the literature as it relates to the use of language fMRI in the context of assessing the risk of post-operative language decline and impairment. The search terms language function, cognitive fMRI and language fMRI, were used.

The overview covers the impact of epilepsy on cognitive function, including the influence of anti-epileptic dugs. Language representation and reorganisation in the context of surgical risk to language function; and different methods that have been used in the localisation of language function along with insights gained from cortical stimulation mapping are discussed. Cognitive fMRI experimental design and data analysis are reviewed. I present a theoretical model of language that explain language difficulties after epilepsy surgery and introduce language as a function of large-scale networks as a backdrop to the investigations presented in the experimental chapters.

Cognitive function in epilepsy

A range of measures have been used to investigate and report on aspects of cognition, including attention, (Jiang et al., 2017; Shamshiri et al., 2017) working memory (Campo et al., 2013; Stretton et al., 2012; Wagner et al., 2009), long-term memory (Hoppe et al., 2007), encoding and recognition (Centeno, 2010; Sidhu, 2015) and language function (Abbott et al., 2010; Bonelli et al., 2012) reflecting the pervasive impact of epilepsy on cognition.

The spectrum of influences on cognitive function can be divided into fixed factors, such as underlying pathology and others that are more variable such as mood and side effects of AEDs (Baxendale & Thompson, 2010). Seizure frequency and severity are relevant insofar it is related to neuronal death in the context of anoxia, lactic acidosis and progressive hippocampal damage (Meador, 2002; Thompson, 2005). Developmental features of the seizure disorder play a role insofar age of onset together with severity of the disorder, affect the severity of neurocognitive impairments (Baker et al., 2011).

The influence of anti-epileptic dugs

Side effects from AEDs affecting cognition are common: In children, the use of AEDs has reportedly impacted on processing speed, language, as well as verbal learning and memory (Fastenau et al., 2009). Vigabatrin, Tiagabine, and Gabapentin characterised by potentiation of gamma-aminobutyric acid inhibitory neurotransmission, have been associated with sedation and concomitant reduction in processing speed, whereas Lamotrigine and Felbamate, considered to be glutamate excitatory agents have anxiogenic and antidepressant effects (Cavanna et al., 2010).

Different effects are associated with individual AEDs (Gualtieri, 2006; Ijff, 2013). Gabapentin, Lamotrigine, and Levetiracetam have all been shown to produce fewer neuropsychological test performance deficits in adults relative to the most commonly prescribed AED, which is Carbamazepine (Meador et al., 2007).

Imaging has demonstrated the effects of differential effects of individual AEDs which must be considered along with the impact of recent or underlying seizure activity (Jayakar et al., 2002) on fMRI results. Reports consistently find marked cognitive effects for Topiramate (Gomer et al., 2007; Gualtieri & Johnson, 2006; Meador, 2008; Thompson et al., 2000; Wandschneider et al., 2017). Different effects on default mode areas compared to other AED have been demonstrated for Topiramate with a pattern of deactivation in the basal ganglia,

anterior cingulate and posterior visual cortex in the context of language processing (Szaflarski & Allendorfer, 2012; Yasuda & Cendes, 2012). In an interesting study that used verb generation (Tang et al., 2016), task-induced deactivation was found to be a more sensitive fMRI biomarker, than task-induced activation for the impaired language performance in patients on Topiramate.

Whilst drug effects in epilepsy are most often associated with negative side effects, imaging studies have also shown normalising effects of medication on network activation in the context of cognitive tasks. Observation of improved cognitive profiles has been seen for patients suggests that Levetiracetam effects restoration of cognitive network activations patterns (Helmstaedter et al., 2008; Wandschneider et al., 2014).

Atypical language representation in epilepsy

Atypical language lateralisation refers to both mixed and right hemisphere representation. A greater likelihood of change in language organisation is consistent with brain pathology encountered in focal epilepsy so that greater right hemisphere language dominance in right-handed patients with seizures originating from the left hemisphere have been reported (Rausch & Walsh, 1984).

A spectrum of influences and identified brain pathologies are relevant although patients with a normal structural MRI (Wilke et al., 2011) have showed atypical language organisation. In epilepsy an association has been found with handedness, the location of the epileptogenic lesion and epileptic activity (Janszky et al., 2006). Right lateralised language function was observed in 24% of patients with left hippocampal sclerosis. Conversely, patients with right hippocampal sclerosis have all demonstrated typical speech organisation (Janszky et al., 2003). Regardless of the side, hippocampal atrophy impacts negatively on the language network but not on hemispheric language lateralisation (Lopes et al., 2019).

Language reorganisation has been associated with the duration of epilepsy (Wellmer et al., 2009) as well as age of injury (Springer et al., 1999). In general, the earlier the age of injury to the left hemisphere, the more likely reorganisation. When all factors were considered, only left-handedness and a left seizure focus predicted atypical (rightward) language lateralisation (Stewart et al., 2014).

Patterns of reorganisation

Epileptic activity may, over time, cause language sites to adjust and reorganise with intra-hemispheric shits (i.e., assumption of function by ipsilateral regions) (Brázdil et al., 2005; Duchowny et al., 1996; Federico, 2011; Hamberger & Cole, 2011) and inter-hemispheric changes (i.e., a shift in function to contralateral regions) (Brázdil et al., 2005; Gaillard, 2004; Janszky et al., 2006; Liegeois et al., 2004; Powell et al., 2007).

Altered network dynamics specific to epilepsy syndromes have been reported. Language activation in frontal and temporal areas is significantly more left lateralised in controls and right TLE than in left TLE patients (Thivard et al., 2005). Correspondence between measures of function and structure have been observed in left language lateralised patients with right TLE; whereas there is a reduced coupling between the functional and structural measures in the left TLE group (Rodrigo et al., 2008). A reduction in functional connectivity (see Chapter 3) has been demonstrated in patients with TLE within the language network (Vlooswijk et al., 2010; Waites et al., 2006), specifically evidencing connectivity reduction in the left hemisphere (Pravata et al., 2011). It correlated positively with linguistic performance in patients with a left but not in those with a right epileptogenic focus. However increased functional connectivity (FC) in posterior temporal regions for both left and right medial TLE patients (Protzner & McAndrews, 2011) correlates with language task performance.

In observations akin to other findings that relate to lesion focus, greater atypical language representation or lower typical asymmetry indices was associated with left sided seizures (Berl et al., 2005). In patients with FLE there appears to be greater effect on the organisation of function in anterior language areas (Duke et al., 2012).

Preoperative indicators of left hemisphere damage, including early seizure onset, poor verbal IQ, left handedness, and right hemisphere memory dominance have been associated with greater incidence of essential naming and reading areas in the anterior temporal lobe (1.5-3.5 cm from the temporal tip) which falls within the approximate region of a standard anterior temporal lobectomy with patients of higher verbal IQ and later seizure onset being particularly at risk of naming decline (Schwartz et al., 1998).

In cases of left TLE, who retained competence on measures of language, the left frontal lobe is invoked, in response to epileptic activity in the left hippocampus (Bonelli et al., 2011). In line with this observation, it is suggested that several neural systems adopt and share cognitive function, in the context of adaptation and reorganisation so that not all patients suffer language deficits following surgery. Studies have in fact demonstrated abnormal and idiosyncratic patterns of activation in the context of normal task performance (Noppeney et al., 2005), suggesting either pre or postoperative reorganisation. In this regard activation patterns specific to patient specific characteristics have been evidenced: In patients with left TLE and hippocampal sclerosis and left language dominance, increased recruitment of contralateral right hemisphere areas, as well as apparent wider left hemisphere language representation have been observed (Jensen et al., 2011). In an interesting result - a more posterior inferior frontal gyrus (IFG) verbal fluency activation was found in left TLE patients than in controls – a finding that indicates pre-operative reorganisation in patients with chronic left TLE (Voets et al., 2006). These idiosyncrasies observed in patients elaborates the challenge for prediction of language changes after ATLR.

Prevalence of atypical lateralisation

While the concept of the dominant hemisphere that reflects a uniformity of language lateralisation throughout the brain is increasingly being challenged (Tailby et al., 2017), the importance of pre-surgical evaluation towards lateralisation and preservation of abilities is underscored by quantifications from as early as 1990 (Snyder et al., 1990) of the incidence of mixed language representation. In a survey of intracarotid amytal test (IAT) assessment that simulates the effects of surgery by disrupting functional capacity of a hemisphere by means of sodium amytal which is injected into the correspondent carotid artery. Across 47 epilepsy surgery centres just under half of the centres found mixed language representation a rarity (i.e., in 0%–6% of cases) while all the other centres reported it to be prevalent in 10% to 20% of cases. The investigators, however, point out that centres relied on different procedures-and significant differences between centres are apparent in the context of IAT assessments: Left hemisphere dominance has been reported for right-handed patients in 63 to 96% of cases (Risse et al., 1997) and in 38 to 70% for left handed patients (Rasmussen & Milner, 1977; Serafetinides et al., 1965). fMRI studies, likewise, reflect increased atypical language organisation in patients (Gartus et al., 2009; Springer et al., 1999). Thus the literature shows considerable variation of lateralisation indices and different methods and paradigms, should be taken into account, when interpreting and summarising the results of BOLD fMRI maps (Thivard et al., 2005).

fMRI and IAT

A high degree of consensus is seen between IAT and fMRI (Adcock et al., 2003; Sanjuán et al., 2013) and both methods explain more variance in naming decline than age of seizure onset or preoperative naming performance (Balter et al., 2016). On the face of it, fMRI and IAT derive their measures entirely differently. Although concordance between

fMRI-based laterality and IAT has been showed to be much lower in left TLE than right TLE patients (Benke et al., 2006), profoundly different conclusions are rare (Janecek et al., 2013).

fMRI and cortical stimulation mapping

The procedure of cortical stimulation mapping (CSM) involves the use of electrical stimulation that induce temporary functional lesions while patients are asked to perform tasks. It serves to locate essential language areas or tracts for preservation of function (Golby & McConnell, 2005). Good albeit incomplete agreement between fMRI and CSM has been demonstrated. While fMRI has shown high sensitivity it has relatively poor specificity (FitzGerald et al., 1997; Pouratian et al., 2002; Rolinski et al., 2019; Schlosser et al., 1999) and it has been suggested that together they may predict outcome better than the tests alone (Rolinski et al., 2019). Areas activated by fMRI that are not disrupted by CSM demonstrates that fMRI activates networks and areas that are not necessarily vital to the task in question – implying false positives in relation to the question of critical functions. In the surgical context, false-negative findings are critical. Notably, one study observed that speech failed to achieve fMRI activation in articulatory regions beyond the inferior frontal gyrus (Petrovich et al., 2005). Areas and associated function disrupted by CSM with no fMRI activation were observed in two series where such fMRI false negatives were observed in two out of 21 patients. Better results have been achieved when four different tasks were employed to identify common activations and compared with CSM findings (Rutten et al., 2002). In studies that compared fMRI with intraoperative electrostimulation better correlation between the techniques were observed when two fMRI tasks were combined (Roux et al., 2003; Rutten et al., 2002; Spena et al., 2010).

While CSM is a technique that allow direct observation and very precise localisation it is limited by time constraints in the surgical setting and by spatial constraints on regions for mapping (Roux et al., 2003). For patients that are multi-lingual the assessment of localisation

appears to be compounded insofar cortical stimulation has demonstrated both unique and overlapping sites for languages concerned (Lucas, 2004; Polczynska, 2016; Walker, 2004).

Language fMRI in the prediction of surgical outcome

Blood oxygenation level dependent (BOLD) fMRI patterns have been correlated with surgical outcome, specifically predicting language decline after ATLR (Duncan, 2009). Left language lateralisation was related to poorer naming outcome whereas right language lateralisation was associated with relatively little change. Interestingly, temporal lobe asymmetry showed a greater correlation with naming deficits than that in the frontal lobes (Sabsevitz et al., 2003).

Historically, language was understood to be organised along separate motor and sensory systems associated with the inferior frontal gyrus and the superior temporal gyrus, with the arcuate fasciculus facilitating receptive/auditory-expressive/motor interaction. This understanding has both been challenged by surgical outcome, specifically language deficits found after ATLR (Bell, 2003; Bonelli et al., 2011; Bonelli, 2012) and evolved by stimulation mapping, imaging, and lesion studies so that the core neural infrastructure of language processing is seen to be shared rather than divided between expressive and receptive aspects.

fMRI design and analysis

In fMRI studies the *design* references how a stimulus is presented whilst the *model* is a term used to embody the methods that are used to account for the haemodynamic response. *Events* refer to brief stimulus presentation associated with a brief burst in neural activity whereas an *epoch* describes a continuous stimulus presentation thought to lead to sustained neural activity. Specifically, the impulse response describes the BOLD response to events or epochs.

Block design

Block designs refer to discrete periods during which either stimuli or rest (i.e., absence of stimuli) is presented in a continuous series. Statistical summary values reflect the activation in the 'blocks' of time respectively, allowing for 'contrasts' that reflect on the effects of different combinations of block effects to be calculated.

Event related design

Event-related fMRI relates to measurement of haemodynamic responses to brief stimuli or tasks (Josephs & Henson, 1999). Whereas blocked design assumes constant activity, event related designs discretely account for each haemodynamic response to a brief stimulus. It allows for post-hoc classification of trials so that responses can be analysed and contrasted individually (Wagner, 1998). It facilitates the assessment of subjective responses such as memory encoding or emotional responses (Kleinschmidt et al., 1998) as well as paradigms which cannot be blocked such as oddball designs that require unexpected presentations.

Cognitive subtraction

A cognitive task is contrasted by a different task that controls for all processes other than the one being studied. Activations are first measured in a "control state", followed by a measure of activation during stimulus presentation. The control activity is subtracted from the stimulation activity to identify the discrete brain activity that is due to the process of interest. The difficutlties with this approach includes the assumption that another cognitive process can be 'inserted' without affecting active processes in the baseline task (Friston et al., 1996) and that the baseline task does not activate processes contained in the task being studied.

Cognitive conjunction

This approach elaborates the logical operation used in cognitive subtraction paradigms. Tasks that share a common difference (Price, 1997) are employed as opposed to

cognitive subtraction that determines a difference between two tasks. It allows for some flexibility in designing a baseline task as it does not need to conform to the criteria for pure insertion. In a factorial design the individual main effects of two or more variables are calculated as well as the effect of one variable on another, allowing for the observation of interactions (Friston et al., 1996).

Lateralisation of function

Various algorithms have been proposed for quantifying lateralisation. It has involved calculation and comparison of values of both hemispheres such as the number of activated voxels in either ROIs or entire hemispheres (Gaillard et al., 2002). Alternatively it has been established by the number of supra-threshold voxels (Adcock et al., 2003). Positive values are left lateralised. Conversely, negative values reflect right-sided dominance. Low values are thought to reflect bilateral representation. Indices can be extracted by statistical weighing of voxels that correlated positively with a task (Branco et al., 2006) or measurement of the mean signal intensity change within a volume (Adcock et al., 2003). The bootstrapping approach (Wilke & Schmithorst, 2006) employed in the experimental studies in this thesis, is based on multiple sampling at different thresholds, which avoids the limitations imposed by a single threshold and the impact of outlier values.

Localisation

The advantage of fMRI over EEG and neuropsychology is its high degree of spatial resolution. Although the early history of fMRI was marked by great success such delineation of the landmarks involved in hand motor function (Yousry et al., 1997) and face recognition (Kanwisher, 1998), precision localisation for many functions has proved to be difficult. Two broad approaches incorporated in the manual of the Statistical Parametric Mapping 12 (Penny et al., 2007) in relation to localisation have been in use: the first is to retain the acquired signals in native space and to label the activation according to the tasks performed.

In conditions such as epilepsy where the function may be highly idiosyncratic, a single subject approach utilising the position of activation or a pattern of activations across different tasks, intuitively presents an optimal approach to delineating an individual's own networks and functional anatomy. The alternative approach is to match acquisitions to a standardised template for comparison within and across groups, followed by labelling the activity**.** Anatomical labelling is based on structural features, represented by cellular, macroscopic or coordinates in space with the accuracy of comparison in the standardised brain, being a function of the transform of structure and function into standard space.

Limitations of cognitive fMRI in the pre-surgical workup

Impaired neuropsychological function after surgery renders pre-operative assessment essential. fMRI is readily performed and repeatable, and now in widespread use to help establish lateralisation of function. However, despite rapid early advances, concerns and challenges that relate to sensitivity and specificity remain. Accordingly (Duncan, 2010):

1) Areas activated by any one fMRI paradigm may not be required for the performance of that task.
2) All areas involved in a task will not necessarily be activated by a particular fMRI paradigm. Furthermore, the area of BOLD activation varies greatly in size depending on the thresholds used to display the data and the region of maximal BOLD activation does not always correspond to most eloquent cortical regions. Conversely, it cannot be assumed that areas that do not surpass the chosen threshold are not significant to the task.
3) Performance is not quantified by the extent of activation - either in terms of the spatial or intensity characteristics.

For fMRI to evolve its clinical value, it must prove significant predictive power in relation to localising critical language function (Roux et al., 2003). Insofar fMRI tasks and

analytical approaches have reliably localised eloquent cortex on the individual level, it raises the question as to whether it can replace IAP and direct cortical mapping which are also not very predictive of outcomes (Szaflarski, 2019).

The capacity of fMRI to determining language laterality has been reflected in report of a strong one-to-one correlation with measures of diffusion tensor imaging tractography and voxel based morphometry (James et al., 2015). The results of ongoing studies indicate that language fMRI has still not reached its full potential and may also relate to inconsistent application of optimal procedures in language fMRI with marked heterogeneity in all aspects of fMRI was evident across 63 epilepsy surgical programs (Benjamin et al., 2018).

Evolving fMRI Specificity

Interpretation of BOLD Maps: The neural architecture of language

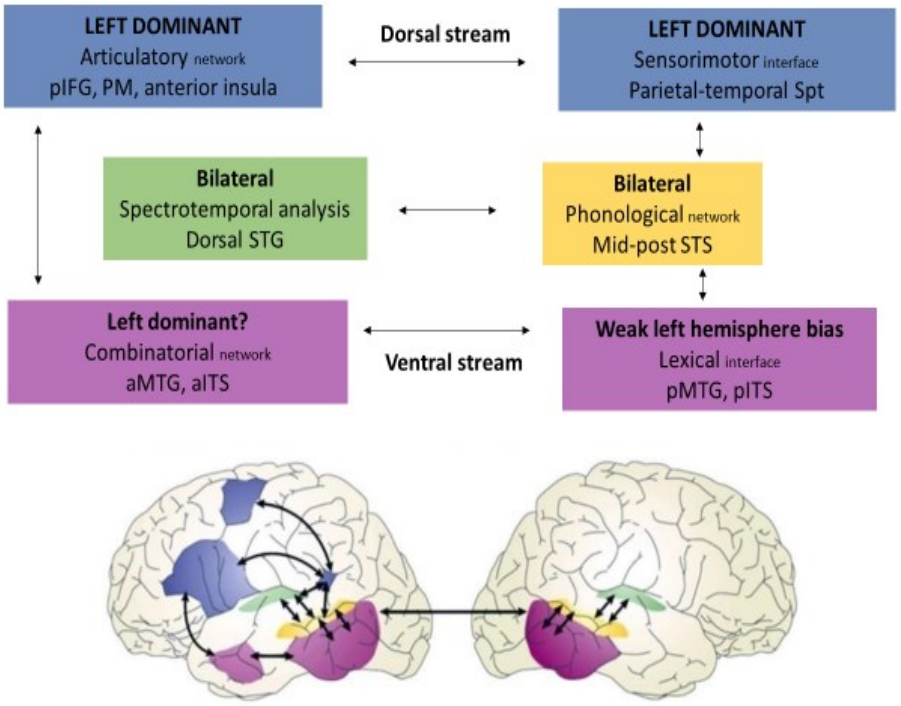
Recent models of cortical language organisation feature different streams of information processing (DeWitt & Rauschecker, 2013; Duffau, 2017b; Duffau et al., 2014; Poeppel & Hickok, 2004; Rauschecker & Scott, 2009) akin to the visual dual stream system (Goodale & Milner, 1992). In the language domain, the dual stream model provides an explanation of classical language disorders (Hickok & Rogalsky, 2011; Poeppel & Hickok, 2004). In essence, the model holds that the language system involves parallel processing across cortical and subcortical regions: Unlike historical models, often simplified in terms of a dichotomy between language reception and production, these "dorsal" and "ventral" pathways, account for a range of distinct sensory and semantic processes. Bilateral auditory regions on the dorsal superior temporal gyrus processes speech initially (Hickok & Poeppel, 2007; Poeppel & Hickok, 2004). Subsequently it is conducted along a temporal lobe ventral stream that involves comprehension (syntactic and lexical processes), and a strongly left-dominant dorsal stream that supports sensory-motor integration and also involves the parietal-temporal junction and frontal areas.

Various roles have been associated with subcortical grey matter structures, such as the basal ganglia, which are thought to be involved in the retrieval of knowledge from declarative memory (Ullman, 2006) and preverbal monitoring of language such as coordination the timing of intended language into speech (Crosson, 1985). While the prominent models (DeWitt & Rauschecker, 2013; Duffau, 2017a; Duffau et al., 2014; Poeppel & Hickok, 2004; Rauschecker & Scott, 2009) of the dual stream language processing differ in relation to aspects of lateralisation, fMRI studies have observed bilateral dorsal superior temporal gyrus and superior temporal sulcus activation in response to auditory language stimuli suggesting distinct complementary processing in each hemisphere (Hickok & Poeppel, 2007).

Functional imaging indicate that the nondominant hemisphere is involved in processing features such facets of speech act semantics in everyday function (Buchanan et al., 2000; George et al., 1996). Reviews (Price, 2012; Schirmer, 2012) that incorporate PET and fMRI studies reflect on processing differences between the two hemispheres but nevertheless present very good evidence that the ventral stream is bilaterally represented. The dorsal stream which supports sensory-motor integration is considered to be strongly left-dominant (Hickok & Poeppel, 2007; Rauschecker & Scott, 2009; Wise et al., 2001).

Figure 2. 1.

Dual Stream Model of Speech Processing



Note. The dual stream model (Hickok & Poeppel, 2000; Hickok & Poeppel, 2004; Hickok & Poeppel, 2007). The figure shows asymmetric dominance of the two streams (i.e., more bilateral ventral stream, left-dominant dorsal stream): Bilateral auditory regions on the dorsal superior temporal gyrus that support spectrotemporal analysis (green) and superior temporal sulcus that supports phonological access/representation (yellow). A temporal lobe ventral stream supports speech comprehension and a "combinatorial network" in the anterior temporal lobe, that include the anterior medial temporal gyrus, and the anterior inferior temporal sulcus that support lexical access and combinatorial processes (pink). A left-dominant dorsal stream supports sensory-motor integration and involves structures at the parietal-temporal junction (Spt) and frontal lobe (blue). IFG, inferior frontal gyrus; ITS, inferior temporal sulcus; MTG, middle temporal gyrus; PM, premotor; Spt, Sylvian parietal-temporal; STG, superior temporal gyrus; STS, superior temporal sulcus. Adapted from Hickok and Poeppel (2007). The model indicates that ATLR and disease affecting the temporal pole associated with semantic dementia, that include general semantic deficits (Compston, 2011; Mummery et al., 2000), disrupts the combinatorial process ascribed to the anterior temporal lobe and give rise to word finding deficits.

The wider neural representation of language is consistent with widespread activations in fMRI studies and consistent with many fMRI language studies that have interpreted results in the context of brain networks rather than specific brain areas (Ferstl et al., 2008). However, the importance of specific brain areas should not be understated: The challenge to clinical fMRI is not only to sample the wide-ranging components involved in everyday language function but to isolate function that critically require the regions to be resected. This challenge is consistent with both the proven capacity of fMRI to map distinctly essential functional cortices and graph theoretical concepts that have explicitly drawn attention to components and specialised core regions that are essential to function (Fedorenko & Thompson-Schill, 2014; Hagoort, 2014). In this regard, the dual stream model (Hickok & Poeppel, 2007) proposed a "combinatorial network" in the anterior temporal lobe which relates to conceptual semantic combination/processes (Rogalsky & Hickok, 2008; Westerlund & Pylkkänen, 2014). A lexicon or vocabulary is considered to comprise phonological, syntactic, and conceptual aspects. That is, the combination of a word class, a pronunciation, and a meaning provides a "full picture of a word" (Murphy, 2010). In line with this model ATLR and conditions such as semantic dementia (Compston, 2011; Mummery et al., 2000) are likely to disrupt the combinatorial process ascribed to the anterior temporal lobe and thus give rise to word finding deficits.

Interpretation of BOLD Maps: Language as function of large-scale brain networks

For the most part, interpretation of results in fMRI studies, have focused on regions of interest or areas of peak activation. While many studies have referenced networks, considering the language network as emergent from the whole brain connectome, requires consideration of the brain functional network architecture.

The functional connectivity of the whole brain has been studied using spontaneous fluctuations as observed by resting state fMRI (rsfMRI) (Power et al., 2011; Yeo et al., 2011),

that has provided different information than pure anatomy (Wig et al., 2011). The BOLD time courses in distributed brain regions have been found to correspond to known functional systems (Laird et al., 2013; Smith et al., 2009) including sensorimotor (e.g., somato-motor), auditory, visual, and frontoparietal (Smith et al., 2009) and the default mode system (Fox et al., 2005; Raichle et al., 2001).

More recently a whole brain functional brain network architecture was derived using network analysis of resting state functional connectivity (rsFC) data between every pair of voxels in the brain (Power et al., 2013) with hub regions that are in canonical language areas. A whole-brain rsFC study in a large dataset identified a language system, at individual brain level, that emerged from a supervised learning algorithm at a much later stage of iteration than used to identify larger scale resting state networks (Hacker et al., 2013), demonstrating that networks can be found from subtle features of the BOLD correlation structure, either constituting minor sub-components within hierarchically organised resting state networks (RSNs) or as entities that extend over multiple levels across RSNs. The left supramarginal gyrus and inferior frontal cortex have been singled out as comprising a language-related system in task based seed-based analyses (Koyama et al., 2010; Lohmann, Hoehl, Brauer, Danielmeier, & Bornkessel-schlesewsky, 2010), suggesting some convergence in findings across different levels of analysis (Vogel et al., 2014). However, comparison of the FC network configurations during a language task and during resting state, associated changes in FC with a "pruning" of the broader RSN FC. The authors argue that while the RSNs may be affected by pathology, they reflect a different and broader view of network functionality for a given cognitive domain, and are less informative about the more localised regions called upon to perform a given task (Doucet et al., 2017).

Language paradigms

Pre-operative language fMRI is used primarily to lateralise language functions. Task paradigms to engage language areas associated with expressive as well as comprehension function (Adcock et al., 2003; Duke et al., 2012; Gonzálvez et al., 2016; Liégeois et al., 2004; Trimmel et al., 2018; Woermann et al., 2003) have been used to observe language organisation. Employing a panel of tasks (reading comprehension, verbal fluency, auditory comprehension) was shown to reduce inter-rater variability and help establish language laterality (Gaillard et al., 2004).

Language and memory

Studies to date suggests that fMRI language lateralisation may have clinical utility beyond the prediction of language outcome (Balter et al., 2016): The neural and functional relationship between language and memory is reflected in observed association between verbal memory scores and lateralisation of language on psychometric tests which is likely to reflect the substantial connections between inferior frontal cortex and hippocampus (Everts et al., 2010; Sanjuán et al., 2013).

While most left language dominant subject have been found to be typically lateralised for recognition memory involving faces and written words, these functions tend to be reversed in individuals with right language dominance (Gerrits et al., 2019): A possible role for the hippocampus in language function is indicated by results that show patients with left hippocampal sclerosis to have higher atypical language dominance in temporal and frontal regions than patients with left frontal and lateral temporal lesions (Weber et al., 2006). Moreover, preoperative fMRI language dominance, has been correlated with postoperative verbal memory decline (Binder et al., 2008, 2010).

ATL resection: Achieving greater specificity in prediction

Whilst the literature attests to a well-established role in language comprehension, and both the dorsal and ventral paths contribute to both repetition and naming (Schwartz & Dell, 2016), it is clear from post-surgical decline that the ventral route makes an essential contribution to the retrieval of words based on their meaning. Although the ATL has been described as part of a larger language network its vulnerability to postsurgical language deficits for patients selected for ATLR is underscored by the fact that it is considered a hub that supports multimodal processes such as semantic memory, abstract conceptualisations, object concepts, biographical and social knowledge (Bonner, 2013; Olson, 2013; Simmons, 2009; Wong, 2012).

Various elements (syntactic structure, prosody, combinatorial semantics, lexical-semantics) engage large frontal-temporal-parietal networks, of which the ATL is one component (Hickok & Poeppel, 2007; Poeppel & Hickok, 2004). The challenge for fMRI studies is compounded by observation that posterior regions are also sensitive to syntactic structure and semantics (Griffiths et al., 2013; Wilson et al., 2014). To date, functional imaging suggests that the ATL is engaged by a variety of lexical and semantic tasks, including categorisation, naming, lexical decisions, and semantic knowledge decisions (Noppeney & Price, 2002; Peelen & Caramazza, 2012). The ATL is closely associated with semantic memory (Simmons et al., 2009) and semantic dementia that result from atrophy in the temporal pole, effecting domain general semantic deficits manifest in the naming, categorisation and discrimination of objects (Compston, 2011; Mummery et al., 2000). Naming and semantic deficits are also observed after anterior temporal resection (Drane et al., 2009; Emerton et al., 2014) with the severity of decline correlated with the extent of lateral temporal neocortex resected (Hermann, 1999).

Thus, as seen from the literature, the dual stream model of language accounts for phonological (sound), lexical (word), and semantic (meaning) processing and is consistent with the widespread neural activation observed with language fMRI. In the surgical context such widespread activation conflicts with the degree of precision achieved by CSM which identifies crucial cortical sites with high spatial specificity (about $10mm^2$) (Ojemann et al., 1989). Further context for the current limitations of fMRI is provided by the fact that permanent postoperative language deficit has been attributed to proximity of crucial cortex to resection margins. Generally permanent deficit is avoided by a margin of up to 1 cm (Gil-Robles & Duffau, 2010; Haglund et al., 1994). However the critical contribution of language fMRI was illustrated in recent findings which showed that the extent of fMRI activation that was resected in TLE had the greatest impact on naming ability compared to (a) resection volume; (b) overlap between resection and preoperative activation; and (c) overlap between resection and Wernicke's Area, age at seizure onset, preoperative naming score, and resection side and its relationship to language dominance (You et al., 2019).

Insights from cortical stimulation mapping

It must be considered that the errors and disruptions in response to cortical stimulation during naming tasks, can help to delineate linguistic anatomy. Interestingly, semantic errors, have been elicited on inferior frontal gyrus, the posterior middle temporal gyrus (MTG), and the anterior supramarginal gyrus (Bello et al., 2007; Corina et al., 2010).

Implications for the design of task paradigms in the context of ATLR, particularly towards localisation is that auditory naming has shown a more anterior temporal localisation than picture naming (Hamberger, 2007) and that noun and verb naming, respectively are associated with different localisation albeit the precise locations vary across individuals (Corina et al., 2005).

Diffusion tensor imaging tractography

Diffusion tensor imaging tractography (Behrens et al., 2003; Berthier et al., 2012; Catani & de Schotten, 2008) has identified long-range fiber bundles considered most important for language, which are: The arcuate fasciculus and parts of the superior longitudinal fasciculus that connects the frontal cortex and the temporal cortex (Frey et al., 2008; Friederici, 2011; Friederici & Gierhan, 2013). Collectively it comprises a dorsal language network. A ventral network system is collectively comprised of the uncinate fasciculus (Lu, 2002), inferior longitudinal fasciculus (Ashtari, 2012) and the extreme capsule fiber system or the inferior-fronto-occipital fasciculus (Mandonnet, 2007; McDonald et al., 2008), and the middle longitudinal fasciculus (Catani & Dawson, 2017). The uncinate fasciculus connects the anterior inferior frontal cortex with the anterior temporal cortex. The inferior-fronto-occipital fasciculus connects the frontal cortex with posterior parts of the brain, that is, the posterior temporal cortex, the occipital cortex and also the parietal cortex (Friederici & Gierhan, 2013). The majority of tractography studies on semantic dementia in patients have attributed semantic processing to the ventral pathways, specifically the anterior temporal aspects (Catani & Dawson, 2017).

The diffusion tensor imaging tractography measures of fractional anisotropy or mean diffusivity may be crucial in developing insights into factors that determine and predict outcome after ATLR (Osipowicz, 2016). Several studies (Kucukboyaci, 2014; McDonald, 2008; Wang, 2010) have shown that microstructural white matter integrity is sensitive to language impairment in TLE. Tractography and derived metrics, typically fractional anisotropy or mean diffusivity have been associated with asymmetries in fMRI language activations (Powell, 2006; Vernooij, 2007) and arcuate fasciculus lateralisation index (LI) have largely been concordant with fMRI (Ellmore, 2010). These measures have identified right hemisphere contributions and structural and functional reorganisation of language in

TLE (Powell, 2007; Pustina, 2014) as well as intra-hemispheric (Yogarajah, 2010) and interhemispheric (Pustina et al., 2014) postoperative reorganisation and adaptive changes that may be crucial in determining outcome after ATLR.

fMRI language paradigms

Not only are word finding difficulties, readily observed in cases of TLE where the epilepsy is lateralised to the speech-dominant hemisphere (Bell et al., 2003; Bonelli et al., 2011) but naming also, has been established, at least since the late 90's as the most commonly affected function following language-dominant ATLR (Davies et al., 1998; Saykin et al., 1995). Significant reductions in naming abilities after resection of the speech-dominant temporal lobe is observed in left TLE (Bonelli et al., 2012) and word-finding and verbal fluency in right TLE patients (Bonelli et al., 2012; Helmstaedter, 2003).
fMRI paradigms such as object naming using visual (Hamberger et al., 2007; Hermann, 1988) and auditory stimuli (Hamberger, 2009; Specht, 2009) that specifically activate areas that are removed by ATLR (Duncan, 2009), providing for greater specificity (Rosazza et al., 2013) have been suggested.

Verbal fluency tasks

Verbal fluency (VF) tasks are commonly employed and achieve distinct lateralisation of expressive language functions in the dominant inferior frontal gyrus (IFG) and the middle frontal gyrus (MFG), rather than in the medial temporal lobe in healthy controls and TLE patients (Bonelli et al., 2012; Friedman et al., 1998). Despite sensitivity to post-surgical change in function, the VF paradigm shows poor specificity - that is, activation in the ipsilateral frontal lobe is not always correlated with naming impairment. Tasks have demonstrated reliability in clinical studies and lateralisation indices are obtained regardless of the patients' cognitive abilities (Weber et al., 2006). Sensitivity has been demonstrated in the context of lateralisation - a greater loss in naming abilities was observed after left ATLR

(Bonelli et al., 2012) in cases where there was a stronger preoperative activation in the left middle frontal region in the context of a verbal fluency task (Bonelli et al., 2012; Friedman et al., 1998). Tasks are covert and a difficulty is that performance cannot be monitored. Moreover, interpretation of activation maps is compounded by the fact that these language networks lends themselves to many other non-linguistic cognitive tasks (Fedorenko & Varley, 2016).

Naming tasks

Compared to fluency paradigms, auditory and visual naming paradigms may yield greater predictive specificity with regard to naming difficulties after ATLR (Binder et al., 2011; Duncan, 2009; Hamberger & Seidel, 2009; Rosazza et al., 2013). Suggestions include object naming paradigms involving visual (Hamberger et al., 2007; Hermann et al., 1988) and auditory stimuli (Hamberger et al., 2007; Hamberger, 2009; Specht et al., 2009). Promising results have been reported for overt naming tasks using visual and auditory naming stimuli (Gonzálvez et al., 2016) and highly reliable centres of activation have been identified over time using an overt picture naming paradigm (Nettekoven et al., 2018).

Covert and overt paradigms

The majority of clinical fMRI studies have applied covert paradigms (Deblaere et al., 2002; Gaillard et al., 2002). While overt tasks are penalised by greater motion and magnetic susceptibility artifacts (Barch et al., 1999; Birn et al., 1999) it offers direct control of task performance during scanning (Barch et al., 1999) and resemble the requirements for everyday task performance. In a formal comparison of covert paradigms with their overt analogues overt sentence and word generation achieved similar localisation but lower lateralisation capabilities (Partovi, 2012). Greater activation and lateralisation have also been seen for covert paradigms in other studies (Palmer et al., 2001; Zaca et al., 2013) that compared localisation and lateralisation between paradigms.

Summary

In this chapter, I reviewed the limitations of language fMRI primarily as it relates to specificity, particularly, in predicting language impairment after ATLR. While language fMRI presents with good sensitivity and spatial coverage, convergence of results and specificity is compounded by different methods, idiosyncratic patient characteristics, and the influence of medication as well as seizure activity on activation maps. Methods are required that will selectively delineate ATL function over other structures and therewith serve as a predictor for post-surgical language decline.

This chapter included description of language as function of large-scale network streams. Language activation in ATL structures may be a function of larger scale networks. This chapter cited the advantages of overt language paradigms and naming over that of previously employed covert fluency tasks in activating temporal lobe structures and a body of fMRI results, suggests that a panel of tasks, comprising a range of linguistic features, is more likely to provide features to specifically identify ATL activation. In the following chapters I describe canonical large-scale networks, an atlasing method and a panel of tasks that may help in the assessment of the role of disease features and in the prediction of language impairment following surgery.

Chapter 3

Functional Brain Connectivity Networks

In neuroimaging, study in relation to brain function encompass localisation – that is, regions that specialise in specific aspects of behaviour; and connectivity, which refers to the way in which brain regions communicate with one another. These notions date back to the phrenologists who attempted to assign mental functions to specific brain areas based on the shape of the skull (Zola-Morgan, 1995). The history of functional mapping includes correlating deviations from normality in behaviour to lesioned brain areas. Study of localisation has been retained as reflected by the concept of functional specialisation (Friston, 1994) while functional integration is considered necessary to fully explain brain function (Friston, 2005; McIntosh, 2000). The study of brain function has further distinguished between the brain as an input-output system driven primarily by external interaction and the view that it operates autonomously, with external factors as a modulating and secondary influence (Fox et al., 2007).

The BOLD signal provides a window on neural activity across task and resting states (Raichle, 2011b): This view is afforded by the association of local field potentials with the BOLD signal (Logothetis, 2008; Raichle et al., 2006) in the slow frequency range associated with rest as well as coherence of power in the gamma frequency band associated with cognitive function (Fries, 2009; Uhlhaas et al., 2009).

The use of fMRI to identify areas of synchronous activity as well as the influence of one area upon another was pioneered by studies (Biswal et al., 1995) that showed synchronisation between BOLD fluctuations within the motor system. In neuroimaging the concept of connectivity has been invoked to reflect quantified relationships between brain regions. It has proved to be more sensitive to the effects of disease than difference in activations between regions (Rowe, 2010). It has sought to reframe investigation of higher-

level brain function in terms of its underlying neurobiology (Shine & Poldrack, 2018), which could significantly benefit the current use of behavioural indices (such as lists of signs and symptoms) to investigate the neural basis of human function (Satterthwaite et al., 2018). In this regard, functional connectivity represent a vehicle for furthering insights into epilepsy which is associated with dysfunctional networks (Tracy & Doucet, 2015).

In this chapter I review networks using the construct of connectivity that describe functional relationships expressed in unique patterns of spatial coherence that are similar for spontaneous and task evoked activity. I distinguish between the patterns observed during rest and task and in this regard clarify the role of cognitive task, internal speech and unconstrained mind wandering. I consider how slow fluctuating hemodynamic patterns can be related to task activated fast neuronal activity and how different large-scale functional networks cooperate, compete and coordinate their activity during complex cognitive behaviour. The mechanism of the BOLD signal, including the neurophysiology underlying the bold signal are reviewed along with challenges to fMRI data quality. Approaches to the study of functional brain connectivity are considered as a backdrop for investigation of the impact of epilepsy and surgery on cognitive function and a potential role underlying the manifestation of seizures, namely semiology. The search terms *epilepsy, brain connectivity and resting state networks* were used.

Synchronised neuronal activity

First noted by Luria in the mid twentieth century (Luria, 1973) functional systems are comprised of dynamically coupled sub-regions of the brain. fMRI, cortical thickness and diffusion tensor imaging studies have shown collections of neurons that have high within cluster but "sparse" long distance connectivity (Chen et al., 2008; Hagmann et al., 2008; He et al., 2009) - organisation consistent with maximum efficiency and global coordination of information flow (Buzsaki et al., 2013; He et al., 2009).

Synchronisation which is based on neurotransmitter dynamics is thought to be central in facilitating signalling: It is held to be dynamically modulated, so that a particular neuron could belong to any number of cell assemblies. The activity of neurons are combined for signalling when their spike activity is synchronised allowing for "coded states" (that is, a near infinite number of signals are possible) to exceed the number of neurons (Shadlen & Movshon, 1999). The degree of interaction between clusters of neurons and the rest of the brain varies over time, (de Pasquale et al., 2018) and neural synchronies present a mechanism for long-range neural integration during functional tasks (Breakspear & Terry, 2002; Freeman & Rogers, 2002; Lachaux et al., 1999; Sauseng & Klimesch, 2008).

Quantitative EEG and MEG analyses have elaborated different aspects of neuronal synchrony and demonstrated that directed coherence, phase delays, phase locking and phase shifting of different frequencies is critical in cognitive functions (Buzsáki, 2006; Sauseng & Klimesch, 2008) and fundamental to the dynamic and spatial distributed coordination of neuroelectric signals. Imaging studies have shown synchronised activity in association with motor function, cognition (Babichev & Dabaghian, 2016; Mechelli et al., 2004; Stephan, 2003) and emotion (Canli et al., 2002; Stevens & Hamann, 2012). More specifically, EEG phase synchronisation that involve 1) phase coupling between brain sites, 2) phase synchronisation across frequencies, and 3) phase-locking to external events, are thought to reflect communication between distant and functionally related neural populations (Lachaux et al., 1999).

Synchronous spatial patterns of activity

The foundations of specific patterns of synchronised activity relates to activity at a microscopic level where changes to and reinforcement of synaptic strengths have been described in terms of the "Hebb rule" (Hebb, 1949). Accordingly, synaptic connections tend to settle into patterns (Amit & Fusi, 1994; Siegel, 1991) insofar activity at a cell is influenced

by a stored configuration (Amit, 1992b; Amit et al., 2001). The principle was later elaborated to models of storage and retrieval of memories in the hippocampus (Rolls, 1990), which proposed that axonal outputs that wind back upon the dendritic inputs of neighbouring cell bodies (recurrent collaterals) serve as feedback mechanisms. It provided good evidence that synapses can be reinforced according to a Hebbian principle (Babichev & Dabaghian, 2016; Kelso et al., 1986; Kirkwood & Bear, 1994; Wills et al., 2005) and that neural systems rely on feed forward and on recurrent feedback connections.

Functional connectivity

Temporal similarity in signal forms the basis of an assumption that the regions are functionally connected (Friston et al., 1996). These spatial patterns are specific to either a particular activity or rest and are often different from structural connectivity (Sporns et al., 2000; Vincent et al., 2007; Zhang et al., 2008) and while dynamic changes in the context of performance have linked FC and structural connectivity more closely (Fukushima et al., 2018), FC is often seen between regions with no direct structural connection (Honey et al., 2009; O'Reilly et al., 2013; Vincent et al., 2007). These different aspects of brain connectivity, mostly, show at least some level of convergence (Eickhoff et al., 2010). Furthermore, correlated activation between regions could be induced by a third area that do not have direct interaction (Eickhoff 2015). While analyses of FC have provided new perspective on brain function (Biswal et al., 1995; Snyder et al., 2012) the elaboration of insight has been limited by the fact that the construct is agnostic to causality and direction (Friston, 2011) which can be investigated in the context of effective connectivity (Friston et al., 2010; McIntosh et al., 1991; Roebroeck et al., 2005).

The first fMRI study (Biswal et al., 1995) to show that intrinsic fluctuations at rest hold information about the inherent functional organisation of the human brain, used voxels identified during a finger tapping task as a 'seed'. These voxels were correlated with the

timeseries of every other voxel in the whole brain during rest. The resultant resting state correlation map showed strong spatial similarities with the task activation map. Examination of connectivity has since revealed spatially coherent low frequency correlations, while similar spatial patterns observed during task (Beckmann et al., 2005; Biswal et al., 1995) and rest (Fox et al., 2009) potentially sub serve important brain processes (Gopinath et al., 2015).

Dynamic activity and connectivity

FC studies have shown similarities in connectivity patterns across brain states, such as wakeful rest and task (Smith et al., 2009) as well as different connectivity patterns across different states of consciousness (Greicius et al., 2008), wakefulness (Haimovici et al., 2017), arousal (Wang et al., 2016), sleep (Larson-Prior et al., 2009) and seizure states (Massimini et al., 2005), which indicate that these patterns are not solely the result of aimless cognition (Christoff et al., 2016; Morcom & Fletcher, 2007).

Connectivity studies have elaborated insights into the large-scale functional organisation in the brain (Bassett et al., 2017; Cole et al., 2014; Sporns et al., 2016) and its distinct relevance to behaviour and cognition (Biswal et al., 1995; Cocchi et al., 2013; Cole et al., 2014; Power et al., 2011; Shine et al., 2018; Smith et al., 2009a; Yeo et al., 2011). The strength and interactions between large-scale functional brain networks have been related to age (Fair et al., 2008), successful cognitive aging (Tsvetanov et al., 2016), task complexity (O'Connell & Basak, 2018) and disease (Zhang et al., 2010). While the configurations are consistent and generally preserved throughout the lifespan, age related changes in spatial and temporal features of functional brain networks have been seen in particularly cognitive networks (Hutchison & Morton, 2015; Vij et al., 2018).

Individual differences

While resting state functional connectivity (rsFC) has provided highly reproducible group maps (Power et al., 2011; Yeo et al., 2011) idiosyncratic variations in the spatial

configuration of functional regions are important for studies of individual difference (Bijsterbosch et al., 2018) and prediction of performance (Greene et al., 2018) and differences in large-scale functional networks across individual subjects elicited by task appear to be a function of individual factors and not related to cognitive or daily variation (Gratton et al., 2018).

Integration of large-scale networks

Dynamic segregation - indicated by strong within and weak FC between networks, and integration that indicate strong functional connectivity across large scale brain networks (Shine et al., 2018; Sporns, 2013) have been seen for different tasks and stimuli (Cohen & D'Esposito, 2016; Gonzalez-Castillo et al., 2015; Liljestrom et al., 2015; Lord et al., 2017; Shine et al., 2016; Xie et al., 2019). Increased integration have been associated with the cooperation of sensory, motor and cognitive control systems in cognitively demanding tasks such as N-back working memory while different degrees of integration have been associated with performance related to reasoning (Hearne et al., 2017), working memory and motor execution (Cohen & D'Esposito, 2016), memory encoding (Keerativittayayut et al., 2018) and automatic processing (Mohr 2016).

Measuring functional connectivity

FC may be determined by a variety of modalities and approaches to analysis, rendering it a concept rather than a single method (Eickhoff & Müller, 2015). Temporal similarity in haemodynamic or electrical signal have been used to assess the presence of FC within and across segregated spatial areas.

Electrocortical techniques. FC can be observed in correlation of spiking patterns or electrical field potentials recorded directly from implanted electrodes between different sites (Eickhoff & Müller, 2015) or by correlating them with cortical signals as measured by MEG or EEG (Gaudet et al., 2020). It includes the delineation of coherence from various aspects of oscillatory activity such as frequency (Dittinger et al., 2018; Ruchkin, 2005) or cross frequency phase coupling (Canolty et al., 2006).

Different electrocortical techniques including electrocorticogram (Hebbink et al., 2019; Rolston & Chang, 2018) used intraoperatively to confirm the location of epileptic tissue and to delineate areas of motor, sensory, and language function (Sirven, 2014). Cortico-cortical evoked potentials provides an opportunity to track connectivity, including language areas (Kanno et al., 2018; Koubeissi et al., 2012; Matsumoto et al., 2004; Ookawa et al., 2017; Umeoka et al., 2009).

Physiological processes and the BOLD signal

The notion that cerebral blood flow can be a marker of stimulus induced brain function dates back to the experimental work of Roy and Sherrington in the 1890s (Friedland & Iadecola, 1991), and was elaborated with investigation into the role of nitrous oxide (Kety & Schmidt, 1948). Fox and colleagues showed that an increase in the cerebral metabolic rate of oxygen was surpassed by an associated increase in cerebral blood flow (Fox et al., 1988; Fox et al., 1986). The resultant mismatch between changes in cerebral blood flow and cerebral metabolic rate of oxygen and an increased capillary and venous oxygen, presented a novel physiological index for localising function. Shortly after, in 1990, it was shown that brain function could be mapped by the venous BOLD MRI contrast (Ogawa et al., 1990; Seiji Ogawa et al., 1990). The BOLD signal, essentially an endogenous paramagnetic contrast agent, is a function of change in deoxyhaemoglobin (Ogawa et al., 1990; Pauling & Coryell, 1936): Local changes in the deoxyhaemoglobin concentration, specifically the paramagnetic

quality impacts the MR signal (Thulborn et al., 1982): It decreases the T2 value quadratically with field strength (Logothetis & Wandell, 2004). Even more profound deoxyhaemoglobin effects are produced on T2* (Ogawa et al., 1990): Increased deoxyhaemoglobin levels induces faster dephasing of excited spins, which shortens or reduces T2* signal sampled at the echo time – a parameter which is specified by the investigator to maximise the BOLD contrast. The contrast is thought to be a direct reflection of neuronal activity because cerebral blood flow changes and the glucose metabolism are coupled (Logothetis & Pfeuffer, 2004; Logothetis & Wandell, 2004).

Neurophysiology underlying the BOLD signal

The BOLD signal (Logothetis, 2008; Raichle et al., 2006) is closely associated with local field potentials – complex signals comprised of integrated electrical activity that reflect the sum of pre and postsynaptic electrical current in the brain as measured by microelectrodes placed within brain tissue (Logothetis & Pfeuffer, 2004), rather than neuronal spiking (Logothetis et al., 2001; Logothetis & Wandell, 2004).

Scalp EEG and electrocorticography represent the summation of populations of LFPs that are often characterised by frequency bands (delta, 1-4 Hz; theta, 4-8 Hz; alpha, 8-12 Hz; beta, 13-24 Hz; and gamma, > 24 Hz). LFP activity in the so called slow cortical potential (SCPs) range (0.01-4 Hz) are represented by spontaneous BOLD fluctuations (He & Raichle, 2009; He et al., 2008) that reflect fluctuations in cortical excitability. Both the spontaneous BOLD fluctuations and the spatial patterns exhibited by slow cortical potentials are evident across different levels of consciousness, including wakefulness, rapid eye movement and slow wave sleep (He et al., 2008). Resting state and task EEG correlates of BOLD changes have shown negative correlations in the alpha frequencies and positive correlations in the gamma range (Goense & Logothetis, 2008; Mukamel et al., 2005; Niessing et al., 2005). In comparison, paroxysmal fast activity in the13 to 30Hz range is commonly seen at seizure

onset in animal and humans (Gnatkovsky et al., 2008; Wendling et al., 1996), suggesting predominant BOLD increases at the seizure onset. Gamma power is spatially correlated with BOLD during wakefulness (He et al., 2008; Lachaux et al., 2007) and rapid eye movement sleep (He et al., 2008) - consistent with coherence of power in the gamma band (Leopold et al., 2003) which is associated with higher cognitive function (Fries, 2009; Uhlhaas et al., 2009). Thus coupling across frequencies facilitate representation of the full spectrum of function in the BOLD signal (Raichle, 2011a):

Properties of the BOLD signal

A biomechanical balloon model that incorporates effects of dynamic changes in blood volume and oxygenation has been used to describe changes in blood volume associated with brain function. It shows an initial dip, a peak and a long post-stimulus undershoot (Buxton et al., 1998). The time course of the BOLD response - the hemodynamic response function (HRF) (Logothetis & Wandell, 2004) has a number of important characteristics, including peak height which is most directly related to the amount of neuronal activity in the tissue.

The HRF rapidly ascends and generally peaks within a window of 4–6 seconds and returns to baseline by 12–20 seconds after the stimulus onset (Logothetis et al., 2001). The late undershoot, which is relatively small in amplitude compared to the positive response and persists up to 20 seconds or more after the stimulus. It has been attributed to volume changes but also with a marked inhibition in the neural response, so it could at least in part, be accounted for by neural activity (Logothetis et al., 2001). A very small signal – an initial dip within the first 1–2 seconds of the BOLD signal, thought to reflect early oxygen consumption (Buxton, 2001) has been seen in some studies but appears to be ignored in most models of fMRI data.

Substantial differences have been observed for HRF features across brain areas and across individuals. The time until peak has been showed to varied in voxels in a single

subject (Kruggel et al., 1999). Furthermore, the width of the HRF differed within subjects between brain regions and across subjects, with inter subject variability higher than intrasubject variability (Handwerker et al., 2004) while studies have shown different response magnitudes (D'Esposito et al., 2003) in healthy young and elderly subjects.

Linear characteristics. Given consensus that the transform from neuronal activity to BOLD signal is largely linear time invariant (Dale & Buckner, 1997) the general linear model (GLM) has widely been adopted as an approach to analysing the neuronal signal in fMRI studies and a natural approach to creating an expected BOLD signal from a given neural input is to convolve two functions in linear time invariant fashion. To obtain the predicted BOLD response using convolution, an estimate of the HRF based on the combination of two gamma functions, known as the canonical HRF, was adopted (Glover, 1999) with the shape of the initial stimulus response modelled by the first gamma function and the undershoot by the second.

Static and dynamic functional connectivity

The conventional use of an average value (such as a correlation between two ROIs) of the full time series using BOLD signals acquired over a period of minutes has more recently been elaborated by dynamic functional connectivity that investigate variability in pairwise correlations as it appears in a series of overlapping windows (Allen et al., 2014; Chang & Glover, 2010; Hutchison et al., 2013; Liu & Duyn, 2013). This approach has revealed time varying patterns, including intermittent anticorrelation between the default-mode network (DMN) and dorsal attention network (Fox et al., 2005; Greicius et al., 2003). Recurring patterns are thought to reflect different brain states (Allen et al., 2014; Du et al., 2018; Hutchison & Morton, 2015; Samann et al., 2011; Vanhaudenhuyse et al., 2010) in much shorter intervals such as 30–40 seconds (Braun et al., 2015; Mohr et al., 2016; Wang et al.,

2016) than the typical period in which resting state data is acquired (Karahanoglu & Van De Ville, 2015; Xiao Liu & Duyn, 2013).

Data quality

Efforts to link behaviour and brain network organisation should take account of the importance of data quality (Ciric et al., 2017) insofar artefact, that can have spatial or spectral similarities with activation, influence identification as well as quantification of relevant connectivity.

Proposals aimed at improving signal to noise ratio have included adjustment of the acquisition parameters: Specifically, a dual-echo approach that sees physiological motion related confounds in resting data identified and removed if the echo time of the first echo is short enough to minimise its BOLD weighting (Bright & Murphy, 2013; Kundu et al., 2012) has been proposed. Other measures to account for signal variations associated with physiological 'noise' such as pulse effects have sought to make adjustments in the fMRI modelling (Bagshaw et al., 2004; Liston et al., 2006; Mullinger et al., 2008; Tierney et al., 2016).

Head motion presents particular difficulties for all applications of fMRI affecting voxel content/number of spins, changing the distortion and signal dropout areas that influences the magnetic field that has been adjusted for head position. Minutiae in-scanner head motion can significantly impact resting-state functional connectivity (Power et al., 2012; Satterthwaite et al., 2012, 2013; Van Dijk et al., 2010, 2012): Tissue may move from one slice to the next which introduces spin history effects (the magnetisation M0 until steady state is reached) with associated changes to the expected BOLD signal (Muresan et al., 2005).

In the SPM design matrix motion has been characterised by six motion regressors corresponding to translation and rotation (estimated from the algorithm that optimally register each brain volume in the series). A more comprehensive approach registers up to 36 motion-

derived correlates at individual time points (Satterthwaite et al., 2013) and has led to greater power in explaining variation and better modelling (Friston et al., 1995; Lemieux et al., 2007; Wilke, 2012). Volume censoring techniques, such as "scan nulling" (Lemieux et al., 2007) and "scrubbing" (Power et al., 2012) have been employed that remove volumes with motion signature, characterised by frame wise displacement or rate of change in the BOLD signal.

Connectivity metrics

Functional connectivity measurements can be obtained in the frequency or time domain with metrics that reflect coherence, phase synchrony or correlation. A wide range of statistical dependencies have been employed including cross correlation of time series (Biswal et al., 1995), mutual information in EEG (Jeong et al., 2001), power spectrum methods (Yang et al., 2007; Zou et al., 2008; Zuo et al., 2010) and cross coherence (Sun et al., 2004).

Correlation and cluster analysis

Correlational analyses including Kendal and particularly Pearson's correlation coefficient have been widely employed in connectivity studies. In the so called seed-based analysis, single voxels or ROIs are user identified and their temporal signals are correlated with other voxels in the brain (Biswal et al., 1995; Damoiseaux et al., 2006) to yield a measure of whole brain connectivity. Where a region-of interest (ROI) serves as the seed, the average or the first principal component is taken as representative of the ROI – an approach that improves signal-to noise ratio at the seed and problems associated with spatial normalisation.

Some studies (Cordes et al., 2002; Wang et al., 2013) have employed hierarchical clustering to obtain patterns of functional connectivity. The resultant networks are typically in line with the networks obtained with other techniques such as independent component

analysis. Some results have shown the DMN and visual system to fractionate into hierarchical sub- networks (Wang et al., 2013).

Data driven analyses

Independent component analysis is aimed at orthogonal decomposition of the total signal (McKeown et al., 1998) that yields unique time courses expressed in three-dimensional spatial maps. The prediction of a response associated with an event of interest (the 'model') is not required. Components need to be labelled and are generally interpreted as networks (Beckmann et al., 2005; Calhoun et al., 2001) but conclusions are challenged by subjective specification of dimensionality (Ray et al., 2013) and the potential inclusion of components that reflect non-neural activity (Griffanti et al., 2014).

Independent component analysis of fMRI has widely been used in several fMRI studies of epileptic activity (LeVan et al., 2010; Moeller et al., 2011; Rodionov et al., 2007; Thornton et al., 2010) that have shown distinctive albeit overlapping results in relation to the model based approach (Caballero-Gaudes et al., 2013; Moeller et al., 2011; Thornton et al., 2010; van Houdt, de Munck, et al., 2010).

Validity and reliability of resting state connectivity networks

The nature and validity of the network depiction of slow neural modulations have been questioned insofar the oscillations could reflect brain function or a large source of 'noise' (Schroeder et al., 2008). Most data support a functional network depiction: Highly reliable estimates of rsFC have been seen in the same individual (Biswal et al., 2010; Chen et al., 2015; Shehzad et al., 2009; Zhang et al., 2018; Zuo et al., 2014) between subjects (Damoiseaux et al., 2006; Shehzad et al., 2009; Zuo et al., 2010) in typical resting-state acquisition which is similar to paradigm task-based fMRI protocols of approximately six minutes duration (Van Dijk et al., 2010).

Questions remain as to the validity of dynamic functional connectivity particularly for resting-state conditions: dynamic functional connectivity during the resting state have been explained by statistical idiosyncrasies and sampling variability such as duration and window length (Hindriks et al., 2016; Leonardi & Van De Ville, 2015), head motion and fluctuating sleep state (Laumann et al., 2017). Network observations can reflect "a small fraction of the population undergoing large variations or a large portion undergoing small deviations" (Hyder & Rothman, 2010) and could reflect random synchrony (Handwerker et al., 2012), physiological noise (Birn et al., 2006; Chang & Glover, 2009) or incidental coupling of other neural events (Shirer et al., 2012).

Canonical brain networks

Resting state and task networks

Large scale rsFC associated with unconstrained mind-wandering (Bzdok et al., 2016) has yielded patterns that have been formalised with the term resting state networks (RSNs) with the whole cerebral cortex divided into a small number of networks (Hacker et al., 2013a; Yeo et al., 2011). RSN topography have been consistent across behavioural states (Arfanakis et al., 2000; Fransson, 2006) and have been characterised by spatial similarity with activation patterns seen in task fMRI experiments (Laird et al., 2011; Smith et al., 2009). Spatial similarity with task activation provide further support for observations that resting-state BOLD fluctuations are involved in development and maintenance of the brain's functional organisation (Doria et al., 2010; Laumann et al., 2017; Pizoli et al., 2011; Supekar et al., 2010; Zielinski et al., 2010).

The default mode network (Raichle et al., 2001) is the most studied RSN. It is thought to be closely associated with attention and working memory (Raichle et al., 2006) and BOLD changes during GSWDs and IED have been reported in association with changes in consciousness (Gotman et al., 2005; Laufs et al., 2006). During rest, it is active and

characterised by slow fluctuations (Greicius et al., 2003). It is deactivated during goal-driven behaviour (Danielson et al., 2011). Anatomically it is comprised of the mesiofrontal/anterior cingulate cortex, the precuneus/posterior cingulate cortex and the temporoparietal junction areas (Heine et al., 2012). Several other resting networks have been identified, including visual (medial), visual (occipital pole), visual (lateral), cerebellum, sensorimotor, auditory, executive control, frontoparietal (perception-somesthesis- pain) and frontoparietal (cognition-language), in terms of major functional networks by correlating explicit activation networks with the covarying resting networks (Laird et al., 2011; Smith et al., 2009).

A system robustly opposed to the DMN that corresponds to task positive networks (Chai et al., 2012; Golland et al., 2008; Power et al., 2011; Zhang et al., 2011) has been associated with various and distinct attentional functions (Corbetta & Shulman, 2002) and tasks (Chai et al., 2012; Golland et al., 2008; Power et al., 2011; Zhang et al., 2011). The work of Smith (Smith et al., 2009) and others (Kellermann et al., 2013; Laird et al., 2013, 2011; Ray et al., 2013) showed matches for resting and task networks which, in turn, could be fractionated into a greater number of smaller networks.

The relationship between rest and task networks, and performance. It is important to note that spontaneous BOLD fluctuations persist during task and account for significant variability in human BOLD responses (Becker et al., 2011; Fox et al., 2007; Scheeringa et al., 2011) and task performance including motor response (Fox et al., 2007), attentional control (Sapir et al., 2005) and working memory (Pessoa et al., 2002). While differences between resting-state and task FC have been seen for a small number of tasks (Buckner et al., 2013; Hasson et al., 2009; Mennes et al., 2013), a range of studies (Cole et al., 2014; Geerligs et al., 2015; James et al., 2016; Kelly et al., 2008; Tavor et al., 2016; van den Heuvel et al., 2009) showed correlations between resting-state and task FC, supported by meta-analysis (Laird et al., 2013; Smith et al., 2009) which showed that resting state and co-

activation networks are not explicitly identical but exhibit “strong” similarity. Overall these findings suggest that spontaneous and evoked activity while not equivalent flow through the same functional network architecture, with minor albeit significant changes for tasks across contexts (Cole et al., 2014). Thus, observed FC correlations during tasks are largely driven by spontaneous activity (Fox et al., 2007) and shapes task-evoked activation patterns and efficiency of behaviour.

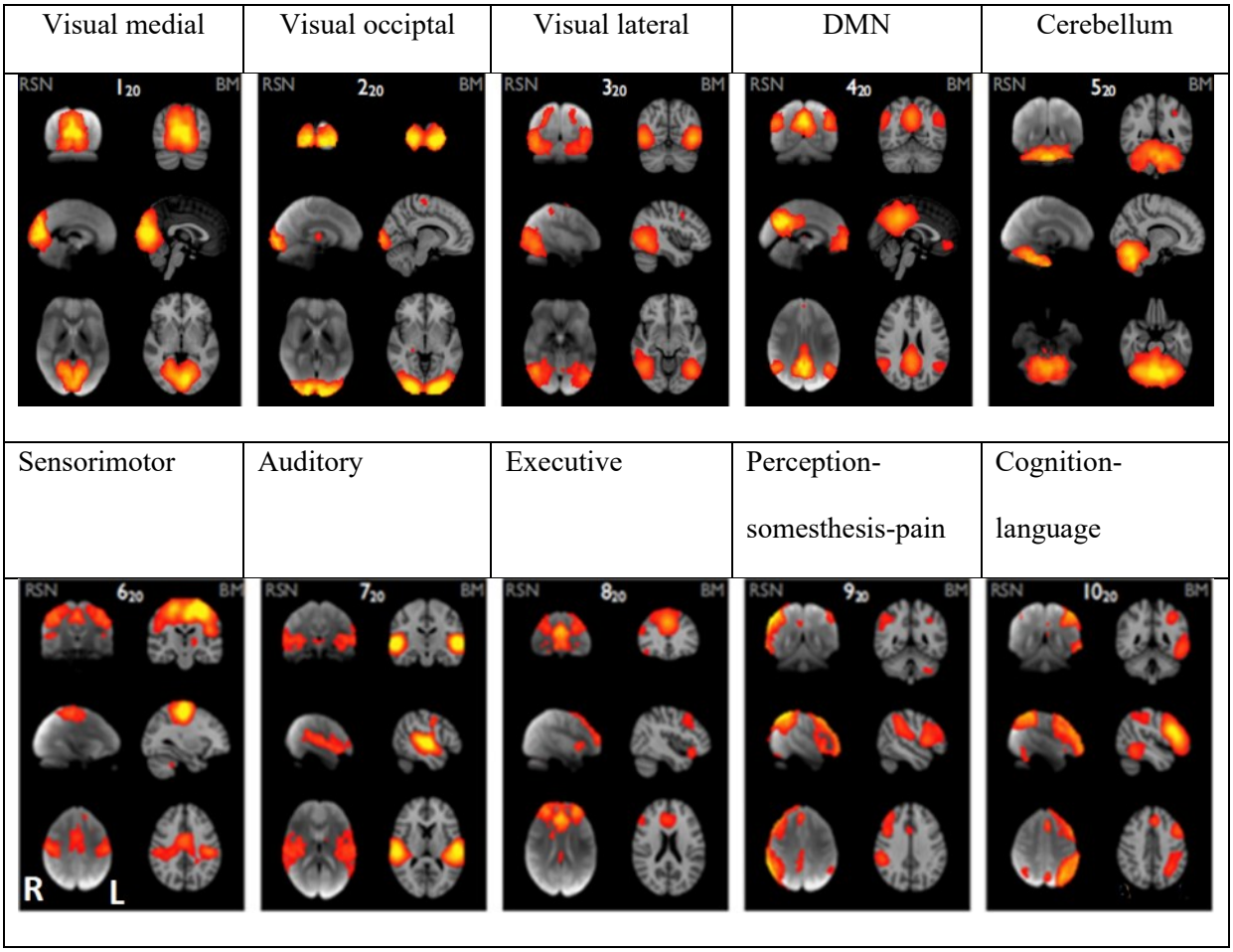
Task-specific neural activity has been linked to plausible recombination of resting-state networks (Bzdok et al., 2016) and it has been suggested that resting connectivity networks tune the brain for task engagement involving reconfiguration for task dependent interactions (Fornito et al., 2012; Gao et al., 2013).Differences are further evident from observation of trait-relevant individual differences in patterns of rsFC that are amplified by task (Finn et al., 2017; Greene et al., 2018; Satterthwaite et al., 2018). Compared to resting networks, the amplification of differences, has provided for better prediction of performance (Greene et al., 2018) and confirms the view that brain-behaviour relationships are better identified by task based compared to resting functional connectivity analyses (Laird et al., 2013).

Cognitive task, internal speech and unconstrained mind wandering. While results to date, indicate that the relationship between resting state and task networks which show a high degree of spatial similarity (see Figure 3.1), reflects the relationship between external and internal orienting of attention (Laird et al., 2013), it has further been refined by work (Scheibner et al., 2017) that distinguished the neural correlates of mindful attention (including specific meditative practises and internal speech) from mind wandering. Specifically, during mindful attention, brain regions typically associated with the DMN, showed significantly less neural activation compared to mind-wandering: Reduced activity of the DMN was found during both external and internal attention mindful attention compared

to mind-wandering, independent of the practitioner's attention focus (i.e., internal vs. external) (Scheibner et al., 2017). Thus, active attention whether external or internally oriented (such as internal speech) depicts task networks and are distinguished from resting networks associated with mind wandering.

Figure 3. 1.

Correspondence between Ten Resting State and Task Networks in the Normal Brain



Note. The figure shows the anatomical correspondence (spatial similarity) between ten networks extracted from 36 subjects resting state (RSN) (left) data and the networks derived from task studies that comprise Map data (BM) (right). The connectivity patterns extracted from resting studies and the connectivity patterns extracted from tasks studies that show spatial correspondence are shown in coronal, sagittal and axial planes in MNI standard coordinates according to radiological convention (i.e., patient-left on the screen-right). *Adapted from Smith, S.M. (2009) PNAS 106(31):13040-5.* These networks that reflect inherent connectivity patterns observed during resting state and task activation have

collectively been termed intrinsic connectivity networks (ICNs) and have been used to identify the functional organization of the language (Kelly et al., 2010; Lohmann, et al., 2010). RSN 10 (cognition-language), a frontoparietal resting state network has been associated with language function. Although, a high degree of spatial similarity is evident, the relationship between task connectivity patterns and resting state connectivity patterns appear quite complex: Resting state network, in other words networks when subjects are asked not to engage attention (either internal or external) in any task – is thought to reflect an inactive state of "idling" - a prior to task (network) engagement (Betti et al., 2013).

EEG power and spatial correspondence to intrinsic connectivity networks

Multiple neurophysiological patterns that resemble fMRI RSNs, have been observed in separate sessions including MEG (Tewarie et al., 2016) and electrocorticography (He et al., 2008). Simultaneous EEG-fMRI have shown temporal correlates in band-limited (Laufs et al., 2003; Mantini et al., 2007; Sadaghiani et al., 2010) and full-band power bands (Hiltunen et al., 2014; Keinanen et al., 2018), in brain regions that overlap with RSNs. Recent electrophysiological correlates that are spatially and temporally specific have been identified for fMRI-RSNs (Yuan et al., 2016) and is consistent with similarity seen for phase synchronisation clusters obtained for resting state and stimulus-driven 7T fMRI – a finding that suggest a common neuroanatomy (Gravel et al., 2018). In fact the underlying neurophysiology discourages a strict distinction between the large-scale, dynamic networks based on SCP mediated fluctuations evident in BOLD patterns and evoked activity, insofar SCPs provide a window on the interplay between the brain's ongoing oscillations and stimulus driven responses (Raichle, 2011b).

Slow fluctuating hemodynamic patterns and task activated fast neuronal activity

Perceptual studies have linked the phase and/or frequency of ongoing neural oscillations that represent fluctuations in excitability to the integration or segregation of upcoming information (Morillon et al., 2015; VanRullen, 2016; 2014). Oscillatory synchrony across neuronal populations and distributed cortical networks play a vital role in

selective communication and integration of attended to stimuli (Fries, 2015; Gregoriou et al., 2015) by amplifying neuronal readiness to inputs (Morillon & Schroeder, 2015) with indication that distinct frequency bands facilitate multisensory processing and functional connectivity (Keil & Senkowski, 2018).

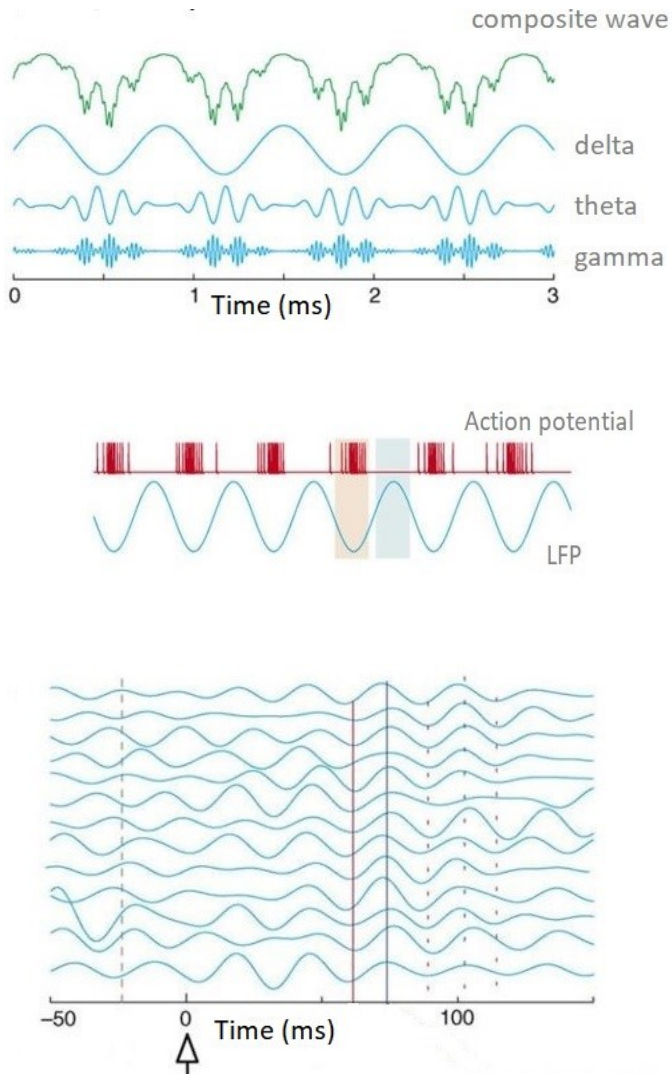
The LFP frequency spectrum that include spiking activity of neurons, are influenced by ongoing oscillations through strong cross frequency phase–amplitude coupling, in which the amplitude of a higher-frequency oscillation is systematically related (coupled) to the phase of a lower frequency oscillation (Schroeder et al., 2008). This exchange is thought to form the basis of information processing (Ronconi & Melcher, 2017) by coordinating fast, spike-based signals with slower events to integrate functional systems across spatiotemporal scales and facilitate perception, cognition, and action (Canolty & Knight, 2010).

Low-frequency oscillations, specifically, are thought to play a role in anticipatory mechanisms that are attenuated by behavioural significance of the expected events (Stefanics et al., 2010). A link (Raichle, 2011b) between changes in cortical excitability associated with anticipation and a negative SCP reflected in the BOLD signal has been related to performance (Giesbrecht et al., 2006; X. Li et al., 2008; Sapir et al., 2005). Along with neurophysiological observations from perceptual and fMRI studies it underlies the proposal that large-scale, dynamic networks based on SCP mediated fluctuations evident in BOLD patterns, links stimulus-evoked, cued-attentive, and intrinsic activity (Raichle, 2011b). Accordingly attention (defined beyond goal-directed conscious awareness) modulates spontaneous fluctuations and tunes the brain's excitability to the "temporal dynamics of behaviorally relevant event streams" (Besle et al., 2011; Schroeder et al., 2010) across a number of cortical areas. It formalises the relationship between resting state and task activation networks and posits that RSNs represent a mechanism to constantly generate predictions to optimise information processing (Friston, 2012).

The neurophysiology that links phase and/or frequency of slow ongoing neural oscillations to integration/segregation of incoming information is illustrated in Figure 3.2.

Figure 3. 2.

Oscillatory Coherence and Phase Amplitude Coupling



Top: The green trace shows recorded oscillations - fluctuations in cortical excitability - that are typically comprised of mixtures of components at different frequencies. Blue traces show individual oscillatory components in the delta (1.5 Hz), theta (7 Hz) and gamma (40 Hz) band that comprise the composite waveform containing the LFP frequency spectrum.

Middle: The relationship between high and low excitability, as indexed by the firing rate of action

potentials (red) and the phase of oscillation as indexed by a local field potential (blue).

Bottom: When the system is at rest and unengaged (baseline pre-stimulus period to the left of zero) oscillations within a given frequency have a high degree of phase-variability across trials (grey dashed line). An anticipatory stimulus at time zero (arrow) leads to a phase alignment of ongoing neural oscillations. As a result, optimal phases (red lines) and non-optimal phases (blue lines) align separately. Inputs that arrive at the optimal phase (red) are amplified, and those that arrive at the non-optimal phase (blue) are suppressed (Schroeder et al., 2008).

Note. Oscillatory coherence and phase amplitude coupling selectively amplifies neuronal readiness and optimise response to inputs. Figure adapted from Schroeder et al. 2008.

Connectivity networks in epilepsy

Clinical factors, including cognitive processes, changes in alertness and the effects of treatment, have been associated with changes in connectivity, which have in turn, been with associated with the frequency of epileptic events (Centeno & Carmichael, 2014). Seizure networks are comprised of the brain regions involved in the origin and conduction of epileptic activity and production of different patterns of semiology (see Chapter 4) have been associated with changes in brain connectivity (Bartolomei 2017).

Cognitive networks

The role played by large-scale networks in cognitive function is illustrated by work which show that perceptual function such as face-processing is not associated with a single area in fusiform cortex, but with an extended network involving visual, limbic and prefrontal cortical regions (Ishai, 2008; Wiggett & Downing, 2008). In congenital prosopagnosia normal fMRI activation is seen in fusiform but not extended regions (Avidan & Behrmann, 2009), and reduced structural integrity in fibre tracts connecting the fusiform gyrus and anterior temporal and frontal cortices have been associated with impaired face perception (Thomas et al., 2009).

While functional connectivity alterations have been observed in the context of experience and training (Thompson et al., 2016) it has also been identified relative to normal patterns at diagnosis in patients with focal epilepsy (Alonazi et al., 2019). A clear relationship between altered connectivity patterns and neurocognitive impairments in focal epilepsy, are likely to reflect the effects of duration and severity of disease, on involved brain networks (Englot et al., 2015, 2016). For example, patients with Hippocampal sclerosis have demonstrated abnormal interactions of largescale brain networks; with the disturbance more comprehensive for left compared to right- mesial temporal lobe epilepsy (de Campos et al., 2016) (see also section on atypical language representation in epilepsy in Chapter 2). It contributes to a growing body of evidence showing that mesial temporal lobe epilepsy alters hippocampal networks and resting state networks, including the DMN, salience network, and dorsal attentional network (Burianova et al., 2017).

Altered rsFC patterns have been reported in children with absence epilepsy specifically in the DMN (Luo et al., 2011, 2012), orbitofrontal cortex (Bai et al., 2011) and thalamus (Masterton et al., 2012), implicating a role for all these areas in disrupted perception and cognition. Language networks in focal epilepsy identified with data driven approaches, have provided observation as to effects of focal epilepsy on language, specifically in relation to the effects of epilepsy on the organisation of language (Karunanayaka et al., 2011; Mbwana et al., 2009; You et al., 2013).

Summary

This chapter provided a scoping review of the literature that indicated involvement of connectivity networks in seizures and cognitive function. There is evidence that mesial temporal lobe epilepsy alters hippocampal networks and large-scale networks, including the DMN, salience network, and dorsal attentional network. However, the impact of disease features in epilepsy on ICNs have not been addressed. The extent to which large-scale

connectivity networks are affected by epilepsy disease features and their role in language function and prediction of language outcome following ATLR are investigated in experimental studies and reported in Chapters 6, 8, 9 and 10. The extent to which large-scale connectivity networks are recruited and associated with ictal semiology is investigated and reported in Chapter 11.

Chapter 4

EEG-fMRI

Elucidation of whole brain networks are required for understanding idiosyncratic electrographic and haemodynamic fingerprints in pharmaco-resistant epilepsies to aid novel and targeted pharmacological intervention (Koepp, 2014) while new surgical approaches can be informed by network analysis (Bernhardt et al., 2013; Guye et al., 2010; Minati et al., 2013; Onias et al., 2013).

In this context functional MRI with simultaneous EEG (EEG-fMRI) has provided information on electrical and haemodynamic brain networks associated with epileptic events on EEG for focal (Lemieux, 2001) and generalised epilepsy (Gotman et al., 2005; Friederike Moeller et al., 2010; Salek-Haddadi et al., 2003) and presents a method for potentially developing greater understanding of network properties in epilepsy (Centeno & Carmichael, 2014). EEG and video combined with fMRI (Chaudhary, 2010) have been used to study epileptic activity and cognition (Bai et al., 2010; Berman et al., 2010; Killory et al., 2011). Studies have mapped BOLD changes associated with ictal and interictal discharges (IEDs) (Chaudhary, 2012; Gholipour, 2011; Pesaresi, 2011b; Pittau, 2012; Salek-Haddadi et al., 2003; Salek-Haddadi, 2006; Thornton, 2010, 2011; Zijlmans, 2007; Zijlmans, 2008) and used to identify of the seizure onset zone and the epileptogenic zone in the presurgical assessment of refractory focal epilepsy (Ives, 1993; Jacobs, 2008; Lemieux, Salek-Haddadi et al., 2001; Salek-Haddadi, 2006).

While potentially valuable for localisation (Rose & Ebersole, 2009) it may provide insights as to nature and evolution of semiology. Features of epilepsy have been conceptualised in terms of networks (Halasz, 2010; Laufs, 2012b; Spencer, 2002) and the study of brain connectivity is integral to developing understanding of the spread of partial seizures and semiology: In this chapter I review the methods and utility of EEG-fMRI in

view of a potential role in elucidating the origin and propagation of haemodynamic seizure correlates as it relates to clinical signs. Content of this chapter draws on two reviews (van Graan et al., 2013; van Graan, Lemieux, et al., 2015) of EEG-fMRI.

The physiological basis of EEG-FMRI

Simultaneous scalp EEG-fMRI provides a non-invasive solution as well as higher spatiotemporal resolution (Chaudhary et al., 2013; Laufs, 2008; Logothetis, 2008) relative to other localisation techniques including ictal SPECT and PET.

Differences in spatial and temporal resolution

While spatial resolution refers to discernible detail in an image (Degbelo & Kuhn, 2018), temporal resolution relates to correspondence in time of a measured activity (such as the BOLD signal associated with a language task) to the timing of the actual neuronal activity. EEG directly measures neuronal activity (Vidal et al., 2015) and provides temporal resolution of milliseconds or less (Liu et al., 2020). In contrast the temporal resolution of fMRI - a metabolic based technique (Burle et al., 2015) is limited by hemodynamic response time; with the BOLD response typically showing a peak occurring ~5–6s after the onset of a brief neural stimulus which is much slower than the underlying neural processes (Glover, 2011).

Thus, EEG and simultaneous fMRI operate at different temporal resolutions but respectively localise and tracks activity by virtue of the synchrony of haemodynamic and electrographic events. The combined measure (i.e., the EEG-informed fMRI BOLD signal) is derived by utilising the temporal resolution offered by EEG and the spatial resolution of fMRI therewith addressing the limitations of EEG and fMRI alone: Accordingly, the abnormal high frequency oscillations produced by hyper synchronized populations of neurons are sampled directly by EEG and accurate hemodynamic spatial correlates are reflected by fMRI (Abreu et al., 2018; Jorge et al., 2014; Laufs, 2012a; Murta et al., 2014).

The BOLD signal in epilepsy

Notwithstanding the temporal resolution of the BOLD signal (Vulliemoz et al., 2010) and unresolved questions in relation to neural activity (Ekstrom, 2010; Logothetis & Wandell, 2004), fMRI has widely been applied in the investigation of epileptic brain networks. The time course of the BOLD response, the temporal impulse response function, (Logothetis & Wandell, 2004) showed the distribution of the BOLD response to be very similar in sensory regions (Boynton et al., 1996; Josephs et al., 1997). However, marked differences in hemodynamic responses have been seen between subjects (Aguirre et al., 1998; Lindquist et al., 2009) and brain regions (Schacter et al., 1997) with the further caveat of potential changes at the neuro vascular junction in patients with epilepsy (Lemieux et al., 2008; Masterton et al., 2010).

Therefore the choice of mathematical model which embodies the shape and latency of the HRF in epileptiform events potentially limits the validity of localisation (Rosenow & Luders, 2001).

EEG

Neural oscillations are a central feature of EEG and are observed at different spatial and temporal scales throughout the nervous system (Varela et al., 2001) providing for a spectrum of functional activity including perceptual, cognitive, and emotional processes that have been associated with different oscillations (Siegel et al., 2012).

As stated above, EEG offers a high degree of temporal resolution and a direct measure of population-level neural activity in humans (Cohen, 2017). It provides anatomical localisation at a scale of centimetres (Cuffin et al., 2001). The spatial distribution of frequencies and the morphology of electrical potential across the brain provides distinguishing features as well as indication as to the location of seizure focus in epilepsy (Ferree & Nunez, 2007; Nunez & Srinivasan, 2006).

Generation of the EEG

Electrical currents superimpose in the extracellular medium representing the sum of dendritic postsynaptic potentials (i.e., the exchange of electrochemical signalling across the synapse) (Lopes da Silva, 2013; Nunez & Srinivasan, 2009) and generate an electrical potential (at a given location), with respect to a reference potential (at a given location). Difference in electrical potential can be monitored in sub millisecond resolution by electrodes (Buzsáki et al., 2012). The measurement constitutes the EEG when measured from the scalp and the electrocorticogram when measured by subdural grid electrodes on the cortical surfaceWhilst postsynaptic potentials constitute the primary contribution, glial cells and other neural processes, are thought to also contribute to the LFP (Buzsáki et al., 2012; Murakami & Okada, 2006). The relationship between LFP and EEG is multi factorial and is not clearly understood. It is likely that the various contributions to LFP is different than for EEG, as the latter reflects a larger spatial scale of activity (Mazzoni et al., 2010). EEG is thought to measure primarily largescale synchronous activity produced by groups of parallel aligned pyramidal cell (Nunez & Srinivasan, 2009).

Precise localisation is particularly crucial in the context of surgical resection (Rose & Ebersole, 2009) and mathematical reconstruction of a specific intracranial source for EEG signals remains a significant challenge (the so-called ill posed inverse problem) – particularly as all electrodes sum activity from several brain regions (Schoffelen & Gross, 2009), and some potentials can be cancelled out by currents (Hallez et al., 2007) which constrains the location of coherence.

Mathematical modelling of hemodynamic responses in EEG-fMRI studies

The BOLD signal, best delineated in terms of its 'shape' that capture onset, peak latency and duration of the responses, has been represented in several ways (Lindquist & Wager, 2007). The design of the so called " canonical HRF" (Friston et al., 1995) made of

gamma functions (see Properties of the BOLD signal in Chapter 3) may in the context of potential changes related to abnormality not be suitable to studies in epilepsy (Beers et al., 2015).

Deviations from the canonical shape, more often seen in generalised discharges have been observed in a range of studies that have assessed variations using a Fourier basis set (Chaudhary et al., 2012; Lemieux et al., 2008; Thornton et al., 2010), multiple HRFs (Bagshaw et al., 2004; Tyvaert et al., 2008), finite impulse response functions (van Houdt, de Munck, et al., 2010) and gamma functions (Grouiller et al., 2010). EEG-fMRI studies have shown that poor specification of the HRF form can result in the omission of significant fMRI responses from statistical analysis (Bagshaw et al., 2004). The hemodynamic response observed with intracranially recordings deviated from the canonical hemodynamic response function and varied by patient and by location (Beers et al., 2015).

Convolution (the linear combination of functions) of a number of other functions – so called basis functions, has been implemented. The most flexible basis sets are the so-called finite impulse response, and the Fourier basis sets. These models are less constrained by the shape of the HRF and thus helps the detection of hemodynamic changes that are not represented by the canonical HRF. The Fourier series basis set (Josephs et al., 1997) exploits the fact that periodic events can be represented by combinations of sine and cosine functions. It readily captures consistent signal changes. Finite impulse response (Glover, 1999) facilitates greater flexibility and identification of idiosyncratic hemodynamic responses by using deconvolution. It can involve a different number of regressors at various points in the time series. A disadvantage is posed by the fact that it readily models noise.

The GLM employs a prediction model designed to reflect the observed BOLD signal. Thus, the sensitivity of BOLD and the accuracy of detecting changes are dependent on the design of a GLM model specific to the experiment. In EEG-fMRI studies of epilepsy stimuli,

such as IED can be represented as a 'box' function that represent runs of IED or as a 'stick' function of zero duration which is convolved with a selected HRF (Chaudhary et al., 2012; Di Bonaventura, 2006; Thornton et al., 2011; Zijlmans et al., 2007) that represent the duration of such activity. In this way a single box-car function can represent a whole seizure (Tyvaert et al., 2008) or, multiple box-car functions of variable duration (Chaudhary et al., 2012; Thornton et al., 2010) where each function represents a distinct seizure-related phase.

Implementation of EEG informed fMRI

With the EEG-fMRI framework, the epileptic network is assumed to be composed of brain areas that are functionally connected (see Chapter three). Typically, events of interest such as epileptic activity are identified and extracted from the EEG and the brain areas that show correlated BOLD signal are thought to constitute the epileptic network (Abreu et al., 2018; Gotman, 2006, 2011). The first employment of the BOLD signal to localise epilepsy appears in reports in the mid-1990s (Detre et al., 1995; Jackson et al., 1994). It was predated by attempts to combine changes identified by fMRI with EEG identified interictal epileptiform discharges (IED) (Ives et al., 1993) that employed the method of EEG triggered fMRI (Warach et al., 1996) (Krakow et al., 1999; Warach et al., 1996). Early observations (Rosenow & Luders, 2001) showed that spike triggered EEG-FMRI contributed diagnostically to pre-surgical assessment. Continuous simultaneous EEG-fMRI was achieved somewhat later in the context of research aimed at improving localisation of epileptiform events in the presurgical context (Lemieux, 2001).

EEG fMRI Data acquisition and processing

Scalp EEG

Current EEG-fMRI practise employs either standard or modified scalp electrodes, but specially designed MR compatible (battery powered) amplifiers are required. The patient is positioned using available measures to immobilise the head for optimisation of image and

EEG quality that are readily compromised by motion (Benar et al., 2003). EEG signals are digitised and relayed via fibre-optic cables, displayed and recorded. FMRI is typically acquired using T2*-weighted single shot gradient- echo echoplanar images sequence, with acquisition periods of some 6-20 minutes. Experimental studies have typically acquired images using 1.5 and 3Tesla MRI scanners (Difrancesco et al., 2008) with greater sensitivity to BOLD changes seen at higher field strengths (Gholipour et al., 2011). Since EEG is spoiled by scanner gradient switching induced artefacts as well as heartbeat, MR-gradient and pulse related artefact (Allen et al., 2000, 1998) are averaged and removed by an artefact template subtraction. New measures to EEG correction are continually evaluated (de Munck et al., 2013) but EEG correction is determined largely by characteristics of the events of interest, such as their frequency (Grouiller et al., 2007; Ritter et al., 2007).

The accuracy of results is however founded upon a range of uncertainties previously referred to, including a presumption of the extent of haemodynamic delay (which could be different on account of pathological processes). These uncertainties related to time locking events are somewhat redressed by simultaneous and continuous EEG-fMRI that provide in vivo capture of BOLD activity associated with epileptic activity identified on EEG, which facilitates examination of the full range of BOLD signals relative to such activity of interest (Benar, 2002; Masterton, 2007).

A significant limitation relates to spatial coverage: there is little or no EEG recording of epileptiform activity in deep structures or small regions of epileptogenic cortex as the signal reflects summarised activity of pyramidal neurons located near the surface of the brain and requires at least 10–20 cm2 of synchronous activity (Tao et al., 2005).

Intracranial EEG-fMRI

Many of the inherent difficulties associated with scalp recording including motion and muscle artefact (discussed below) is largely avoided when EEG is recorded from depth

electrodes that cover areas of tissue at the tip of the electrode. The spatial resolution of scalp EEG is only 22–37 cm3 when using a routine set of 19 electrodes, and a maximum spatial resolution of 6-8 cm^3 is achieved when using up to 128 electrodes (Ferree et al., 2001). The use of electrode grids attached to the dura mater in the subdural space over the surface of the brain improves spatial coverage and provides direct recordings from the surface of the brain. Localisation of EEG recordings can be aided by post-implantation imaging. A typical intracranial EEG acquisition is represented by a configuration that employs a 1.5T scanner, and feasible co- localisation of BOLD and epileptiform discharges are safely recorded at 3 T (Aghakhani et al., 2015; van Graan, Lemieux, et al., 2015). The configuration includes a head transmit-receive coil, a low specific absorption rate sequence, (SAR ≤ 0. 1W /Kg head average) leads and cables (90cm) external to the head with specific precise lengths and positioning along the RF coils central z-axis, using a foam insert while recording 64- channel invasive EEG recorded with MR-compatible equipment (Carmichael, 2008, 2010). With this configuration, and the MRI protocol used in the patient studies, temperature changes recorded at the electrode positions are ≤ 0.1° C which reflects a safety factor> 10 relative to the statutory temperature limits (Carmichael et al., 2008, 2010, 2012) with the conclusion that iEEG-fMRI presents a low-risk method for consideration of hemodynamic changes of very focal epileptiform activity (Aghakhani et al., 2015).

Mapping EEG events in epilepsy

In epilepsy, there is commonly abnormal activity – interictal electric discharge (IED) or ‘epileptic spikes’, between seizures. These events have a different mechanism from those that characterise ictal onset (De Curtis & Avanzini, 2001) with origin from both within and away from the epileptogenic zone. In the presurgical workup, application of EEG-fMRI is aimed at identifying the brain regions time locked with EEG haemodynamic signatures. As previously discussed, the events of interest (epileptiform activity) are marked on the EEG and

serves as predictors of BOLD change at every voxel (Chaudhary et al., 2013). The flow of analysis of EEG-fMRI in the presurgical workup is illustrated in Figure 4.1.

Sensitivity and specificity of fMRI

Limitations imposed by the time window of EEG fMRI , that is to capture and identify IED with scalp EEG is a major limitation (Salek-Haddadi et al., 2006). It is further compounded by the fact that effects of no interest can affect or mask diagnostic information (Salek-Haddadi et al., 2006). Such confounds are primarily represented by artefact induced by motion and physiological noise. In the context of EEG informed fMRI, several forms of physiological noise have been addressed including changes induced in tissue volume during cardiac cycle (Bagshaw et al., 2004; Liston et al., 2006; Mullinger et al., 2008), respiration (van Houdt, Ossenblok, et al., 2010) as well as a variety of idiosyncratic patient movements. Motion induced signal changes such as caused by eye blinks, and swallowing have been identified with simultaneous video recording (Chaudhary et al., 2012). Typically, signal variations associated with these confounds are addressed by accounting for it in the fMRI modelling procedure.

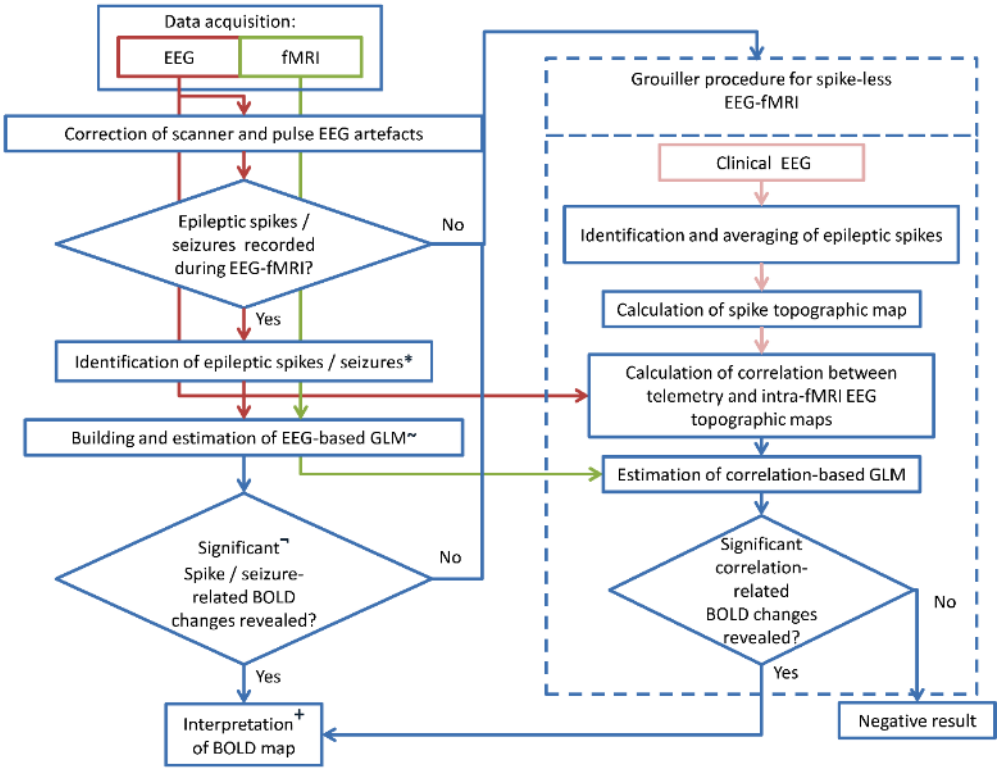
Scalp EEG-fMRI sensitivity and specificity: EEG records signal faithful in time (high temporal resolution), but its scalp application sensitivity and specificity to identify anatomical areas specific events is compromised by the fact that EEG signal specifically on the scalp result from averaging potentials over large areas of the cortex so that patterns associated with specific events of smaller magnitude may be undetected. (In contradiction is the iCEEG which is restricted by greater limitations in spatial sampling).

Time window challenges to EEG- fMRI studies, referred to above, are illustrated by the report that roughly 40% of patients did not demonstrate IED during studies. In 30% of cases where IED were identified and marked on EEG, significant BOLD changes were not seen which may have reflected inadequate modelling of the fMRI signal (Salek-Haddadi et

al., 2006). Reported advances include capturing previously unaccounted for physiological activities by modelling them into the correlation matrix (Chaudhary et al., 2012). One such approach constructs a topographic map that represent epileptic activity observed with long term video-EEG monitoring (Grouiller et al., 2011). The topographic features are correlated with the EEG recorded during fMRI. This technique has claimed sensitivity of 80% and has been prominent in the context of improving results in cases where no epileptiform activity has been observed in the time windows afforded by EEG-fMRI studies (Elshoff et al., 2012; Grouiller et al., 2011). Results of a relatively large cohort of TLE patients demonstrated that the likelihood of seizure-freedom correlated with significant IED related BOLD change in the resection area (Coan et al., 2016). In contrast to sensitivity achieved in IED studies, better results for investigation of ictal events probably reflect the greater magnitude of associated BOLD changes. Sensitivity ranging from 66% up to 100% has been reported in cases where at least one seizure has been recorded (Ales, 2010; Archer, 2010; Hamandi, 2006; LeVan, 2010; Salek-Haddadi, 2009; Thornton et al., 2010; Tyvaert, 2009). It must be noted that differences in reported sensitivity may be influenced by differences in the concordance criteria (reviewed below) to localise BOLD changes but also patient selection criteria, and different in modelling approaches.

Figure 4. 1.

Flowchart of Presurgical Analysis of Interictal and Ictal Scalp EEG-fMRI



Note. In the presurgical workup the events of interest (epileptiform activity) are marked on the EEG and serves as predictors of BOLD change at every voxel.
*Seizures are divided into phases according to their spatiotemporal evolution ~ One GLM for epileptic spikes and seizures with additional regressors for effects of no interest such as: motion, pulse and error corrected or $p < 0.001$ uncorrected + evaluation of BOLD clusters and global maximum for concordance with the seizure onset zone. This figure is taken from van Graan 2013 (van Graan et al., 2013).

The Problems of Interpretation of fMRI maps

Cluster interpretation in presurgical evaluation

The inherent limitations and questions of sensitivity and specificity in ictal imaging is by no means the only challenge posed to the technique: BOLD maps produced by EEG-fMRI studies are frequently poorly understood with the challenge of identifying activity clusters that may best be concordant with the epileptogenic zone and irritative zone. Such maps show

a spectrum of activity which is best understood and consistent with network activation as opposed to spatial zone delineation (van Graan, Lemieux, et al., 2015). The potential spectrum of information provided by EEG-fMRI studies includes the interpretation of BOLD activation cluster for localisation of epileptogenic zone.

The conventional development of EEG-fMRI employed clusters as identifiers of interictal and ictal activity in a context of presurgical localisation (Laufs, 2006; Lemieux et al., 2001; van Houdt, 2010b). Correspondence between the epileptic zones mapped by EEG-fMRI and other techniques are well documented (Elshoff et al., 2012; Kobayashi, 2006; Krakow et al., 1999; Pittau et al., 2012; Salek-Haddadi et al., 2006; Thornton et al., 2010; Tiege, 2007; van Houdt, 2013a). Spatial accuracy and multimodal integration – specifically co registration of fMRI maps and icEEG with a structural MRI brain image presents a significant challenge. Approaches to the interpretation of clusters for localisation (Chaudhary et al., 2013) include selection of the BOLD cluster that show 1) the greatest statistically significance compared to other clusters (Salek-Haddadi et al., 2006; Thornton et al., 2011; Vulliemoz, 2009), 2) the earliest BOLD increase, thresholded for statistical significance and spatial extent (Donaire et al., 2009); 3) the greatest statistically significance together thresholded for spatial extent (i.e., greatest number of voxels) (Di Bonaventura et al., 2006); 4) with greatest statistically significance (Tyvaert et al., 2008); 5) values above a priori statistical and spatial thresholds (Gotman et al., 2005); and 6) the greatest statistically significance in the individual lobes (Hamandi et al., 2006). Clinical validation of fMRI cluster interpretation has been conducted in relation to icEEG results and also surgical outcome.

Clinical utility: Localisation of epileptic focus

Scalp

EEG-fMRI has yielded results that led to reconsideration of the surgical option negated by the results of other investigations (Zijlmans et al., 2007; 2008). Conversely, surgical intervention, has been contraindicated by EEG- fMRI results (Zijlmans et al., 2007). It may comment on likely surgical outcome, such as demonstrated in cases of focal cortical dysplasia where IED related BOLD networks are widespread (Thornton et al., 2011). Findings in ictal studies (Chaudhary et al., 2012; 2013) as well as fortuitous capture of seizure (LeVan, 2010; Thornton et al., 2010; Tyvaert et al., 2008; 2009) have in many cases localised the seizure onset zone at sub-lobar level. However, IED-related BOLD localisation of the epileptic focus (defined on icEEG), used to guide the implantation strategy (Gholipour et al., 2011; Pesaresi et al., 2011; van Houdt et al., 2013) has shown greater specificity than scalp EEG on its own (Pittau et al., 2012).

EEG-fMRI and connectivity network recruitment in epilepsy

Conclusions from EEG-correlated fMRI studies include those that summarise connectivity with a single static value (Abreu, 2018; Gotman et al., 2006; Jorge et al., 2014; Laufs, 2012a; Marques, 2009; Moeller, 2011; Murta et al., 2014) as well as dynamic FC that take account of continual changes in FC across different time-scales (Calhoun et al., 2014; Chang & Glover, 2010; Hutchison et al., 2013) which is especially important as spontaneous epileptic activity is interchanged with normal brain states (Chang et al., 2013; Preti et al., 2017).

EEG-fMRI data can be used to characterise propagation-related BOLD changes (Chaudhary, 2012; Chaudhary et al., 2013; Meletti, 2012; Vaudano, 2012) with implication for greater understanding of seizure and interictal networks (Bettus et al., 2009, 2011). The concept of epileptogenic networks is key to identifying the anatomic distribution of the

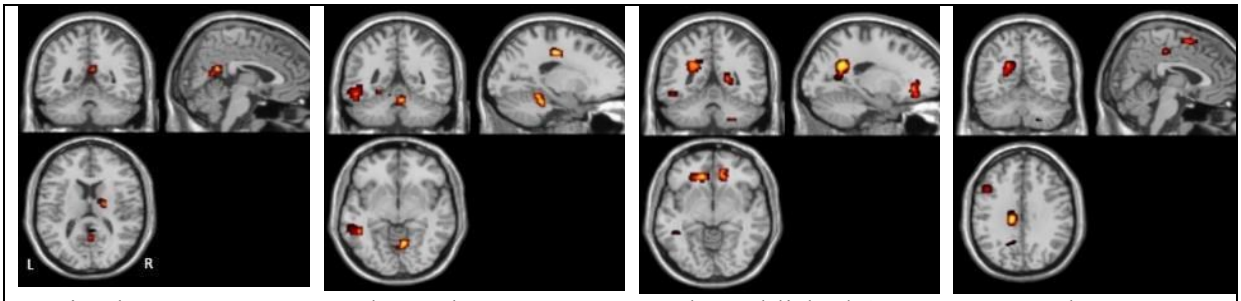
epileptogenic process and has been used to address the limitation of a focal understanding to account for focal epilepsy (Bartolomei, 2017). In line with the concept that networks are comprised of functionally connected brain areas (see Chapter three) the EEG-fMRI approach assumes that brain regions within the epileptic network are functionally connected: In generalised epilepsy, EEG-fMRI has shown a pattern of BOLD intensity increases in the thalamus commensurate with reduced intensities in the medial as well as lateral frontal, superior parietal, posterior cingulate, the precuneus , the caudate (Archer, 2003; Gotman et al., 2005; Moeller, 2008; Salek-Haddadi et al., 2003) and the reticular formation (Carney et al., 2010). It has showed relevance of cortico-subcortical connectivity and implicated the default mode network (DMN) (Raichle et al., 2001) during GSWDs. Findings that develop this observation – also in line with the cortical focus theory, described mechanisms for initiation of absences (Meeren et al., 2005) and associated BOLD changes in the precuneus (part of the DMN) that may facilitate GSWDs (Benuzzi, 2012; Vaudano, 2009).

Whilst the DMN has enjoyed a majority of recent scientific attention, BOLD signatures of other networks and epilepsies have been demonstrated in EEG-fMRI studies (Laufs, 2012b). Commonly observed BOLD patterns implicates networks in the generalised epilepsies (Aghakhani et al., 2004; Gotman et al., 2005; Hamandi et al., 2008, 2006; Salek-Haddadi et al., 2003). In this regard BOLD patterns revealed by EEG-fMRI studies have demonstrated recruitment of different resting state networks in refractory focal seizures (Chaudhary et al., 2013), a visual attention network in children with photo paroxysmal response (Moeller, 2009), network patterns in musicogenic seizures (Marrosu et al., 2009; Morocz et al., 2003), reading epilepsy (Salek-Haddadi et al., 2009; Vaudano et al., 2012) and a network in epilepsia partialis continua (Vaudano, 2012). Thalamic and DMN related regions demonstrated BOLD changes in Dravet syndrome (Moehring et al., 2013) which is one of the syndromes in which a specific network has not been described.

Interestingly, EEG fMRI results have posed challenging observations that relate to the temporal window and spatial distribution of BOLD changes associated with epileptiform activity: BOLD changes have been seen before the onset of epileptic activity and manifestation of such activity on EEG. In addition changes have been more widespread for seizures (Chaudhary, 2012; Donaire, 2013; Federico, 2005) than for the focal patterns of IED (Jacobs et al., 2009). BOLD changes distant from the identified epileptic zone with different temporal features relative to seizure onset on EEG provides apparent support for the network hypothesis (Bartolomei, 2008, 2011; Vaugier, 2009) in epilepsy. It has been proposed that this BOLD activity in apparently healthy structures reflect neuronal activity not visible in the EEG (Ray et al., 2007; Yu et al., 2009) or ictal-related BOLD changes in the resting state networks may reflect neuronal baseline activity (Damoiseaux et al., 2006) or changes in brain state that favour seizure activity (Vaudano et al., 2009). Alternatively, it represents the recruitment of normal RSNs in the initiation and/ or propagation of seizure activity (Chaudhary et al., 2012; Mantini, 2007). Figure 4.2 shows preictal BOLD signal in remote areas from the seizure onset as well as other phase-related BOLD changes in a patient with TLE who had seizures during EEG-fMRI.

Figure 4. 2.

Ictal Phase-related BOLD Changes



Pre ictal – 80-0s No clinical changes	Early Ictal 5.3s No clinical changes	Ictal Established 4.9s Jaw clenching/head jerks	Late Ictal 7.8s No clinical changes

Note. This patient with TLE had seizures during EEG-fMRI. The seizure was partitioned into four phases: **Top**: SPM (p=0.001, unc) for each ictal phase (pre, early, established and late ictal phases) overlaid on single subject's anatomical MRI shown in coronal, sagittal and axial planes according to neurological convention (i.e., patient-right on the screen-right). **Bottom**: median duration of each phase and the observed clinical signs.

The image shows preictal BOLD signal in remote areas from the seizure onset. It may represent changes in the resting state networks (Schwartz et al., 2011) or involvement of wider networks (Bartolomei et al., 2001; Truccolo et al., 2011) before the seizure onset. These BOLD changes away from areas conventionally defined as epileptic, and a wide temporal spectrum relative to seizure onset identified on EEG supports the network hypothesis in epilepsy. It has been suggested that the initial BOLD decreases may correspond to the active inhibitory circuits (Gnatkovsky et al., 2008; Trombin et al., 2011; Fabrice Wendling et al., 2005) followed by an increase in neuronal activity driven by glutamatergic neurons (Huberfeld et al., 2011)).

Resting state fMRI results have demonstrated abnormal connectivity, commonly reduced connectivity within the DMN and associated epileptogenic regions (Haneef et al., 2012; Liao et al., 2010; Mankinen et al., 2012; Widjaja et al., 2013; Zhang & Raichle, 2010; Zhang et al., 2010) in focal and generalised epilepsies (Masterton, 2012; McGill, 2012; Song, 2011; Wang, 2011; Yang, 2012, 2013) while analyses integrated with simultaneous EEG have identified dynamic network connectivity changes associated with epileptic activity (Laufs et al., 2014; Lopes et al., 2014; Omidvarnia et al., 2017). Networks dynamics are

evident in the focal (Terry et al., 2012) and generalised epilepsies (Moeller et al., 2008; Vaudano et al., 2009). A number of clinically relevant factors, have been implicated in connectivity changes, including the effects of treatment, cognitive activity, and changes in levels of consciousness. In turn connectivity changes have been associated with changes in the frequency of epileptic events (Centeno & Carmichael, 2014).

Engagement of intrinsic connectivity networks have shown seizure related BOLD changes in different areas recruited during different ictal phases (Kozak et al., 2017); (albeit it did not describe the temporal evolution in recruitment of these areas within individual phases). In this context, the use of EEG-fMRI and a whole brain perspective of network engagement will allow for identification of the status of many networks simultaneously. The question arises as to whether the effect of epileptic transients and semiology can be measured and characterised in terms of normal canonical intrinsic connectivity networks (Laird et al., 2011; Smith et al., 2009).

Semiology and connectivity networks

As opposed to a classical concept of regional brain disorder seizures in focal epilepsy, begin in the epileptogenic zone, and subsequently recruit other brain areas – either focal or distant (Proix et al., 2017) and clinical signs are thought to involve interactions within neural networks (Bartolomei et al., 2017; Spencer, 2002).

Electrical activity in brain structures where seizures are initiated reflect synchronized activity in an epileptogenic zone network, followed by transient desynchronisation and the appearance of fast oscillations. Other cortical and subcortical structures are recruited in a second phase which is marked by slower synchronised oscillations that comprise the propagation network, that determines semiology that “mimics” normal cerebral functions associated with cognitive and emotional processes, or disrupt normal function some distance from origin of dysfunctional discharge (Bartolomei et al., 2005, 2008; Chauvel &

McGonigal, 2014; Olmi et al., 2019). While clinical semiology depends on interaction between the anatomical origin and areas of ictal propagation, mapping of the entire ictal network provides information as to origin of onset (Chauvel & McGonigal, 2014). Stereo electroencephalography (SEEG) has shown significant changes in connectivity during seizure onset that are correlated with patterns of semiology as the epileptic discharge evolves in space and time (Bartolomei et al., 2017; Chauvel et al., 2014). A recent study showed that seizure propagation was qualified by a systematic sequence of brain states and by patient-specific connectivity in largescale brain networks (Olmi et al., 2019). Insofar seizure propagation invokes disturbance or recruitment of normal neural network oscillations that underlie cognition, perception and consciousness, clinical signs are a function of electrical activity within existing neural pathways (Chauvel & McGonigal, 2014; Spencer, 2002).

EEG-fMRI allows for study of electrophysiological correlates of spontaneous changes of FC connectivity (Tagliazucchi & Laufs, 2015). Clinical signs, specifically changes in awareness have been linked to epileptic activity and correlated BOLD decreases in the DMN (Laufs et al., 2007; Laufs, Lengler, et al., 2006). This association has been corroborated in studies that showed correlation between BOLD changes in the DMN and loss of consciousness during refractory focal seizures (Chaudhary et al., 2012; 2013) and further informed by changes in EEG power in the alpha and theta bands associated with different levels of consciousness and arousal that have been associated with decreased connectivity between DMN and task-positive networks during periods of high arousal (Chang et al., 2013).

Summary

This chapter has cited findings that describe changes in connectivity that are correlated with clinical signs, during seizure. In addition, seizure propagation invokes disturbance or recruitment of normal neural network oscillations that underlie cognition,

perception and consciousness, so that clinical signs are a function of electrical activity within existing neural pathways.

Insofar, seizure propagation has been qualified by patient-specific connectivity in largescale brain networks (Olmi et al., 2019) and clinical signs are a function of electrical activity within existing neural pathways (Chauvel & McGonigal, 2014; Spencer, 2002), the question arises as to whether the effect of epileptic transients and semiology can be measured and characterised in terms of normal canonical intrinsic connectivity networks (Laird et al., 2011; Smith et al., 2009). BOLD changes associated with epileptiform activity have been quantified in terms of intrinsic connectivity network engagement (Kozák et al., 2015) and it has been suggested that a functionally derived map interpretation framework (Kozák et al., 2014) based on the correspondence of resting state and task-based fMRI (Laird et al., 2011; Smith et al., 2009) can be used to characterise epileptic discharge-related BOLD patterns (van Graan et al., 2015) particularly in the context of a relationship between activations and seizure semiology (Chaudhary et al., 2012; Thornton et al., 2010; Tyvaert et al., 2008). In this context, the use of EEG-fMRI and a whole brain perspective of network engagement will allow for identification of the status of many networks simultaneously. The extent to which seizure propagation and semiology are accounted for by canonical connectivity networks as quantified by an atlasing method are investigated in experimental studies and reported in Chapter 6 and 11.

Chapter 5

Common Methodology

This chapter describes the common methods used in studies described in subsequent chapters: It includes details of patient and healthy subject recruitment, psychometric testing, MRI acquisition, image processing and statistical analyses, language fMRI studies and cognitive tasks used during pre-surgical evaluation. Elaboration of the common methods unique to, and description of methods specific to individual studies are presented in the results chapters.

All research studies were approved by the Research Ethics Committee of the UCL Queen Square Institute of Neurology and UCL Hospitals. Written informed consent was obtained from all patients and healthy controls.

Subject Recruitment

Language fMRI studies

All patients in the language fMRI studies were recruited from the National Hospital for Neurology and Neurosurgery, London, United Kingdom, and the Epilepsy Society, Chalfont St Peter, United Kingdom. All patients had medically refractory unilateral TLE and underwent pre-surgical evaluation at the National Hospital for Neurology and Neurosurgery.

The aim of this study was to investigate the predictors of language impairment following ATLR. In line with previous studies in our group (Bonelli et al., 2012; Bonelli et al., 2010; Yogarajah et al., 2010) patients were assessed for cognitive function and invited to participate in a second fMRI language session at an early postoperative stage of four months. It allowed for the assessment of an impact on early post operative social and occupational function and capacity for and rate of functional and structural, reorganisation after surgery.

Healthy controls were invited to participate in a second fMRI language session four months after their first fMRI session. The control subjects were recruited via poster invitations displayed in public areas and were fluent English speakers with no history of neurological or psychiatric disease. Details on healthy volunteer and patient demographics, neurological and neuropsychological test results, and surgical outcome data are included in the relevant chapters.

Ictal EEG-fMRI studies

Imaging data for the EEG-fMRI studies were obtained from a previous study (Chaudhary et al., 2012) conducted by the EEG-fMRI group at the National Hospital for Neurology and Neurosurgery, London, United Kingdom, and the Epilepsy Society, Chalfont St Peter, United Kingdom. Chaudhary and colleagues studied patients taken from a cohort of 55 patients who demonstrated ictal events during long-term video-EEG monitoring. In that study, simultaneous video-electroencephalography and functional MRI (vEEG-fMRI) were employed to improve the localisation of the seizure onset zone by mapping haemodynamic changes before and during seizures using simultaneous EEG-fMRI. Of the 55 patients, 20 patients had typical seizures during vEEG-fMRI and comprised the dataset employed in the experimental studies. The acquisition of data, including EEG-fMRI imaging, semiology (ictal signs), data processing, contrasts, and thresholds for assessment of ICN activation and image normalisation are described in Chapter 11.

Clinical data – language fMRI

Clinical characteristics

The number of AEDs, monthly seizure frequency, age of onset and disease duration was obtained from patient history and clinical reports. Electro-clinical assessment was carried out in all patients using prolonged interictal and ictal video-EEG monitoring at the National Hospital for Neurology and Neurosurgery that confirmed seizure onset in one temporal lobe, ipsilateral to the side of a lesion, if present. In addition, all patients had structural MRI at 3T (Duncan, 1997), including qualitative assessment by neuro-radiologists as well as quantification of hippocampal volumes and T2 relaxation times (Bartlett et al., 2007; Woermann et al., 1998).

All patients had normal medial temporal lobe (MTL) structures on the side contralateral to their epilepsy. All patients underwent psychological and psychiatric assessments and were treated with antiepileptic medication at the time of their assessment. All patients' first language was English. Handedness was determined using the Edinburgh Hand Preference Inventory (Oldfield, 1971).

Surgical resection. Left or right ATLR was carried out by one of two neurosurgeons, Mr A McEvoy and Ms A Miserocchi, following a standard anterior temporal lobe resection (ATL) that included the lateral temporal and mesial temporal structures.

Neuropsychological and psychiatric evaluation

All patients had standard neuropsychological and psychiatric evaluations. Neuropsychological evaluations were obtained pre- operatively and repeated four months after surgery for 26 of all TLE patients that proceeded to surgery. Assessments were performed more than 24 hours of a secondarily generalised seizure and six hours after focal seizures.

General intellectual ability (IQ). IQ was measured using the Wechsler Adult Intelligence Scale - III (Tulsky et al., 1997; Tulsky et al., 2003). In healthy control subjects, IQ was estimated using the Nelson Adult Reading Test (Nelson, Wilson, 1991; Nelson, 1982).

Language function. Three language measures, including tests of verbal fluency and a test of naming were used, as patients with TLE are at particular risk of developing naming deficits after ATLR (Davies et al., 1998). Verbal fluency tests usually focus on either phonological or semantic aspects. The tests involve producing as many words as possible which belong either to the same phonological category (e.g., starting with the letter 'S') or semantic category (e.g., 'animals').

Phonemic verbal fluency (VF). All subjects completed a VF test outside the scanner. The subject is given 60 seconds to produce as many words as possible starting with a given letter (''S''). Performance is measured by the total number of words correctly produced. This is a non-standardised test frequently employed in clinical practice at the Epilepsy Society, Chalfont St Peter.

Semantic fluency (SF). Healthy control subjects completed a task that required them to name as many members of the category "animals" in 60s (Bird et al., 2004). Subjects were audio recorded relating a favourite topic over a period of 10 minutes which provide a sample of every day linguistic proficiency. Subjects provided age, gender, education level, medical status and history. A measure of handedness (Edinburgh handedness questionnaire) was obtained.

Naming. All subjects completed the McKenna Graded Naming Test. It is a stringent test of nominal functions that is also used routinely in clinical and experimental settings (Chan et al., 2001; Garrard et al., 2001; Swainson et al., 2001), sensitive to gradual changes in performance over time and widely used to assess long term retrieval in the language domain. The subject is required to name 30 black and white line drawings of increasing difficulty. The total number of items correctly named is the performance indicator (McKenna, 1983).

Test–retest reliabilities, practice effects and reliable change indices. Changes in scores at retest can be the product of factors such as measurement error, increased age, differences in ability due to injury, disease or medical intervention, and increased familiarity with testing procedure and learning in the context of repetition. Some of these factors such as learning, also known as a practice effects, serve to increase scores at retest, while others, such as age, injury, disease or surgery may result in a relative decline. The clinical interpretation of differences in test scores requires that the aggregated effect of these influences be taken into account (Knight et al., 2007).

Given the purpose of repeated assessments, namely monitoring of changes in cognitive function, information concerning the psychometric properties of the tests used is of paramount importance (Bird et al., 2003; Lowe & Rabbitt, 1998; McCaffrey et al., 2001). These properties include test–retest reliability, practice effects and measures to establish whether significant change has occurred. Insofar clinical changes among the surgical groups are complicated by masked practice effects (Chelune et al., 1993) these measures include reliable change (RC) indices corrected for practice. The RC indices provide a measure of how large an individual's change in scores between two assessments must be to exceed normal variation and therefore be indicative of significant improvement or decline.

Published practice effects are not available for TLE patients. RC indices for phonetic and semantic fluency and naming were obtained in a sample of healthy controls over a 4-month interval. It was employed to assess significant changes in the patient group.

Anxiety and depression. As cognitive functions, can be affected by anxiety and depression (Bierman et al., 2005; Cherbuin et al., 2015), all patients and controls were tested for comorbid anxiety and depression preoperatively and again four months after surgery, using the Hospital Anxiety and Depression Scale as a measure of self-reported symptoms of anxiety and depression (Zigmond & Snaith, 1983). It comprises 14 items that assess current levels of anxiety and depression. The score is derived from responses on a four-point Likert-type scale. A score of seven or above is considered positive and scores classify the severity of symptoms as follows: normal (0–6), mild (7–10), moderate (11–13), severe (14 and above).

Correlations with fMRI activation patterns

Matrix correlation was employed to obtain 1) predictive value of subjects' fMRI activations within anatomical and ICN ROIs in relation to postoperative language function and deficits; and 2) to assess the association between subjects' fMRI activations within ROIs and language performance (naming and fluency) outside the scanner, as well as IQ and medication load. The influence of these factors was assessed separately for healthy controls, LTLE and RTLE patients to independently investigate their effects on language networks. For each analysis, two matrices variously comprising 1) a matrix of language performance, IQ and medication load; and 2) a matrix of the fMRI activation patterns for each paradigm contrast in four anatomical areas and 12 ICN ROIs were constructed.

Matrices were reordered by hierarchical clustering to produce ordered sequences. In the final step Kendall correlation (Conover, 1999) analysis was performed to assess the relationship between activation strength and factors that may affect language performance, as

well as the relationship between activation patterns and changes in performance following surgery.

Functional MRI acquisition details

MR data acquisition

MRI studies were performed using a 3T General Electric Signa MR750 scanner (GE, Wisconsin), using standard imaging gradients with a maximum strength of 50 mTm^{-1} and slew rate 200 $TM^{-1}\ s^{-1}$. All data were acquired using the standard eight-channel RF receive head array coil and the body RF coil for transmission.

FMRI of language function was obtained in 32 control subjects and repeated for 18 subjects four months later. FMRI was obtained pre-operatively for 26 patients and repeated post-operatively for 17 patients: Gradient-echo planar T2*-weighted images were acquired (TE = 22 ms, TR = 2500 ms), providing BOLD contrast. Each volume comprised 50 contiguous 2.4 mm slices (0.1-mm gap) with a 24cm field of view, 64 × 64 matrix, giving an in-plane pixel size of 3.75 × 3.75 mm. The field of view was positioned to maximise coverage of the frontal and temporal lobes and minimise signal drop-out from the temporal and orbitofrontal lobes. To mitigate geometric distortions, ASSET (the GE implementation of parallel imaging) was used.

All subjects underwent a structural MRI scanning protocol on the same scanner, which included an axial T1 Bravo sequence as well as a neurite orientation dispersion and density imaging (NODDI) diffusion sequence. Patients additionally underwent a standard clinical imaging protocol including an axial and coronal T2-weighted sequence, an axial susceptibility-weighted sequence, and an oblique coronal 2D dual-echo proton density and T2-weighted image sequence.

Experimental design

The paradigms were designed to engage word selection and retrieval (Picture Naming; PN, Auditory naming AN), as well as word and sentence generation (verbal fluency (phonemic fluency VF), semantic fluency; SF; free fluency (ideational fluency, FF). The range of paradigms constitutes a panel that provides wide ranging mapping of naming and fluency functions likely to be involved in everyday word finding difficulties: AN and PN encompasses, receptive and expressive function; auditory comprehension (listen and name) and visual comprehension (visual perception and name) in confrontational tasks. Accordingly, the paradigms should engage a range of language networks involved in confrontational word selection and retrieval (picture naming; PN, auditory naming AN), as well as spontaneous or nonconfrontational word and sentence generation (free fluency, FF; semantic fluency, SF; verbal fluency, VF). Four of the paradigms required overt language responses. Recruitment by non-linguistic cognitive processes were controlled for by using active control conditions, namely, reversed speech in the auditory naming task and scrambled pictures/faces in the visual naming task, followed by an irrelevant overt response (saying out loud 'one, two') by the participants. The use of these active conditions in the contrasts diminishes activations caused by the type of stimulus presentation (auditory versus visual input) as well as motor cortex activations and movement artefacts caused by overt language production (Gonzalvez et al., 2016). Rest provided an interval between tasks and was not used as a control condition: The default mode network, a task-negative network which activates in the resting state, shows significant overlaps with brain areas related to semantic processing, which can lead to subtraction of task related activation in those areas (Raichle et al., 2001; Binder et al., 2009). Overt language tasks, offered the benefit of monitoring performance during fMRI acquisition, as well as active control condition for task performance (Croft et al., 2014; Gonzalvez et al., 2016) including subtraction of activation of

perisylvian cortex associated with overt speech production (Gartus et al., 2009; Leuthardt et al., 2012).

All tasks were explained, demonstrated, and practised with the aid of a slide presentation. The paradigms utilised a blocked experimental design. An initial 10-s of dummy scans preceded all tasks. Subjects responded to visual stimuli, via a magnetic-resonance compatible screen viewed through a mirror (Bonelli et al., 2012), and auditory stimuli via a magnetic-resonance compatible audio-system (headphone and microphone devices).

Auditory Naming, AN

Auditory Naming consists of 5 blocks, each block contains a 30 second stimulus task and 2 control tasks, auditory reversed (AR) and "+", each one lasting 15 seconds. In stimulus tasks, subjects were asked to name objects while hearing descriptions. For example," a colourful insect with wings" and the answer should be "butterfly". In control tasks, subjects were asked to count "1, 2" while hearing reversed speech, which made no sense, and rested when "+" appeared on the screen. As noted above, the control task that was used involved reversed speech and counting. It allowed for the preparation of contrasts that controlled for non-linguistic activation (motor function and auditory input). Total task duration was 300 seconds.

Picture Naming, PN

Picture Naming includes 5 blocks, each block comprising 4 modules: 30 seconds of object pictures, which contained common objects, animals or plants with black and white line drawings; and 15 seconds of scrambled faces (SF), 15 seconds scrambled pictures (SP) and 15 seconds "*" for rest. Subjects were asked to name the black and white line drawings, and to count "1, 2" when shown SF images and SP images, and to rest when"*" images were shown on the screen for a total task duration of 375 seconds. The control task involving

scrambled faces (SF), and scrambled pictures (SP), allowed for the preparation of contrasts that controlled for non-linguistic activation (motor function and visual stimuli).

Semantic Fluency, SF

Semantic or category fluency includes 5 blocks, each block contains a 30 second stimulus task and 2 control tasks each lasting 15 seconds: 30 seconds of on-screen word presentation such as “games,” which served as a category in which the subject expressed as many words that fitted within the category. Subjects were asked to read and repeat a word that was prefixed with “R” and to rest when"*" images were shown on the screen. Total task duration was 300 seconds. The control task involving read and repeat allowed for the preparation of contrasts that controlled for non-linguistic activation (motor function and visual stimuli).

Free Fluency, FF

Free Fluency includes 5 blocks, each block contains a 30 seconds stimulus task consisting of on screen word presentation, which served as a stimulus to free association and expression of words as ideas and 2 control tasks each lasting 15 seconds Subjects were asked to read and repeat a word that was prefixed with “R” and to rest when "*" images were shown on the screen. Total task duration was 300 seconds. The control task involving read and repeat allowed for contrasts that controlled for non-linguistic activation.

Letter Fluency, VF

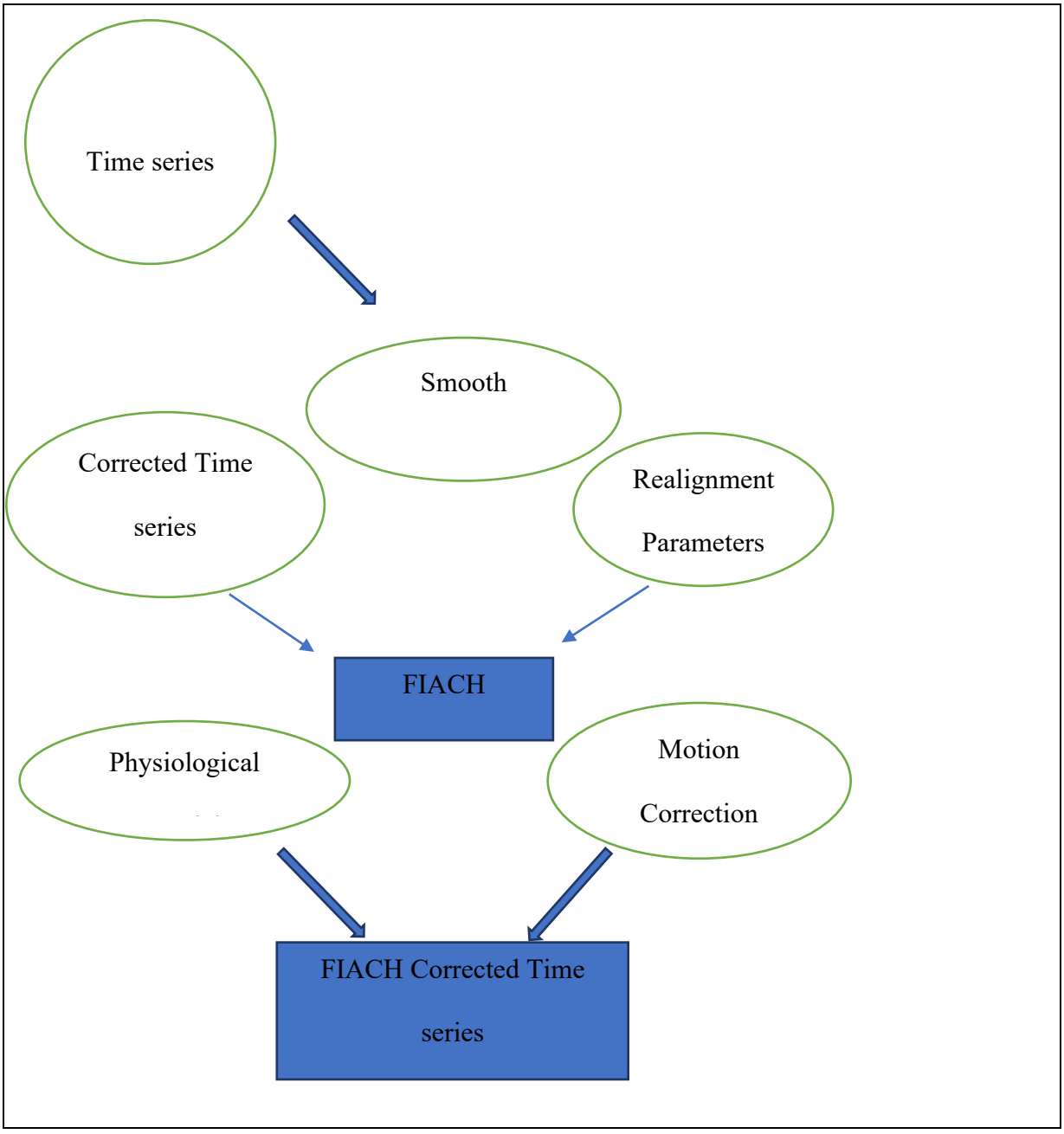
Letter fluency (verbal fluency) had 5 blocks. Each block consisted of two modules, with 30 seconds per module, During the activation phase, subjects were to think of words beginning with a letter projected on the screen (A, S, W, D and E). They rested when "*" images were shown. Total task duration was 330 seconds.

Data analysis

Image processing and data analysis were conducted using the general linear model embodied in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/spm12). MRI pre-processing consisted of volume-volume realignment, followed by pre-processing with FIACH (Tierney et al., 2016) which is a voxel based method that accounts for rapid changes in head position that occur at a timescale less than the volume repetition rate**.** Task responses convolved with the canonical HRF, provided a single regressor for each explanatory variable. Contrasts were generated for the tasks AN, PN, FF, SF and VF corresponding to the main effects of linguistic processing. SPM [T]-images were prepared capturing a total of 16 contrasts across five paradigms to variously identify linguistic, phonological and motor contributions to network engagement. An additional four contrasts were used to observe lateralisation. Smoothing with an 8mm kernel was applied to the FIACH-processed images. The six realignment parameters and six FIACH noise regressors were entered as regressors of no interest. Spatial normalisation of statistical maps was achieved via unified segmentation in SPM12 employing the co-registration of the subjects' own anatomy, mean echo planar and functional images. For normalisation SPM12 employs the reference space defined by the average of the 549 subjects from the IXI dataset linearly transformed to ICBM MNI 452 (https://brain-development.org/ixi-dataset/). The T1 image in Ixi549 space (the reference space of the Tissue Probability Map) was obtained by applying the transformation obtained from the SPM segmentation routine to the T1 image in native space. Pre-processing steps are schematically illustrated in Figures 5.1-5.3 below:

Figure 5. 1.

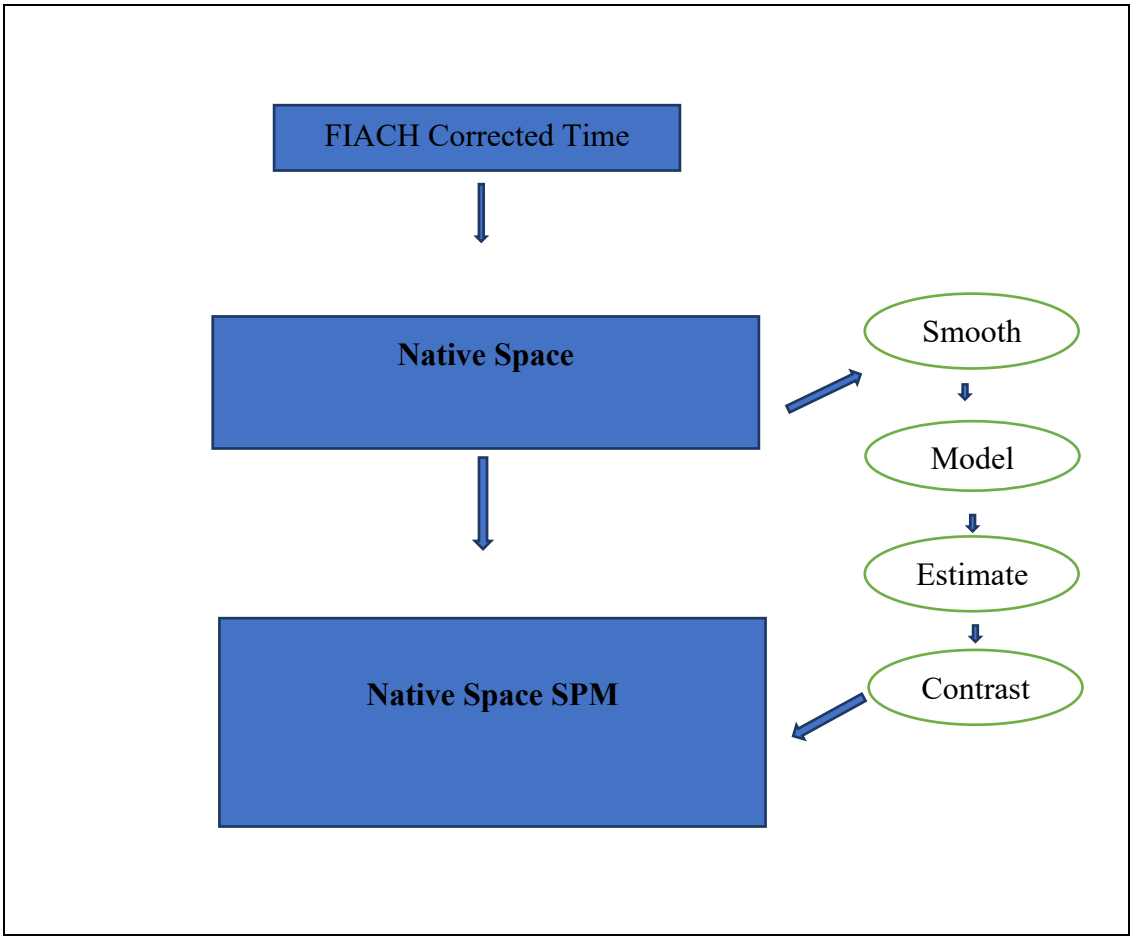
Pre-processing using FIACH



Note. Schematic representation of pre-processing using FIACH for retrospective motion and physiological noise correction.

Figure 5. 2.

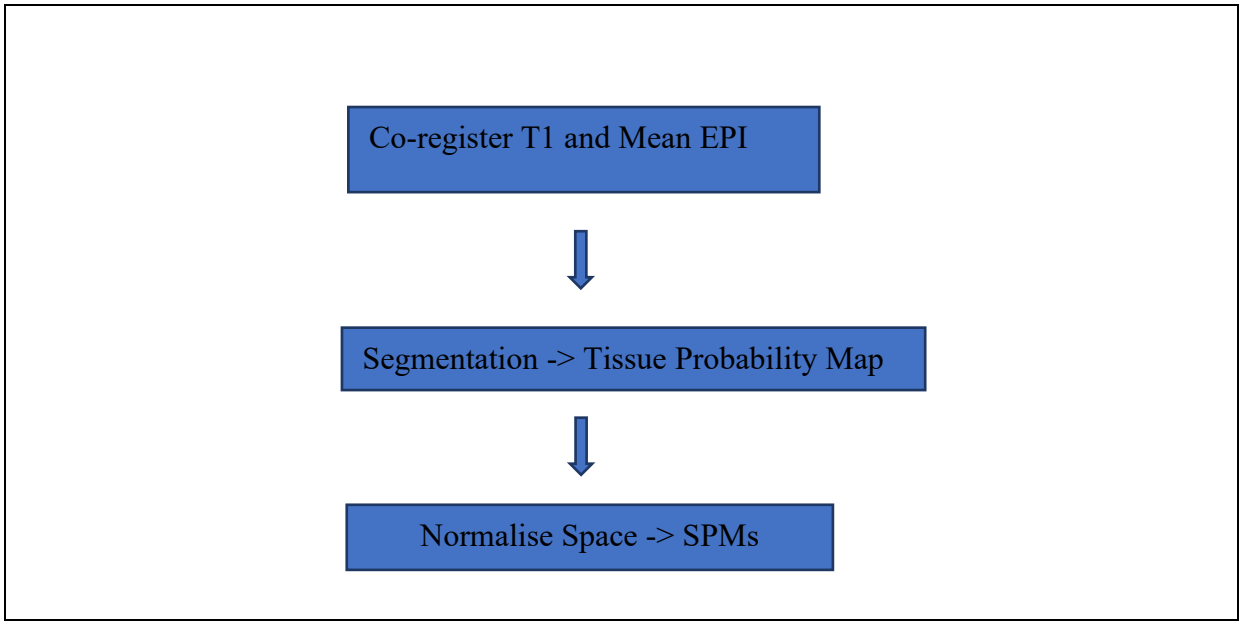
Modelling and Contrast Estimation



Note. Schematic representation of pre-processing conducted for language maps: Modelling and contrast estimation in SPM12 using FIACH corrected time series.

Figure 5.3.

Normalisation



Note. Schematic representation of the normalisation process followed using unified segmentation in SPM12.

Describing BOLD maps in terms of intrinsic connectivity networks

Connectivity measures are implicit to a number of proposals to help characterise seizures and structural abnormality including a framework (Centeno & Carmichael, 2014) that calculates a proportion of change produced over specific periods by epileptic transients relative to normal controls. I employed quantified connectivity measures (ICN_atlas metrics) and LI to inform activations in BOLD maps.

Advantages of an atlasing approach

While the use of rsFC (resting state functional connectivity) has been limited in clinical settings, it has potential for identifying epileptic networks and predicting surgical outcome, as well as providing insights into suboptimal cognitive and psychiatric function in epilepsy (Tracy & Doucet, 2015). The experimental studies presented in this thesis employs an atlasing approach that allow consideration of multiple and different connectivity networks in ictal signs/semiology and language function. An atlasing approach, specifically in relation

to unthresholded maps, as implemented in the current experimental studies offer a number of advantages to facilitate and distinguish clinical populations as well as person-specific signatures of the functional connectome (Miranda-Dominguez et al., 2014).

Objectivity and standardisation. The correlational model employed to create BOLD maps contain multiple clusters that pose significant interpretative challenges. Peak-level tests and probability values corrected for the multiple dependent comparisons permit individual maxima, above a priori defined threshold in an SPM of estimated smoothness to be identified as significant features. Specifically, clusters are interpreted as hemodynamic correlates of specific effects. The limitations incurred with the correlational model is compounded by choices that relate to inference, such as a threshold for height and volume.

The nature of thresholded BOLD maps, specifically multiple clusters can potentially give rise to a number of broad interpretations other than those that concern localisation: For example, in EEG-fMRI maps, ictal related BOLD changes can reflect baseline neuronal activity (Damoiseaux et al., 2006) or physiology that is independent of neuronal activity (Birn et al., 2006). BOLD changes may reflect dynamics that results from or are precipitous to ictal activity (Vaudano et al., 2009). A pertinent question relates to BOLD changes found in deeper structures – interpreted as activation of normal networks consequent to ictal activity (Chaudhary et al., 2012). Furthermore, the contribution of BOLD responses other than conventional peaks to differentiation of auditory or visual stimuli within primary sensory cortices (Harms & Melcher, 2003) indicate that questions raised in the context of network engagement can potentially be better addressed in the context of unthresholded maps.

Thresholding and statistical significance. Accurate co-registration of the fMRI maps structural MRI brain images and the ascertainment of spatial agreement are significant challenges along with summarising the BOLD maps in a meaningful way. Conventionally, the aim of many fMRI studies, and interpretation of clusters in the context of task activation or interictal/ictal activity is localisation. One device is to distinguish clusters, such as the location of global maximum so that their description provides information that can be compared with the results of other localising approaches and information. In the context of IED- and seizure related BOLD maps, validation has been conducted in relation to data provided by icEEG (Chaudhary et al., 2012; Grouiller et al., 2011; Thornton et al., 2010), assuming it to be accurate. In contradistinction to the critical value attributed to the global maximum, it has been argued that threshold BOLD maps, could in fact be neglecting important processes (Lieberman & Cunningham, 2009). Information particularly relevant to network function may, in fact be contained in unthresholded maps and is evident in the analogous approaches used to calculate lateralisation indices (Wilke & Schmithorst, 2006) and relevant detail may be lost in thresholded maps (Gonzalez-Castillo et al., 2012). It is, in fact questionable that localisation can effectively be achieved with thresholded approaches (Jernigan et al., 2003).

Comparison of multiple networks. While the DMN has received much attention and has been the focus of many studies in attempts to describe and elucidate fMRI maps, the presence of multiple networks raises the question of bias. While a prominent influence in neurophysiology may explain the predominance of the DMN in epilepsy studies it may also reflect its historical eminence (Raichle et al., 2001; Shulman et al., 1997) or its relative ease of study. A significant advantage is that the atlas approach yields quantification and a view on the relationship between many networks simultaneously. Evidence of dynamic change in the integration and segregation of networks (Cohen & D'Esposito, 2016; Lord et al., 2017; Shine et al., 2016) suggest that simultaneous assessment may provide insight into the role of multiple networks and related effects of disease on specialised functioning (Bassett et al., 2015; Sadaghiani et al., 2015).

An Atlas Methodology

In the context of available data on the range of canonical networks as derived from normal healthy subjects (Laird et al., 2011; Smith et al., 2009) and the potential for exploring these patterns as markers of change and/or outcome (prediction), I used these patterns of intrinsic connectivity as a way to elaborate interpretation of fMRI BOLD maps in a standardised way. I tested and implemented a new extension in SPM, namely Intrinsic Connectivity Network Atlas (ICN_atlas). The script has been conceptualised and developed within the UCL Institute of Neurology EEG-fMRI research group. It provides a description of fMRI maps by quantifying the involvement of ICNs in terms of spatial overlap as well as the degree of BOLD activation in regions of interest in cognitive task and seizure-related fMRI data. Thus the similarity between resting state and co-activation networks (Smith et al., 2009), referred to as intrinsic connectivity networks, is exploited and elaborated into a neuroimaging instrument that contribute to image analysis (Kozak et al., 2017).

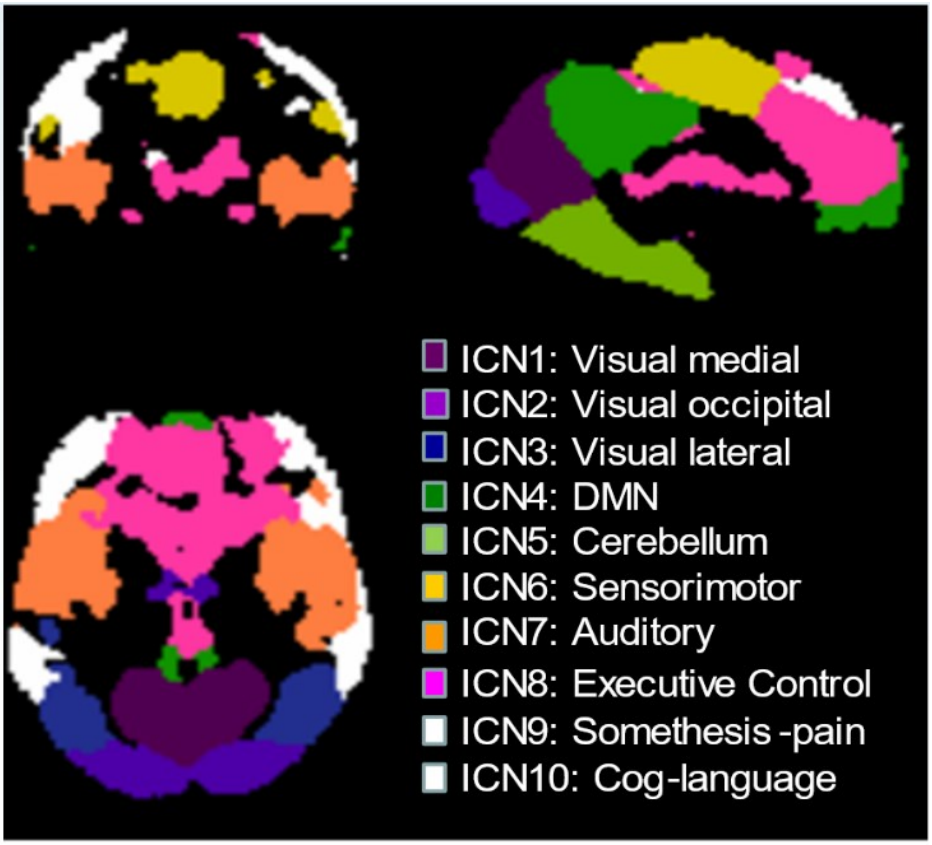
ICN_atlas

The novelty of the framework lies in: (1) the use of functionally derived atlas base maps based on ICNs; and (2) it outputs a series of estimated activation-based metric values to describe the functional activations (input) based on intrinsic functional connectivity embodied in the atlas base maps/masks (Kozak et al., 2017). For ICN engagement, two sets of atlas base maps that are available in *ICN_atlas*' current implementation, respectively representing ICNs resulting from group-wise resting-state fMRI data (Smith et al., 2009) and BrainMap Project meta-analysis data from activation studies (Laird et al., 2011; Smith et al., 2009) were employed. The Smith10 atlas is based on resting-state fMRI data, while the Brainmap20 atlas is based on ICA decomposition of task-based fMRI data (Laird et al., 2011; Ray et al., 2013; Smith et al., 2009). ICN_atlas background, development, cluster algorithm and equations, hard segmentation and output are described more comprehensively in the original paper (Kozak et al., 2017).

ICN analysis. Voxel level changes in BOLD signal, in regions of interest across the brain, were assessed in unthresholded maps using ICN_atlas (Kozak et al., 2017). ICN_atlas provides a set of 15 metrics to quantify and interpret BOLD maps in terms of intrinsic connectivity networks. In this work ICNs derived from resting-state fMRI fMRI (rs-fMRI) data are referred to as "rest ICNs" while ICNs derived from task fMRI (t-fMRI) data are referred to as "task ICNs." Atlas metrics and lateralisation indices provided a function-oriented, objective, and quantitative way to quantify the degree of 'engagement' of ICNs in fMRI-derived statistical maps.

Figure 5. 4.

ICN_atlas



Note. ICN_atlas (Kozak, L 2014 – personal communication. Reproduced with permission) overlaid on Colin Brain Copyright (C) 1993–2009 Louis Collins, McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University. The figure shows ten ICN masks in coronal, sagittal and axial planes in MNI standard coordinate space. The masks delineate networks as extracted by independent component analysis of BOLD maps of 36 subjects at rest (Smith et al., 2009) and comprises resting state intrinsic connectivity networks used as a set of atlas base maps in ICN_atlas (Kozak, van Graan 2014). The individual network masks are colour coded along with descriptions of interpretation of each component as extracted from the behavioural domain categorisation in the Brainmap database, that comprised of a wide range of fMRI activation studies involving 29,671 subjects. Thus the 10 maps correspond to interpretable functional categories and can be considered the major representative' functional networks as derived independently from both activation meta-analysis and resting data. The atlas provides a means to describe activations in the context of of ICNs by matching fMRI activation data to atlas templates.

ICN_atlas metrics. The 15 measures used to quantify the level of involvement of ICNs have been designed to reflect variance of ICN involvement along the broad dimensions: spatial extent (voxel numbers), intensity (voxel statistical scores) and density (combination of intensity and voxel numbers). The metrics also include a correlation measure. The range of measures are likely to facilitate capture of the full spectrum of activity that otherwise may be lost in conventionally thresholded maps and provide the benefit potentially accrued from both spatially and intensity extended signals (Hayasaka & Nichols, 2004).

The metrics are either ICN-specific (vector quantities: one value for each ICN) or global (scalar quantities: calculated over all ICNs). In addition to a distance of centres metric that measures the distance between the centres of mass of brain activation areas, a total of 11 ICN-specific metrics and 4 global metrics are implemented in ICN_Atlas. The metrics are described in Table 5.1.

Table 5. 1.

ICN_atlas Metrics

Metric	Abbreviation	Description
ICNi Spatial Involvement	I_i	Ratio of the number of activated ICNi voxels to ICNi.
ICNi Relative Spatial Involvement	IR_i	Ratio of the number of activated ICNi voxels over the total number of activated ICN voxels
Spatial Overlap with ICNi	OL_i	Spatial overlap between the thresholded activation map and ICNi
Sørensen-Dice coefficient with ICNi	SQ_i	Spatial similarity between the thresholded activation map and ICNi:
Jaccard index with ICNi	J_i	Spatial similarity index between the thresholded activation map and ICNi.
Mean ICNi Activation	MA_i	Ratio of the sum of ICNi statistical values to the number of activated ICNi voxels
Normalised Mean ICNi Activation	$MA_{N,}i$	Ratio of the mean of normalised voxel-wis estatistical values and the number of activated voxels in ICNi
Relative Normalised Mean ICNi Activation	IR^{M}_{i}	Ratio of the sum of normalised statistical values for ICNi over the number of activated voxels in all ICN; equivalent to the mean of voxel-wise statistical values over activated voxels in all ICN
Normalised Relative ICNi Activation	$RA_{N,i}$	Ratio of the summed normalised activation in the given ICN and the total normalised activation in all ICN

Normalised Mean ICN Activation Density	I_i^M	Ratio of the sum of normalised statistical values for ICNi to ICNi volume:
Pearson's spatial correlation with ICNi	r_i	Measures the similarity between the full activation map and ICNi along the voxel dimension and provides a joint measure of activation extent and level similarity
Total ICN Spatial Involvement	I_T	Ratio of the total number of activated ICN voxels over the total ICN volume
Global Mean ICN Activation	MA	Mean of voxel-wise statistical values and the number of activated voxels in all ICN.
Normalised Global Mean ICN Activation	MA_N	Ratio of the mean of normalised voxel-wise statistical values over the number of activated voxels in all ICN.
Normalised Global Mean ICN Activation Density	I_T^M	Ratio of the sum of normalised statistical values over all ICN to total ICN.

In the experimental studies, I obtained atlas data for ROIs corresponding to 10 canonical resting state networks (resting ICNs) (Smith et al., 2009) and ROIs corresponding to 18 task networks (task ICNs) (Laird et al., 2011). Multiple nomenclatures, including anatomical, directional, functional and cytoarchitectonic that serve as macroscopic indicators of inexact boundaries, but which serves as estimation of the anatomical regions encompassed by each spatial map were used (Laird et al., 2011). The primary anatomical regions for ICNs are described in Table 5.2.

Table 5.2

ICN ROIs

ICN	18 "Task" ICNs	10 "Resting State" ICNs
1	Limbic and medial-temporal areas	Visual – medial
2	Subgenual ACC and OFC	Visual – occipital pole
3	Bilateral BG and thalamus	Visual – lateral
4	Bilateral anterior insula/frontal opercula and the anterior aspect of the body of the cingulate gyrus	DMN
5	Midbrain	Cerebellum
6	Superior and middle frontal gyri	Sensorimotor
7	Middle frontal gyri and superior parietal lobules	Auditory
8	Ventral precentral gyri, central sulci, postcentral gyri, superior and inferior cerebellum	Executive control
9	Superior parietal lobule	Frontoparietal (perception-somesthesis-pain)
10	Middle and inferior temporal gyri	Frontoparietal (cognition-language)
11	Lateral posterior occipital cortex	
12	Medial posterior occipital cortex	
13	Medial prefrontal and posterior cingulate/precuneus areas, DMN	
14	Cerebellum	
15	Right-lateralised fronto-parietal regions	
16	Transverse temporal gyri	
17	Dorsal precentral gyri, central sulci, postcentral gyri, superior and inferior cerebellum	
18	Left-lateralised fronto-parietal regions	

Network engagement. Three quantitative indices of network engagement were obtained: 1) activations, and 2) deactivations within each rest ICN and task ICN. Insofar the association of function and clinical ictal signs with activations within ICN ROIs may be affected by deactivations, measures of 3) net engagement, which is the sum of activation and deactivation, reflecting either a net positive engagement (activation) or a net negative engagement (deactivation) was employed to characterise the entire ICN ROI.

Anatomical atlas

ICNs can be characterised with greater detail than the estimated anatomical boundaries (Table 5.3) provided by Laird (2011): The human Brainnetome Atlas (Fan et al, 2016), with 210 cortical and 36 subcortical subregions, was used to obtain greater anatomical reference for ICNs. ICN specific masks were calculated from the hardsegmented Smith10 and brainMaps20 atlases (Kozak et al., 2017) and overlaid with the human Brainnetome Atlas. The results are shown in Table 5.3.

Table 5. 3.

Percentage ICN ROI overlapped by Anatomical Structures

Anatomical area	**left**	**right**	**Anatomy**	**left**	**right**	**Anatomy**	**left**	**right**
task ICN 1			**task ICN 4**			**task ICN 12**		
OrG	10.3%	4.8%	SFG	16.9%	15.3%	FuG	2.6%	0.3%
STG	20.6%	21.7%	IFG	29.6%	32.1%	PhG	0.8%	0.8%
MTG	14.3%	21.6%	OrG	12.9%	14.4%	IPL	0.8%	0.0%
ITG	10.1%	8.3%	PrG	1.4%	3.9%	Pcun	12.6%	16.7%
FuG	10.0%	9.0%	STG	2.6%	3.7%	CG	4.2%	4.0%
PhG	7.6%	7.7%	IPL	2.1%	1.9%	MVOcC	55.3%	61.8%
INS	6.3%	5.9%	INS	20.5%	15.8%	LOcC	20.5%	12.3%
Hipp	13.2%	14.2%	CG	13.5%	12.2%	Hipp	2.7%	2.4%
BG	6.9%	6.5%	BG	0.3%	0.7%	Tha	0.5%	1.7%
Tha	0.7%	0.2%						

task ICN 5			task ICN 13			task ICN 17		
ITG	0.2%	4.5%	SFG	29.1%	20.2%	IFG	2.0%	0.6%
FuG	40.8%	50.5%	PCL	6.0%	4.7%	PrG	48.1%	30.6%
PhG	40.1%	33.5%	pSTS	0.8%	0.0%	IPL	2.1%	17.3%
CG	4.1%	6.2%	IPL	30.6%	32.9%	PoG	32.9%	39.4%
MVOcC	3.3%	0.2%	Pcun	18.2%	25.9%	INS	14.9%	8.3%
Hipp	3.1%	1.0%	CG	15.2%	16.3%	BG	0.0%	3.8%
Tha	8.4%	4.1%						
task ICN 16			**rest ICN 4**			**rest ICN 7**		
PrG	5.1%	1.5%	STG	0.7%	3.2%	IFG	6.2%	3.0%
STG	43.6%	40.3%	OrG	7.8%	10.2%	OrG	3.3%	2.1%
MTG	15.5%	24.2%	MTG	4.0%	6.2%	PrG	6.2%	2.9%
ITG	0.7%	0.04%	IPL	27.9%	18.0%	STG	36.0%	35.0%
pSTS	4.4%	10.6%	Pcun	36.1%	41.1%	MTG	2.0%	6.9%
IPL	14.9%	10.6%	CG	19.6%	14.9%	pSTS	3.9%	10.1%
PoG	9.8%	6.1%	MVOcC	3.9%	6.4%	IPL	12.2%	10.0%
INS	5.9%	6.8%				PoG	7.0%	4.7%
						INS	20.5%	20.8%
						BG	2.6%	4.4%
rest ICN 8			**rest ICN 9**			**rest ICN 10**		
SFG	14.2%	15.9%	SFG	94.4%	7.5%	SFG	0.8%	12.5%
MFG	27.6%	22.8%	MFG	0.0%	20.1%	MFG	2.5%	0.0%
IFG	0.1%	1.1%	IFG	0.0%	11.5%	IFG	1.3%	0.0%
OrG	5.5%	6.5%	OrG	0.0%	3.5%	OrG	0.3%	0.0%
PrG	0.2%	0.1%	PrG	0.0%	8.1%	PrG	0.8%	0.0%
SPL	0.2%	0.2%	STG	5.6%	2.3%	MTG	0.4%	0.0%
Pcun	2.0%	2.9%	MTG	0.0%	8.0%	ITG	0.5%	0.0%
INS	3.3%	2.4%	ITG	0.0%	1.4%	FuG	0.1%	0.0%
CG	23.7%	18.7%	pSTS	0.0%	0.5%	pSTS	0.0%	0.0%
LOcC	0.4%	0.2%	SPL	0.0%	4.3%	SPL	0.8%	62.5%
BG	15.5%	18.6%	IPL	0.0%	29.1%	IPL	2.7%	25.0%
Tha	7.4%	10.6%	Pcun	0.0%	0.2%	Pcun	0.1%	0.0%
			PoG	0.0%	2.0%	PoG	2.0%	0%
			INS	0.0%	0.3%	INS	0.3%	0%

	CG	0.0%	0.1%	
	LOcC	0.0%	1.0%	

Note. Cortical and subcortical areas that overlap with ICN ROIs dilineated by the Human Brainnetome Atlas (Fan et al., 2016).
BG, Basal ganglia; CG, Cingulate gyrus; FuG, Fusiform Gyrus; Hipp, Hippocampus; IFG, Inferior frontal gyrus; INS, Insular gyrus; IPL, Inferior parietal lobule; ITG, Inferior temporal gyrus; LOcC, Lateral occipital cortex; MFG, Middle frontal gyrus; MTL, Medial temporal lobe; MVOcC, Medioventral occipital cortex; OrG, Orbital gyrus; PCL, Paracentral lobule; PhG, Parahippocampal Gyrus; Pcun, Precuneus; PFC, Prefrontal cortex; PhG, Parahippocampal gyrus; PoG, Postcentral gyrus; PrG, Precentral gyrus; pSTS, Posterior superior temporal sulcus; SFG, Superior frontal gyrus; SPL, Superior parietal lobule; STG, Superior Temporal Gyrus; Tha, Thalamus.

Lateralisation

An established bootstrapping approach (Wilke & Schmithorst, 2006) was used to assess and obtain LI in individual subjects. Weighted mean values were obtained with bootstrap default settings for each subject. Left lateralisation was defined LI>+0.2, right-hemisphere dominant LI >−0.2 and atypical dominance (−0.2 ≥ LI ≤ +0.2), comprising both bilateral and right distribution (Centeno et al., 2014; Gonzálvez, 2016). Highly lateralised was defined LI >+0.5/<−0.5. Lateralisation indices were obtained in three anatomical regions, using three custom inclusive masks, constructed in house, comprising inferior and medial frontal gyrus, as well as anterior and posterior temporal lobe masks, to give correspondence to previous results and a framework for prediction of surgical outcome. Lateralisation indices were obtained in 26 ROIs corresponding to 10 resting state ICNs and 18 task ICNs using custom inclusive masks.

Data Management and Statistical analysis

Software

I wrote scripts and used functions (MATLAB 2016a, The MathWorks, Natick, 2016 software version 3.13.1; R Core Development Team, 2017), and used MedCalc (v 19.9.5), JASP (v 0.8.2) and MATLAB (MATLAB 2016a, The MathWorks, Natick, 2016 software version 3.13.1) to conduct data summaries and statistical analyses. SPM8, SPM12 (http://www.fil.ion.ucl.ac.uk/spm), MRICron (v 6.6), and Matlab (MATLAB 2016a, The MathWorks, Natick, 2016) functions were employed to visualise data.

Statistical analyses

Statistical tests were selected on the basis of independence of groups. Data distributions were assessed with the Kolmogorov-Smirnov test. The Shapiro Wilkes which is more sensitive to smaller sample sizes (Ahad et al., 2011) were used for comparisons involving patient groups. The F-test of equality of variances was used to test normal distributions and Levene's test was used for nonnormal distributions (O'Brien, 1981). Kendal tau correlations which are suitable for small group sizes and tied ranks, considered superior to the Spearman rank correlation (Newson, 2002) were employed and allowed for comparison across control and patient groups. Unless otherwise reported all significant values were $p < 0.05$.

Multiple comparisons. Where multiple tests were conducted on the same null hypothesis, the probability of making one or more Type I error was limited by a family wise error rate (FWER) of less than 5%, using Bonferroni adjustment of the observed probability values (p-values). The family was qualified as the group of tests used to accept or reject the null hypothesis. To reduce Type II error/increase power, sample size was maximised by testing relevant hypotheses across patient groups and healthy controls.

In view of the high number of comparisons in correlational analyses, the FWER was controlled by permutation tests that also control for type II error (Good, 2005). It estimates statistical significance directly from the data being analysed and has been recommended in studies that involve multiple statistical testing (Belmonte & Yurgelun-Todd, 2001; Nakagawa, 2004).

Essentially, permutation comprises re-sampling the observations N times, to build an empirical estimate of the null distribution from which the test statistic has been drawn (Belmonte & Yurgelun-Todd, 2001). Accordingly test statistics for all observations were first calculated without use of permutations. It was followed by 10000 iterations that each comprised calculation of a new test statistic for each observation. The value of the maximum test statistic across all observations were stored. It was followed by a two-sided test that computed the 95^{th} quantile which represented the values of the 0.05 alpha level. The resampling-based p-value is the proportion of resampled data sets yielding a statistic to compare with the original test statistic (Westfall, 1993).

Bayesian inference. Statistical null hypothesis significance testing was employed to ascertain validity of observations. To know whether non-significant results were indicative of data insensitivity or provided support for or support against alternate hypotheses (Dienes, 2014), the relative evidence of one hypothesis over another was evaluated with Bayes factors (BF). Specifically, for hypotheses that anatomical and ICN ROI can reflect the influence of disease characteristics and provide indication of change in language function following ATLR, the likelihood ratio expressed as Bayes factors were calculated to quantify evidence for the alternative hypotheses relative to the null hypotheses.

Bayes factors were reported alongside p-values where the likelihood ratio provided strong support for the alternate hypothesis (H_1) over the null hypothesis (H_0), expressed as H_1 over H_0 (BF_{10}). In the absence of prior information, a uniform prior distribution was employed, and the width of the Beta* prior probability distribution was set at 1 which renders it non-informative, that is, flat for all possible values of the parameter. The decisiveness of the evidence provided by BF was graded (Jeffreys, 1961). Accordingly it provided anecdotal support (BF= 1-3), moderate support (BF = 3-10), strong support (BF =10-30), very strong support (BF = 30-100) and extreme evidence (BF >100) for the tested hypotheses (Wagenmakers, 2013).

Multivariate methods. Data matrices that represent multiple observations raises the question as to the number and nature of domains that are represented and how well measures represent the domains. In this thesis these questions related to fMRI observed haemodynamic correlates of language function and seizure activity and were addressed using factor analysis (FA), principal components analysis (PCA) and hierarchical cluster analysis (HCA).

Factor analysis. Factor analysis is a multivariate data reduction technique that identifies the structure of data, providing meta variables/factors that are based on common variance in the correlation matrix. The number of metrics available in ICN_atlas introduced a large spectrum of data and potential redundancy.

Exploratory factor analysis (EFA) was employed to 1) identify and confirm latent dimensions in datasets and to identify correlated metrics. It was used to 2) identify the most representative metrics to summarise BOLD language maps in the language and ictal datasets. In other words, the metric with the highest loading on a specific factor was taken as representative of that factor/dimension. As the number of factors extracted is crucial, three different objective methods were used to determine the optimal number of factors/dimensions and interpret in the context of the data and metrics. The number of factors extracted to best represent the correlation matrix was, therefore, informed by consensus between Very Simple Structure Criterion (VSS) (Revelle & Rocklin, 1979) and Velicer's Minimum Average Partial (MAP) (Velicer, 1976) and the number of principal components. All analyses were aimed at identifying dimensions in the data that are unrelated and employed orthogonal (Varimax) rotation that changes the distribution of the proportion of variation explained by each factor and simplified interpretation. Varimax tends to associate individual variables with only one factor and each dimension represents only a small number of variables.

Principal component analysis. Principal component analysis (PCA) aimed to reduce the number of variables of the data sets, thereby simplifying analyses while preserving as much information as possible. It summarizes and helps to visualize the information in a data set containing observations described by multiple inter-correlated quantitative variables (Kassambara, 2017b).

Geometrically speaking, the goal of PCA is to identify directions, that is the lines (or principal components) along which the variation in the data is maximal (Kassambara, 2017b). The larger the dispersion along a line, the more the information it has. Reducing the dimensionality in this way helps to identify commonalities and pattens in data. In other words, principal components provide the best angle to see and evaluate the data, so that the differences between the observations are clearer. In so doing it establishes a new coordinate system in which every point in a dataset or cloud of data has a new coordinate (x,y) value. Principal components are new variables that are uncorrelated - constructed as linear combinations or mixtures of the initial variables and are ordered by the percentage fraction of the total information. PCA was performed in order to convert all possibly correlated variables such as fMRI activations in the context of language and ictal studies, or ictal signs into a smaller number of linearly uncorrelated variables (principal components) that served to identify commonalities and patterns.

Hierarchical clustering analysis. Cluster analysis allows for identification of homogenous subgroups within diverse samples based on shared characteristics (Allen & Goldstein, 2013). It uses pairwise distance matrix between observations as clustering criteria. In relevant studies, the merging or the division of clusters was performed either according to (dis)similarity measured by euclidean (maximum linkage), squared euclidean distance (Ward's method) and correlation-based distances between each pair of observations (Kassambara, 2017a).

Agglomerative clustering (*Agglomerative Nesting*) was performed throughout. It is a method that proceeds by a series of successive fusions of the objects (Kaufman & Rousseeuw, 1990) and follows a bottom-up manner so that that each object or datapoint is initially considered as a single-element cluster (leaf). At each step of the algorithm, the two clusters that are the most similar are combined into a new bigger cluster (nodes). This

procedure is iterated until all points are members of just one single big cluster (root) (Kassambara, 2017a). Maximum, also known as complete linkage clustering minimises the distance within and maximises the distance between clusters produces more compact clusters (Romesburg, 2004). Ward's method minimizes the total within-cluster variance and tends to produce clusters of equal size (Allen & Goldstein, 2013). The resultant tree or cluster object can be segmented at progressively lower levels producing ever-smaller subgroups of patients, each sharing specific features.

Hierarchical Clustering Analysis (HCA) was employed in language and EEG-fMRI studies to order variables such that their proximity within the dendrogram represents their degree of similarity. It was variously used to partition subject and variable space, and to reduce the complexity by forming fewer variables comprised of homogeneous observations. In language and ictal studies, HCA was variously conducted on distances represented in the raw data and distances based on new coordinates (coordinates refers to a position in space, specifically a new value as determined by the intersection of the PCA derived x and y axes).

Chapter 6

Validation of ICN_atlas

Abstract

Aim. In this chapter the validity of ICN_atlas was examined.

Methods: Three different analyses were conducted. Synthetic maps with known ICN involvement were created and assessed for correspondence of 1) spatial extent, and 2) BOLD intensities. Construct validity was examined in four different datasets: A latent factor model of spatial and intensity/density dimensions was assessed using factor analysis on the spectrum of metrics provided by ICN_atlas.

Results: ICN_atlas outputs provided accurate spatial extent and activation levels. Two factors corresponding to intensity and spatial dimensions demonstrated construct validity in healthy controls. The ICN construct was upheld in the language maps of TLE patients but was not evident for ictal phases or in simulated ICN_atlas data.

Conclusions: Recruitment of canonical resting state and tasks networks as delineated in ICN_atlas are valid for cognitive fMRI studies in healthy controls and TLE patients. The results do not support recruitment of ICNs during seizures. A review of the metrics to align more uniformly with spatial and intensity dimensions of ICNs is recommended.

ICNs have been described as tightly coupled functional neural networks in the brain that are also observed as correlated spontaneous fluctuations at rest. It has been proposed that such oscillatory activity and its content, distinguished as different networks by spatial segregation and congruence of fMRI signals, is a prerequisite for action and cognition. Accordingly, "representation" of external reality is a function of learning (Buzsáki, 2006). This principle is elaborated by the "oscillatory selection" hypothesis (Schroeder & Lakatos, 2009) that proposes functional gains through a mechanism, specifically cross-frequency, phase amplitude coupling (Lakatos et al., 2005; Petermann et al., 2009), exploiting the large-scale neuronal excitability shifts that occur during low frequency neuroelectric oscillations (Lakatos et al., 2005; Shu, Hasenstaub, Badoual, et al., 2003) (see Chapter 4).

The central proposal in this thesis is that questions in relation to language function and clinical signs/semiology can be addressed by characterisation of these rhythms or intrinsic connectivity networks and their engagement in individuals with epilepsy. This chapter investigates the validity of an atlas-based approach to quantifying ICN involvement (Kozak et al., 2017). The potential benefits include a different characterisation of language function and insight on seizure spread and semiology that may help address clinical questions raised in the experimental studies presented in Chapters 7-11.

ICN_atlas metrics align into categories: spatial extent (overlap), activation strength, activation density and correlation. Metrics are either ICN-specific (vector quantities: one value for each ICN) or global (scalar quantities: summed over all ICN). A total of 11 ICN-specific metrics and four global (measuring total involvement across all ICN) metrics are implemented in ICN_atlas.

The use of ICN_atlas is predicated upon 1) the accuracy of the metrics, and 2) construct validity, which is crucial for any instrument that purports to measure an hypothesized characteristic (Goodwin & Goodwin, 1991). Insofar these metrics reflect ICNs - the functional units that show synchronized BOLD fluctuations both at rest and while performing specific tasks (Damoiseaux et al., 2006; Laird et al., 2013; Smith et al., 2009) - they can be expected to reflect spatial and intensity dimensions in normal healthy controls performing cognitive tasks.

I hypothesised that:

1. ICN spatial recruitment in synthetic maps would correspond to known spatial engagement of ICNs.
2. ICN activation levels in synthetic maps would correspond to known intensity of ICN engagement.
3. In healthy controls ICN atlas metric outputs would yield two factorial constructs that correspond to the spatial and intensity dimensions that characterise ICNs.

Methods

Analysis 1: ICN Spatial recruitment

Step 1: Creation of synthetic involvement maps. The objective was to create SPMs with known levels of ICN involvement (spatial extent only). Synthetic maps with known ICN involvement were created. The spatial extent of each ICN was calculated using the Smith10 maps (Kozak et al., 2017):

A binary mask was created for each ICN specific to the threshold used to construct the ICN hard segmented image. As input, I used unthresholded ictal EEG-fMRI SPMs to produce SPMs that would provide the most comprehensive activation levels across the whole brain. To construct an ICN specific test for atlas evaluation, I overlaid the unthresholded

SPM with the ICN specific mask to produce an image on which to run the ICN_atlas script. It produced an ICNi specific image with known spatial recruitment.

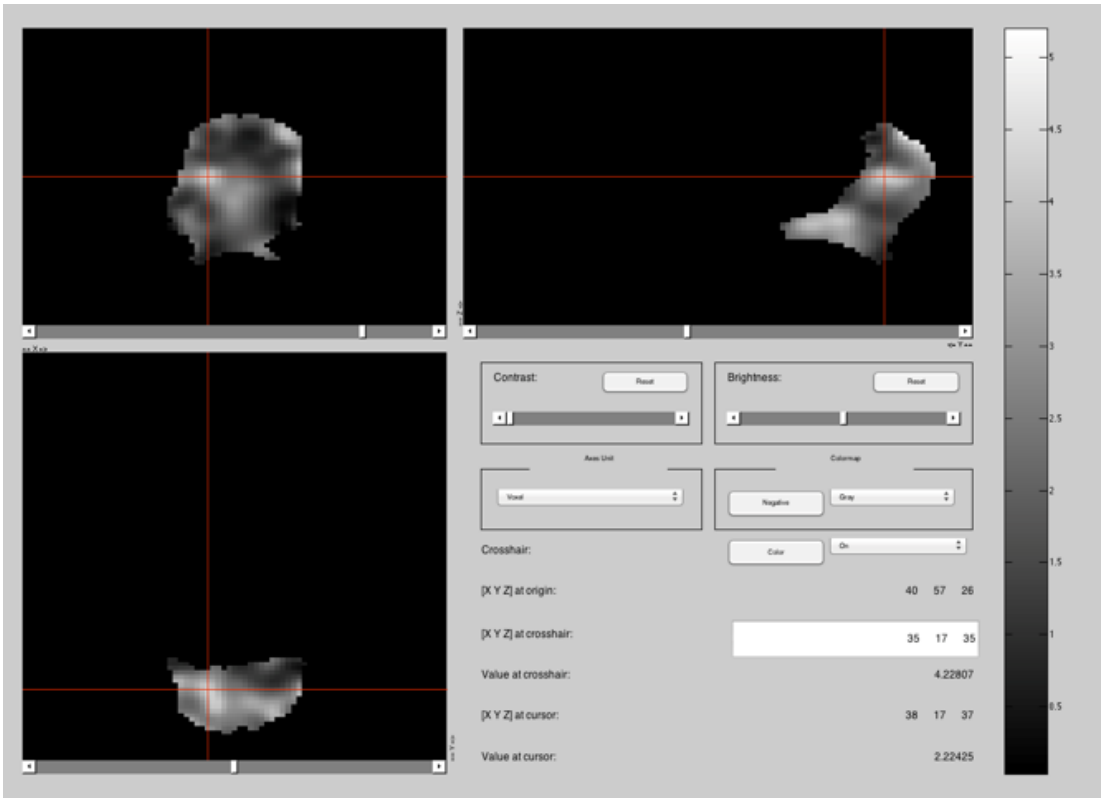
Step 2: ICN voxel numbers and occupation test. Voxel activation levels were set to zero. ICN_atlas was run on the ICN masked SPMs and the outputs inspected in Matlab variables. The results of running ICN_atlas on the ICN specific masked SPM image produced outputs for inspection in the Matlab variables prior to and following changes to the number of active voxels.

Analysis 2: ICN Intensities

Step 1: Creation of synthetic ground truth intensity maps. The objective was to create SPMs with known levels of ICN involvement. To construct an ICN specific test for atlas evaluation I changed voxel intensities in the ICN map (created in Step 1) to produce an image for ICN_atlas comparison. I altered voxels intensities employing Matlab functions (https://uk.mathworks.com/matlabcentral/fileexchange/8797-tools-for-nifti-and-analyze-image) that allowed for crosshair selection of voxel coordinate as well as changes in voxel values.

Figure 6. 1.

Crosshair Selection of Voxel Coordinate to Effect Voxel Changes



Step 2: Voxel-wise activation tests. Three changes were made to intensities in ICN images (created in Analysis 2) and tested with ICN_atlas outputs: In test 1 activation levels in three voxels were reduced to zero. In test 2, a new peak coordinate value of seven was set at an arbitrary voxel (-6 -68 0) in the test ICN.

In test 3 all voxel values above zero (i.e., active voxels) were set to a value of one. ICN_atlas was run on altered ICN images. The results of running ICN_atlas on the ICN specific masked SPM images produced outputs for inspection in the Matlab variables and atlas metrics as described in Kozak et al (2017) prior to and following changes to activation levels.

Analysis 3: Construct validity

ICN_atlas imposes an a priori model of brain function, formally characterised along dimensions of special recruitment and activation intensity. It represents a construct, that is a

feature not readily observable in fMRI maps, akin to models of effective connectivity (Friston, 1994). Measurement invariance is one form of validity evidence that refers to the measurement and comparison of latent constructs across groups. Comparison of a latent factor model can be conducted since the same units of measurement can be assigned to the latent variables for groups in question (Finch & French, 2008). The spectrum of metrics provided by ICN_atlas allowed for assessment of the ICN construct employing factorial validity which represents a correlational approach to construct validation that subsumes nomological validity (Cronbach & Meehl, 1955), convergent and discriminant validity as well as pattern matching. Acquisition of the first three datasets were described in Chapter 5 – Common Methodology: Specifically, data comprising the 1) unthesholded maps of 32 healthy subjects was compared with 2) data of five language tasks performed by 39 TLE patients. In addition, data from 3) all ictal phases of 18 epilepsy patients were analysed together and individually (early, established and late ictal) and compared with 4) a simulated ICN_atlas dataset that was assembled via resampling (R software version 3.13.1; R Core Development Team, 2017) of TLE language data. Accordingly, metric specific vectors were randomly sampled and replaced with elements from the sample space provided by the input vector (Good, 2005).

Factor selection. Principal component analysis (PCA) was used to identify the number of dimensions that accounted for most of the variance in each dataset. It was confirmed by indication from two methods, the Very Simple Structure Criterion (VSS) (Revelle & Rocklin, 1979) as well as the Minimum Absolute Partial correlation (MAP) (Velicer, 1976) as described in Chapter 5 -Common Methods. In the simulated ICN_atlas dataset, two factors were specified so as to yield comparative results obtained in the healthy control language fMRI dataset.

Exploratory factor analysis (EFA). EFA as described in Chapter 5 employed orthogonal (Varimax) rotation. It was performed to identify a latent factor model in each dataset. To make interpretation easier, high correlations or loadings (>0.7) of metric values with factors were used to identify the nature of these latent dimensions. A minimum of three highly correlated variables were used as the criterion to identify a factor (Tabachnick & Fidell, 2007).

Factor interpretation. Interpretation of the factor was conducted by judging the relative sizes of the loadings (the weight of each factor on the observed variables): high loadings suggested stronger factor contributions to those variables. The loadings may have both negative and positive values in the [0,1] interval. Loadings with the same sign contribute within the component in the same way, while those with opposite sign still contribute to the component but in an opposed way. Absolute values indicate the strength of association and were used to conduct interpretation.

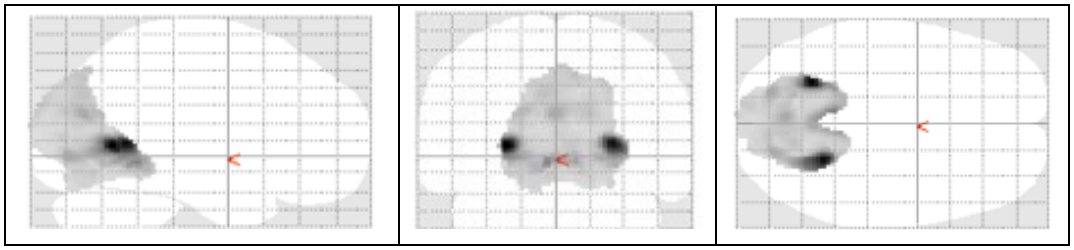
Results

Creation of synthetic SPMs

The output of masking an unthresholded SPM as described above produced images which on visual inspection spatially represented 100% ICN clusters for ICNi: That is, the image yielded an activation blob that visually corresponds to ICNi specific anatomy**.**

Figure 6. 2.

Unthresholded SPM of Rest ICN 1



Note. The image shows an activation blob that visually corresponds to rest ICN 1 (visual medial network) created from the ICNi specific mask. The image comprised 9774 voxels of which 9771 were active. Thus, the known spatial extent and activation levels provided ground truth maps for testing the accuracy of ICN_atlas voxel wise spatial recruitment as well as ICN activation output.

ICN active voxel numbers and occupation test

In some cases, the selected SPM yielded an active voxel-wise cluster occupancy of 100% for test ICNs. For all cases in whom the selected SPM did not yield voxel-wise activity of 100%, the number of inactive voxels in the test ICN completed the total number of available ICN_atlas voxels. The output showed that 100% of available atlas voxels (9774) were mapped in test ICN 1 (see Table 6.1).

ICN voxel intensity activation test

Test 1: The sum of pre-test intensity changes in three voxels (3.8 + 4.0 + 3.8 = 11.6) in the test SPM for ICN 1 was reflected in the output for test ICN 1. The number of active voxels in the test atlas output (9768) was reduced (from 9771) by the number of voxels (3) set to zero. The total sum of activations reduced by a value of 11.6 (from 19257.1 to 19245.6) commensurate with the total sum intensity reduction of voxels set to zero.

Table 6. 1.

Setting Voxels Activation Levels to Zero

ROI	NumAtlasVoxels	NumActiveVoxels	PropActiveVoxels	SumZActiveVoxels	SumZSqActiveVoxels
ICN 1	9774	9771	1.0	19257.1	45556.3
ICN 2	7182	0	0.0	0.0	0.0
ICN 3	11200	0	0.0	0.0	0.0
ICN 4	9782	0	0.0	0.0	0.0
ICN 5	9569	0	0.0	0.0	0.0
ICN 6	14788	0	0.0	0.0	0.0
ICN 7	12050	0	0.0	0.0	0.0
ICN 8	18141	0	0.0	0.0	0.0
ICN 9	14642	0	0.0	0.0	0.0
ICN10	14072	0	0.0	0.0	0.0

ROI	NumAtlasVoxels	NumActiveVoxels	PropActiveVoxels	SumZActiveVoxels	SumZSqActiveVoxels
ICN 1	9774	9768	1.0	19245.6	45511.7
ICN 2	7182	0	0.0	0.0	0.0
ICN 3	11200	0	0.0	0.0	0.0
ICN 4	9782	0	0.0	0.0	0.0
ICN 5	9569	0	0.0	0.0	0.0
ICN 6	14788	0	0.0	0.0	0.0
ICN 7	12050	0	0.0	0.0	0.0
ICN 8	18141	0	0.0	0.0	0.0
ICN 9	14642	0	0.0	0.0	0.0
ICN10	14072	0	0.0	0.0	0.0

Note. The number of inactive voxels (3) that completed the total number of available ICN_atlas voxels (9774) for the test ICN. Test 1: Activation levels in three voxels were reduced to zero: Top: Matlab variables prior to changes. Bottom: Matlab variables after setting intensities in three test ICN 1 voxels to zero.

Test 2: Matlab output variables showed the new value (7) at the new peak coordinate (-6 -68 0) that reflected the change (from 3.4 at [-12 -82 -22]) in the test ICN (Table 6.2).

Table 6. 2.

Changes to Peak Voxel Value

	Peak Coord X	Peak Coord Y	Peak Coord Z	Peak value	RSN01 visual (medial) Vx
Pre-test	-12	-82	-22	3.4	9771
Post-change	-6	-68	0	7	9771

Note. Test 2. ICN_atlas output on the ICN specific masked SPM image: Matlab variables following new peak voxel value in ICN 1.

Test 3: Post change ICN_atlas outputs show metric changes correspondent to active voxels set to a value of one (Table 6.3).

Table 6. 3.

Changes to Active Voxel Intensities

	Pre-change	Post change
Atlas metric	'RSN01 visual (medial)'	'RSN01 visual (medial)'
'NumAtlasVoxels'	9774	9774
'NumActiveVoxels'	9771	9771
'PropActiveVoxels'	1.0	1.0
'SumZActiveVoxels'	19257.1	9771
'SumZSqActiveVoxels'	45556.3	9771
'PropSumZActiveVoxels'	19251.2	9768.0
'PropSumZSqActiveVoxels'	45542.3	9768.0
'MeanActiveVoxels'	2.0	1.0
'MedianActiveVoxels'	2.0	1.0
'ICNiInvolvement'	1.0	1.0
'ICNiRelativeInvolvement'	1.0	1.0
'MeanWithinICNActivations'	2.0	1.0
'NormalizedMeanWithinICNActivations'	0.4	1.0
'NormalizedRelativeWithinICNActivations'	1.0	1.0
'NormalizedMeanWeigthedICNActivations'	0.4	1.0
'NormalizedMeanWeigthedRelativeICNActivations'	0.4	1.0

Note. Test 3: Matlab variables prior to and following changes to active voxel intensities in ICN 1.

Construct validity

The variance captured by two factors exceed 80% in the language and ictal datasets. For the simulated data, the variance captured by two factors was very low (Tables 6.4 and 6.5). Absolute value of loadings showed factors which has a strong effect on the variable. Factor loadings indicated how each underlying dimension or factor is associated with the observable variables used in the analysis and revealed characteristics that are very similar to the associated metrics. In the language data for controls and patients the first factor (f1) was highly correlated with four intensity metrics and the Pearson's correlation metric which is a joint measure of activation extent and level similarity. Thus factor 1 reflected intensity in the fMRI maps.

In the language data for controls and patients the second factor (f2), was associated with four spatial metrics. That is, factor 2 reflected spatial extent of activation in the fMRI maps. Spatial and intensity metrics were strongly correlated with both factor 1 and 2 in the ictal dataset and the factors could not be characterised accordingly. Significant underlying dimensions were not identified in the simulated datasets (where the individual metrics show high uniqueness that reflected low relevance of the metric in the factor model).

Metric correlations showed two factors that reflected spatial and intensity dimensions. Correspondent results were seen in the language fMRI maps of TLE patients. In ictal EEG-fMRI patient maps and simulated ICN_atlas outputs (Table 6.4 and 6.5), high metric correlations were discordant: That is spatial and intensity metrics all correlated highly on the same factors so that latent dimensions could not be ascertained.

Language data – healthy controls

Two factors were identified by consensus of PCA, VSS and Velicer Maps for activations, deactivations in ICNs and net engagement of ICNs. Spatial metrics showed high correlations on factor 1 whilst intensity and density metrics correlated highly with factor 2.

The spatial metric (ICNiInvolvement) did not reach the threshold set for high correlation (>0.7) but in language data it was more correlated with the intensity metrics and factor than the spatial metrics and factor. The spatial correlation metric, PearsonsSCC which represents a complex variable, reflecting a joint measure of space and activation intensity was seen to be highly correlated with an intensity dimension (see Tables 6.4 and 6.5).

Language data – TLE patients

Two factors were identified for activations, deactivations in ICNs and net engagement of ICNs. Spatial metrics showed high correlations on factor 1 whilst intensity and density metrics correlated highly with factor 2. As seen for healthy controls, PearsonsSCC was seen to be highly correlated with an intensity dimension (see Tables 6.4 and 6.5).

Ictal data

Two factors were suggested for activations, deactivations in ICNs and net engagement of ICNs. Metrics correlated highly with factors but a clear predominance and characterisation for spatial or intensity metrics were not evident (see Tables 6.4 and 6.5). The Normalised Mean ICNi Activation Density(I_i^M) metric captured most variance correspondent to neural activation across all ictal phases in the ictal BOLD maps.

Simulated data

For activations, the correlation metric, PearsonsSCC correlated highly with a notional factor 2 and the Distance of Centres metric with a notional factor 1. There were no significant correlations on any factors for deactivations or net engagement (see Tables 6.4 and 6.5).

Table 6. 4.

Factor Loadings - Activations

ICN_atlas metric	Metric description	Language fMRI Healthy Controls		Language fMRI TLE Patients		EEG-fMRI Ictal Maps (all phases)		Language fMRI Simulated Data	
		f1	f2	f1	f2	f1	f2	f1	f2
ICNiInvolvement	Spatial						0.82		
ICNiRelativeInvolvement	Spatial		0.96		0.96	0.95			
MeanICNiActivation	Intensity	0.79		0.82			0.8		
NormalisedMeanICNiActivation	Intensity	0.93		0.93			0.81		
RelativeNormalisedMeanICNiActivation	Intensity	0.77		0.78		0.76			
NormalisedRelativeICNiActivation	Intensity					0.83			
NormalisedMeanICNiActivationDensity	Intensity	0.93		0.91			0.94		
Overlap	Spatial		0.83		0.84	0.77			
Dice	Spatial		0.96		0.96	0.93			
Jaccard	Spatial		0.96		0.96	0.94			
PearsonsSCC	Correlation	0.81		0.84				0.97	
Distance of centres	Spatial								0.85
Cumulative variance		0.43	0.82	0.43	0.82	0.49	0.89	0.08	0.15

Note. Comparison of high correlations (>0.7) on factor 1 (f1) and factor 2 (f2) of activations in ICNs.

Table 6. 5.

Factor Loadings - Deactivations

ICN_atlas metric	Metric description	Language fMRI Healthy Controls		Language fMRI TLE Patients		EEG-fMRI Ictal Maps (all phases)		Language fMRI Simulated Data	
		f1	f2	f1	f2	f1	f2	f1	f2
ICNiInvolvement	Spatial						0.78		
ICNiRelativeInvolvement	Spatial		0.96		0.96	0.97			
MeanICNiActivation	Intensity	0.78		0.81			0.74		
NormalisedMeanICNiActivation	Intensity	0.93		0.93			0.88		
RelativeNormalisedMeanICNiActivation	Intensity	0.77		0.77		0.75			
NormalisedRelativeICNiActivation	Intensity					0.86			
NormalisedMeanICNiActivationDensity	Intensity	0.93		0.90			0.95		
Overlap	Spatial		0.83		0.84	0.78			
Dice	Spatial		0.96		0.96	0.94			
Jaccard	Spatial		0.96		0.96	0.95			
PearsonsSCC	Correlation	0.80		0.84			0.73		
Distance of centres	Spatial								
Cumulative variance		0.45	0.89	0.42	0.82	0.49	0.90	0.006	0.008

Note. Comparison of high correlations (>0.7) on factor 1 (f1) and factor 2 (f2) of deactivations in ICNs.

Discussion

Results

The objective of this chapter was to validate ICN_atlas, that provides cross regional information, in terms of intrinsic connectivity networks. I tested and implementing the script (ICN_atlas) in SPM8 and SPM12. To assess the accuracy of ICN_atlas outputs on SPMs, images were constructed with known spatial and intensity involvement. Construct validity was assessed by obtaining a factor analytic statistical model that reflected a relative spatial and an intensity dimension that varied between ICNs. These dimensions were demonstrated in language fMRI maps of healthy controls and patients but not in ictal BOLD maps or simulated ICN_atlas outputs.

Accuracy of metrics

Active voxel numbers and intensities as well as correspondent quantitative ICN_atlas variables matched the gain or loss of manipulated voxel intensities in the maps. It indicated accurate spatial and intensity metrics for SPMs.

Construct validity

Construct validity is the degree to which an instrument measures the theoretical construct that it is intended to measure (Cronbach & Meehl, 1955). To assess construct validity of ICN_atlas, factorial validity was ascertained. A factor analytic statistical model obtained in healthy controls was consistent with the ICN construct, specifically intensity and spatial dimensions that vary between ICNs. It provided support for ICN_atlas construct validity in language fMRI maps of healthy controls. Correspondent results indicated that the ICN construct was upheld in language fMRI maps of TLE patients, but it was not demonstrated for ictal EEG-fMRI patient maps or for simulated ICN_atlas outputs. The factor solution in ictal and simulated maps did not match that of language data and did not match a priori factor model associated with construct validity. It can be inferred that BOLD

simulated data did not conform to any pattern that could be construed in terms of the ICN construct and that results obtained in healthy controls and patients represent biological patterns rather than metric measurement bias. The results did not support normal recruitment of ICN during seizures, which is not unanticipated given the pathological nature of ictal activation.

The fact that some metrics did not correlate with any of the extracted factors indicated that it did not share variance on these factors, and it may be that the metrics are in fact a single-item measure of other important underlying latent dimensions. The results, nevertheless, do not conform to normal ICN activation patterns that were seen in healthy and TLE patient populations. Therefore, normal patterns of ICN recruitment as seen in these populations were not seen.

Instrument revision

The current results suggest a revision of the ICN_atlas, particularly in relation to its range of metrics: While factor structure consistently showed the spatial and intensity dimension represented by a small subset of metrics including ICN_i Relative Spatial Involvement (IR_i), and NormalisedMeanICNiActivationDensity (I_i^M) the results indicate redundancy and suggest a different conceptualisation of metrics. Specifically, ICNi involvement correlated higher with the intensity factor which suggests that it is a function of intensity of activation rather than a measure of spatial involvement.

Limitations

Given the novelty of ICN_atlas and lack of any published factor analysis, criterion validity using comparison with a gold standard measure was not established. Factorial validation was based on limited samples and groups sizes. Validation was conducted only at a group level. Within and between session repeatability were not assessed.

Chapter 7

Lateralisation and localisation of language function in healthy controls

Abstract

Aim: The objective was to employ an atlasing approach to investigate a potential role of large network areas involved in the specialisation of function for word retrieval, required in naming and fluency tasks.

Methods: We employed an established lateralisation method and a new atlasing approach to functional mapping that provide a range of metrics to capture variance in BOLD language maps. In addition to lateralisation indices, we identified and employed three atlas metrics identified by factor analysis, respectively yielding information on spatial, density and intensity characteristics. We obtained BOLD maps of five language paradigms in 32 healthy controls and used ICN_Atlas to quantify activations and deactivations in ICN ROIS. Net engagement was quantified to complement information provide by activations and deactivations in ROIs. We investigated repeatability for both task and rest ICNs in the context of language fMRI: Subjects participated in a second fMRI language session four months after their first fMRI session. ICNs were selected for further language analysis. Anatomical overlap of ICNs with the ATL was identified by obtaining ICN_Atlas outputs of active voxels from a T1 segmented ATL structure. Hierarchical cluster analysis (HCA) was employed to identity ICNs that demonstrated significant functional connectivity across all contrasts with ICNs that have a clear ATL anatomical overlap. We assessed the effects of contrasts and established the patterns of connectivity by correlating lateralisation of intrinsic connectivity network engagement and lateralisation in anatomical ROIs in 30 right-handed controls.

Results: Our results show network stability between sessions. Amodal linguistic processing was evident in ICN ROIs. Our results are consistent with a predominant left lateralised language network in most right-handed subjects and the relevance of temporal regions for word retrieval in the context of naming requirements relative to word retrieval for fluency that was mediated primarily by ICNs that are frontal.

Conclusions: ICN recruitment was stable between sessions. Amodal linguistic processing was evident in ICN ROIs. Identification and quantification of the patterns of ICNs engagement, including lateralisation of ICNs involved in specialisation of fluency and naming, complimented by quantification of structural involvement provide a normative reference that may quantify abnormality and potentially aid prediction of post-surgical language decline following temporal lobe resection.

Therapeutic interventions in epilepsy have been associated with decline in cognitive function. Specifically, acquired impairment in language functions have been observed in the context of both pharmacological and surgical intervention. While language fMRI is now widely employed to help determine language lateralisation in the pre-surgical work-up, established paradigms have not provided predictive specificity and the mechanisms of possible mediating impact/influence of anti-epileptic medication on networks, lateralisation and localisation have not been investigated extensively.

Relatively early fMRI investigations into the lateralisation of language have focused on whole hemispheres as well as regional areas of interest, particularly the inferior frontal gyrus, prefrontal cortex, temporoparietal cortex, middle/superior temporal gyrus, angular gyrus, or fusiform gyrus (Bethmann et al., 2007; Deblaere et al., 2004; Fernández et al., 2003; Harrington et al., 2006; Spreer et al., 2002). Better reliability for lateralisation has been obtained for regional ROIs, as opposed to whole hemispheres, specifically for frontal lobe regions (Deblaere et al., 2004; Lehericy et al., 2000). Observation of within subject cross dominance of task, has indicated the need for consideration of multiple language processes across different regions and networks to obtain an informed picture of language laterality/localisation (Baciu et al., 2003; Bethmann et al., 2007; Jansen et al., 2006; Ries et al., 2004).

In general, peak activity in anatomical structures have been relied on to arrive at conclusions in fMRI studies of language function (Bonelli et al., 2012; Centeno et al., 2014; Szaflarski et al., 2008; Woermann et al., 2003). This approach differentiated networks (dorsal and ventral) within the language system as well as specific structure-function mappings. However it has failed to engage some of the regions often compromised by surgery (e.g., the ventral and anterior temporal regions). A review and synthesis of the first

20 years of PET and fMRI studies of heard speech, spoken language and reading (Price, 2012) found that a distinction can be made between processes that are localised to specific structures (such as sensory and motor processing) and processes where specialisation arises in the distributed pattern of activation over many different areas that each participate in multiple functions. The challenge for future studies was to understand "how specialisation for language arises at the level of distinct patterns of activation in areas that participate in many different functions".

Recently, the existence of persistent and stable brain networks of functional nature has been revealed; these so-called ICNs, are spatially segregated areas representing underlying functional connectivity (Fox & Raichle, 2007) that appear to link patterns of resting state and task-related state connectivity.

The broad aim of the study was to elaborate methods and approaches to lateralisation and localisation to aid prediction when considering the impact of major interventions. Specifically, we aimed to (1) establish the normative value of recruitment of ROIs corresponding to canonical ICNs as well as the value of a panel of language tasks, in healthy controls, with a view to improve prediction of change in language function after ATLR. We hypothesised that:

1. ICN recruitment would be stable between sessions.
2. Amodal linguistic processing would be evident in ICN ROIs.
3. Word retrieval for naming would be mediated primarily by ICNs that are temporal whereas word retrieval for fluency would be mediated primarily by ICNs that are frontal.
4. Controlling for amodal processing, language recruitment in ICNs and anatomical ROIs would reflect a left lateralised precedence in language tasks.

5. Task activation would show a left lateralised pattern for amodal language processing in anatomical and ICN ROIs whereas task deactivation would show a right lateralised pattern.
6. The ATL will show task connectivity with anatomical ROIs and ICNs.

Methods

Subjects

We studied 32 healthy controls (Table 7.1). Subjects had no history of epilepsy or any other chronic neurological or psychiatric disease. Exclusion criteria for all subjects were non-fluency in written and spoken English, pregnancy, any contraindication to MRI (e.g. metallic implants, pacemakers), and inability to give informed consent. The group was made up of 20 high school, nine undergraduates and four postgraduates. Group level lateralisation and localisation were conducted on 30 right-handed subjects. All participants were fluent in written and spoken English. Subjects were invited to participated in a second fMRI language session four months after their first fMRI session. Demographic data are summarised in Table 7.1. The potential impact and implications of demographic characteristics on results are discussed in the chapters comparing healthy control and patients.

Table 7. 1.

Demographic Data for Control Subjects

Age (yr)	Gender Male/ female	Native English	Handedness Right/left	NART IQ
39 (22-59)	12/20	28	30/2	108 (86-126) (11.08)

Note. NART = National Adult reading test. Estimated intellectual level (IQ) is shown as mean ± standard deviation.

The study was approved by the National Hospital for Neurology and Neurosurgery and the UCL Institute of Neurology Joint Research Ethics Committee. Written informed consent was obtained from all participants.

Neuropsychological tests

All subjects in this study completed the National Adult reading test, the McKenna Graded Naming test as well as a phonemic verbal fluency test outside the scanner. These tests are described in the section on Clinical data – language fMRI (Chapter 5 – Common Methodology).

MR data acquisition

The MRI data acquisition was performed according to the common protocol for language studies as described in Chapter 5 – Common Methodology.

Language paradigms

Subjects in this experiment performed five language paradigms described in the common methods section for language studies in Chapter 5. Auditory naming could not be acquired in one subject due to technical difficulties with equipment.

Langue fMRI repeatability

As stated in Chapter 5 – Common Methodology, subjects participated in a second fMRI language session four months after their first fMRI session.

fMRI data analysis

fMRI data analysis including pre-processing, retrospective physiological noise and movement artifact correction, blocked design analysis and ICN_atlasing in unthresholded maps is described in the common methodology section relating to language studies (see Chapter 5).

ICN metrics. As described in Chapter 5, Common Methodology: I obtained atlas data for ROIs corresponding to 10 canonical resting state networks (rest ICNs) (S. M. Smith et al., 2009) and ROIs corresponding to 18 canonical task networks (task ICNs) (Laird et al., 2011) in the context of the language tasks described in Chapter 5.

Metric selection. Metrics were selected on the basis of factor analysis (FA) as described in Chapter 5 – Common Methodology: The contribution of metrics that quantify ICN involvement in language function were investigated with exploratory factor analysis (EFA) on the ICN_Atlas outputs for 32 subjects in Session 1 to identify the most representative metrics to summarise BOLD language maps: The loadings represent the extent to which each variable correlates with each of the factors and shows the extent to which each of the variables contributes to the meaning of each of the factors. The metric with the highest loading on each identified factor was selected to represent the respective dimensions (spatial extent and intensity) of activation in the language maps.

Activation, deactivation and net engagement of ICNs

As described in the common methods section, network engagement was obtained by quantifying (1) activations and (2) deactivations within ICN ROIs, as well as (3) net engagement which is the ratio of the sum of ICN_i positive and ICN_i negative statistical values to number of ICN_i active voxels - providing either a net positive or negative engagement (deactivation) of the entire ICN ROI.

ICN stability and repeatability

Normal distribution of differences between Session 1 and Session 2 were determined for each ICN by means of the Kolmogorov-Smirnov Test. Bland Altman plots were used to compare the stability of network engagement between sessions over an interval of 3-6 months for 18 subjects using Session 1 as the reference. The Bland-Altman plot provides an intuitive method for comparing measures based on visual judgement (Bland & Altman, 1986). In a

clinical context the Bland-Altman methods require interpretation of the data to compare observed limits of agreement with a priori ones. However, the metrics as well as the ICN ROIs in the context of language activation are novel measures so that any choice of a priori limits are not well informed. In the absence of measures based on clinical judgement we employed repeatability expressed in the repeatability coefficient (RC), which facilitates the comparison and is related to the 95% limits of agreement (LOA) proposed by Bland and Altman. The repeatability has also been termed the smallest real difference, minimal detectable change, and minimum clinical difference, consistent with the smallest difference that can be interpreted as evidence for a real change in the true value of a measure (Bland, 2015).

Between session agreement of rest and task ICN engagement was judged on the basis of three criteria; whether 1) the mean difference falls within 95% CI of zero difference; 2) the differences in each ICN for every subject fell below the coefficient of repeatability; and whether 3) the pattern of differences reflected any bias, either globally (arising from all ICNs) or from specific ICNs that influenced the interpretation of observed differences.

While non-normal distribution of differences is thought not have a great impact on the limits of agreement (J. M. Bland & Altman, 1999) we also, in relevant instances, describe data for between session ICN differences without assuming a normal distribution. In nonnormal distributions Bland Altman plots were augmented with folded empirical cumulative distribution plots (mountain plots) which facilitate identification of the central 95% of the data as well as the estimation of percentiles for large differences. We furthermore calculated and inspected the direction of differences in mean intensity of activation and deactivation for rest ICNs measured by the ICN_atlas metric GlobalmeanICNactivation (MA).

ICNs engagement by contrasts aimed at isolating linguistic processes

To establish modal and amodal linguistic processes we compared contrasts within paradigms for 30 right-handed controls with Wilcoxon test (paired samples) for activations, deactivations and net engagement, Bonferroni adjusted for multiple comparisons.

ICNs engagement in frontal and temporal ICNs

Differences in amodal activations of temporal and frontal lobe ICNs by fMRI naming and fluency contrasts were compared with Wilcoxon test (paired samples) Bonferroni adjusted for multiple comparisons.

Selection of ICNs for language function analysis

ICNs were selected for further analysis on the basis of structural overlap and the results of clustering: Anatomical overlap with the ATL was identified by obtaining ICN_atlas outputs of active voxels from a T1 segmented ATL structure corresponding to an inhouse ATL mask. Hierarchical cluster analysis (HCA) using complete linkage as described in the common methods section – Chapter 5, was employed to identity ICNs that demonstrated significant functional connectivity across all contrasts with ICNs that have identified ATL anatomical overlap.

Lateralisation

LI in ROIs were obtained using the bootstrapping approach (Wilke & Schmithorst, 2006) described in Chapter 5.

Correlation of lateralisation

The level of agreement in lateralisation between temporal and frontal regions as well as ICNs for every subject and task was determined by Kendall correlations adjusted for multiple comparisons with permutation testing as described in the common methods section – Chapter 5.

Results

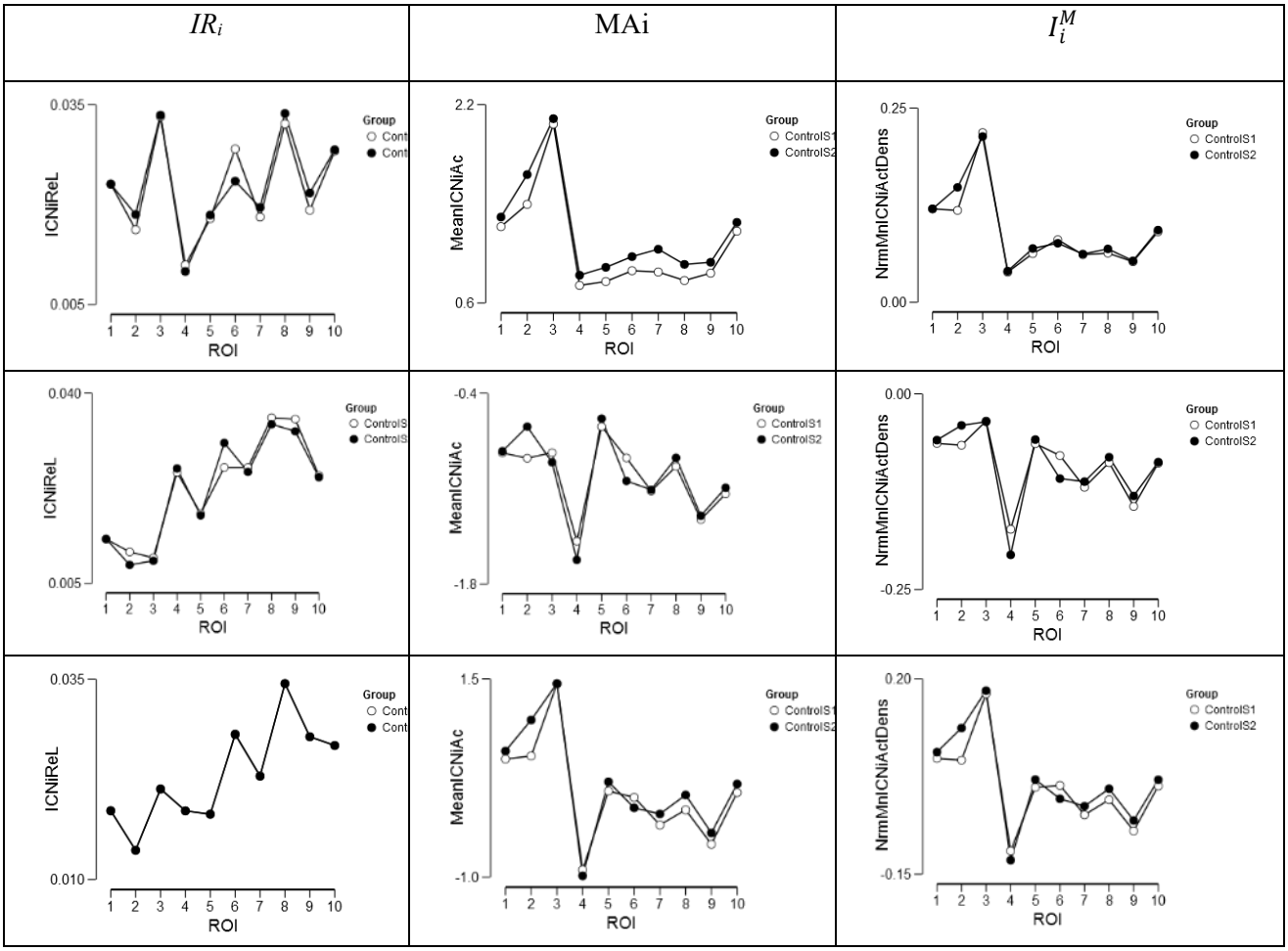
Metric Selection

Two factors emerged from data reduction factor analysis: one that captured spatial engagement and another that captured density/intensity engagement, represented by ICNi Relative Spatial Involvement (IRi), and Normalised Mean ICNi Activation Density (I_i^M): Thus, we respectively employed spatial extent (overlap), activation strength and activation density metrics to characterise language engagement of ICNs. In addition, we included an intensity measure, namely the Mean ICNi Activation (MAi) metric in the assessment of repeatability. Density and mean activation showed similar profiles across ICNs. The capture of paradigms by metrics are shown in Figure 7.1.

Raw data plots showing the configuration of group wise ICN involvement in session 1 (n=32), and Session 2 (n=18) for activations, deactivations and net recruitment of rest ICNs for each metric for the *Picture naming - Scrambled pictures & cartoon faces count* contrast. For net recruitment (bottom row) the intensity and density metrics shows prominent net positive engagement of visual network (rest ICN 3), the cerebellum (rest ICN 5), and the cognition-language network (rest ICN 10), as well as deactivation of the default mode network (rest ICN 4).

Figure 7. 1

Recruitment of Rest ICNs



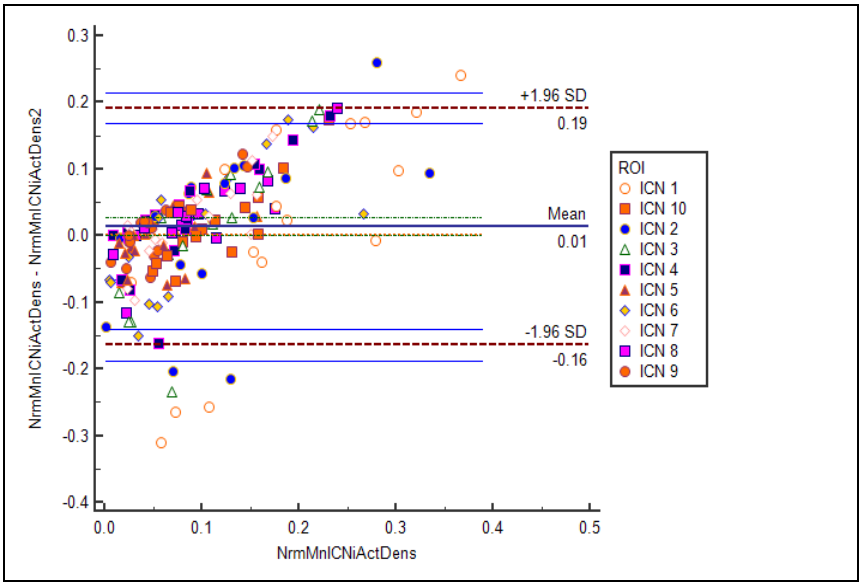
Note. Top Row: Task Positive – Activations. Middle Row: Task Negative – Deactivations. Bottom: Net Recruitment – Both.

ICN stability and repeatability

Lesser intensities of both activations and deactivations were observed in three paradigm contrasts on retest (AN-R, PN-SP&CFc, VF). Greater variance in the magnitude and nature of differences were seen in intensity and density metrics than the spatial metric. The overall repeatability showed good within-subject, within ICN ROI agreement between sessions (Figures 7.2 and 7.3).

Figure 7. 2.

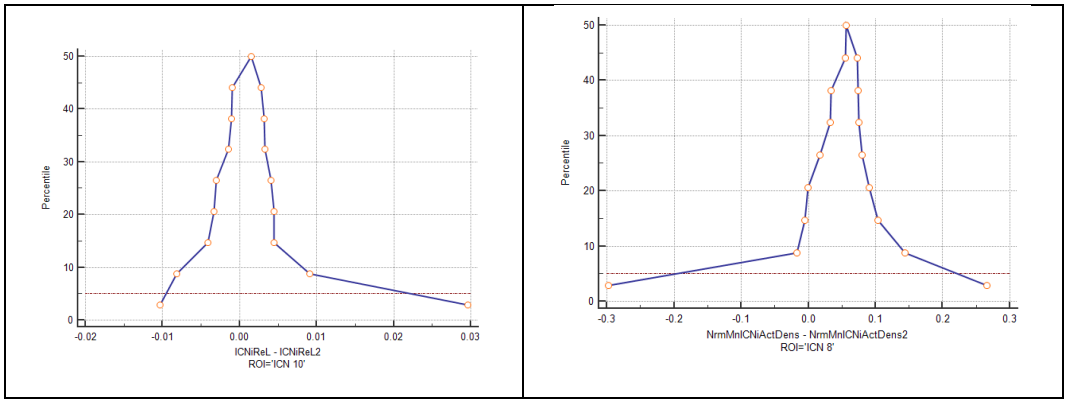
Bland Altman Plots



Note. The Plot shows the difference between Session 1 and Session 2 (n=18) using the ICN_atlas Normalised Mean Activation Density metric for Auditory Naming – reverse. 95% CI shown for upper limit and lower limit. The line of equality falls within the 95% CI for zero difference. The 95% CI is shown for upper limit and lower limits of agreement. The plots show the variance as well as the magnitude of differences to cluster by ICN. Outliers are evident for visual networks, rest ICNs 1, 2 and 3.

Figure 7. 3.

Mountain Plots of Individual ICNs



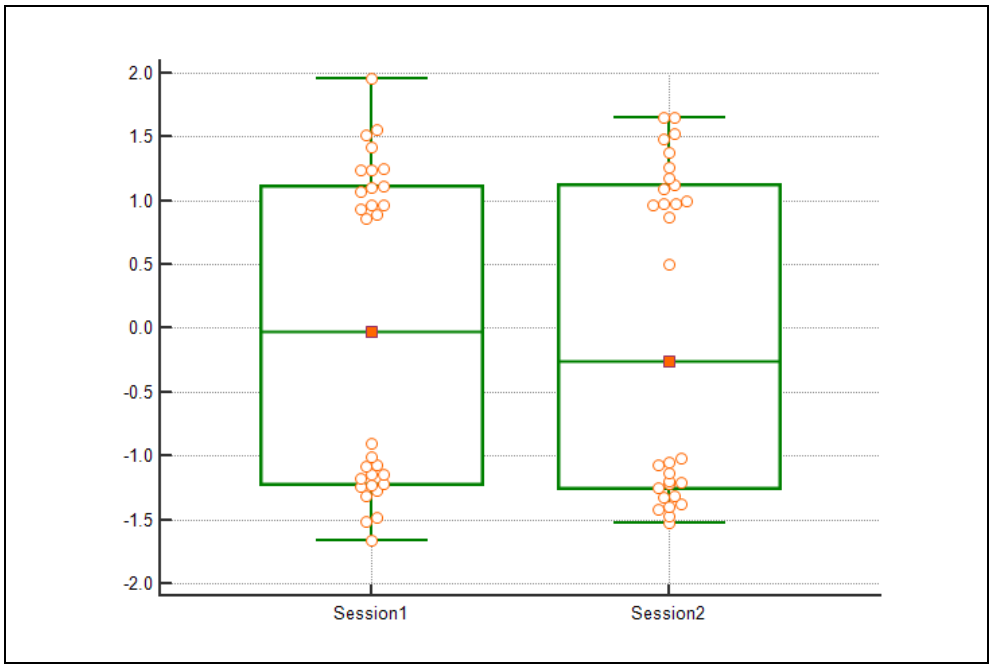
Note. The plots show nonnormal distribution for net engagement of rest ICN 10 and 8 Auditory Naming-Reverse. The differences are almost symmetrical. The median is close to zero indicating compatibility between Sessions 1 and 2. Outliers accounted for differences observed in the long tail. Left: Rest ICN 1. metric = IRi. Right: Rest ICN 8. metric = I_i^M.

Differences in mean global intensity between sessions

A positive difference in 51% (73/144) of Bland Altman plots reflected decreases in the extent of ICN recruitment in session 2 relative to session 1 for rest ICNs. Global mean ICN activation (*MA*) and deactivations of rest ICNs for 15 contrasts across five paradigms show a net decrease (0.94) in the intensity of BOLD signal across all tasks from session 1 to session 2 - consistent with indication provided by the Bland Altman plots (Figure 7.4).

Figure 7. 4.

Global Intensity Comparison



Note. Comparison of session 1 and session 2. Box-and-Whisker plot of global mean ICN activation and deactivation intensities of 15 contrasts in session 1 and session 2.

Engagement of ICN ROIs

Contrasts: Main effects. Significant differences (Kruskal Wallis ANOVA $P < 0.001$) between all fMRI tasks were seen for amodal activations, deactivations and net densities. There was a significant difference in spatial recruitment of activations and deactivations (Kruskall Wallis ANOVA $P < 0.001$) but not for net spatial recruitment. Across ICNs, there was less variance in spatial recruitment, net engagement and density of deactivations compared to activating networks.

Modal vs Amodal recruitment. Across ICNs a high number of significant differences were seen between modal and amodal contrasts for activations, compared to differences for deactivations and net engagement and compared to differences for spatial recruitment.

Fluency contrasts. There were significant differences (Wilcoxon paired samples $p<0.05$; Bonferroni adjusted for multiple comparisons) between modal and amodal FF and between modal and amodal SF for activations, deactivations and net densities across ICNs. There were significant differences (Wilcoxon paired samples $p<0.05$; Bonferroni adjusted for multiple comparisons) between modal and amodal contrasts for FF and SF in spatial recruitment for activation and deactivations across ICNs.

Naming contrasts. There was a significant difference (Wilcoxon paired samples $p<0.05$; Bonferroni adjusted for multiple comparisons) between modal and amodal AN in activation and deactivation across rest and task ICNs. Amodal AN showed significantly higher activation compared to modal AN which showed significantly lower deactivation compared to amodal AN. There was not a significant difference in contrast effects for PN.

Recruitment of temporal and frontal ICNs

Amodal fluency contrasts. The highest densities of activation were seen in frontal ICNs (task ICN 15&18/rest ICN 8, 9&10) rather than temporal ICNs (task ICNs 1, 10&16/rest ICN 7). Fluency paradigms showed significantly higher activations than naming paradigms in frontal ICNs (Wilcoxon paired samples $z= 4.41$; $p < 0.001$; Bonferroni adjusted for multiple comparisons).

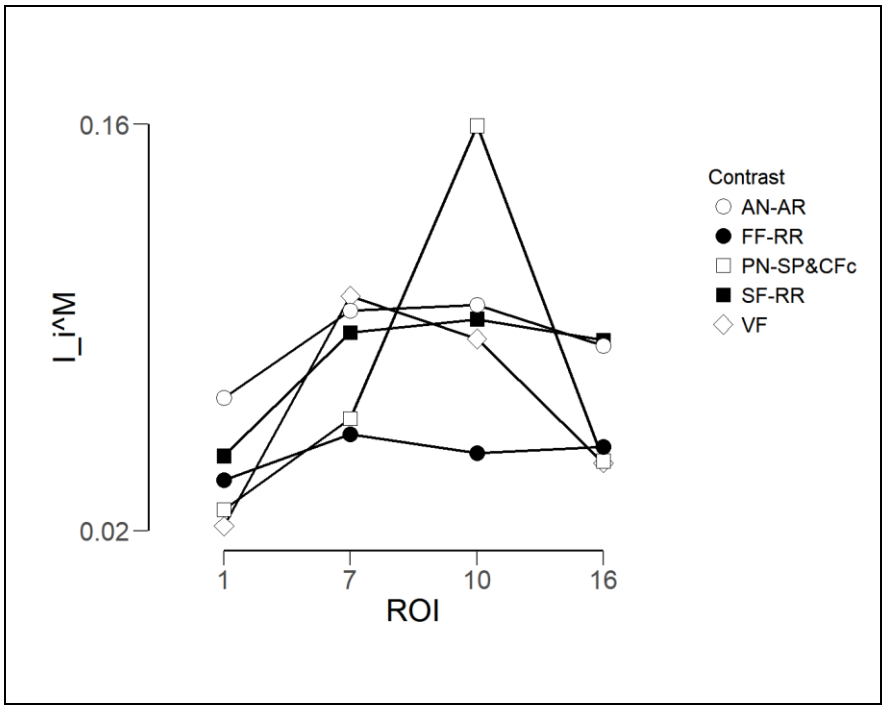
Amodal naming contrasts. Naming contrasts showed greater densities of activation and deactivation in frontal ICNs than in temporal ICNs with the exception of task ICN 10 where PN showed the highest density of activation.

Amodal naming and fluency activations in temporal lobe ICNs. Naming paradigms showed significantly greater activation than fluency paradigms in temporal ICNs (Wilcoxon paired samples z=3.46; p=0.001; Bonferroni adjusted for multiple comparisons). AN showed the highest activations across all temporal lobe ICNs. There was a marked prominence for PN in task ICN 10.

Amodal SF showed higher mean densities of activation across temporal task and rest ICNs than FF and VF. SF showed significantly greater activation (Wilcoxon paired samples z=5.84; p<0.001; Bonferroni adjusted for multiple comparisons) compared to FF in temporal ICNs. Amodal naming and fluency activations in temporal lobe ICNs are shown in Figure 7.5.

Figure 7. 5.

Naming and Fluency Paradigm Comparisons



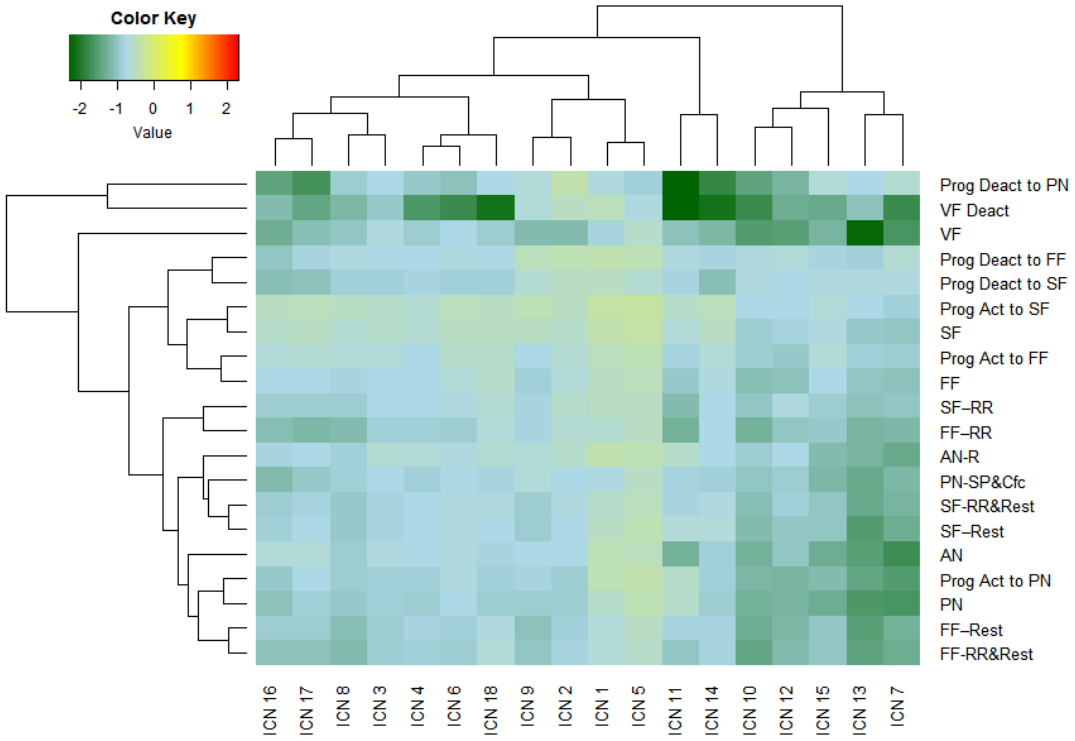
Note. Naming and fluency paradigm comparisons in temporal lobe ICNs**:** NormalisedMeanICNiActivationDensity (I_i^M): Activations

Selection of ICN for language analysis

Rest ICNs 4, 7 and 9, and task ICNs 1, 16 and 4 showed clear overlap (> 100 voxels) with the ATL while structural connectivity was also seen for rest ICNs 8 and 10. Hierarchical clustering of task networks showed that task ICN 5 consistently clustered with task ICN 1 and task ICN 17 clustered consistently with task ICN 16 for activations, net engagement and deactivations (Figure 7.6).

Figure 7. 6.

Heatmap of Deactivations in Task ICNs



Note. Deactivations in task ICNs as a function of colour. Hierarchical clustering show clusters based on similarity as determined by euclidean distance. The clusters represent task ICNs (columns) and contrasts (rows) that are the least distance apart, respectively. The greatest deactivations across paradigms in task ICN 7 and 13 clustered together (columns). Verbal fluency shows the greatest intensity of deactivations across ICNs.

Lateralisation indices

We report the highest incidence (either left or right [LI>+/-0.2]) in the group for each contrast.

Anatomical ROIs. VF and FF were the most prominent in the IFG&MFG that showed the most lateralisations compared to the ATL and PTL across all fMRI tasks. VF showed the greatest incidence of left lateralisation in the IFG&MFG. Deactivating contrasts were predominantly right lateralised across all ROIs. Amodal AN and PN were left lateralised for most subjects across all anatomical ROIs. Amodal FF was predominantly right lateralised for most subjects in the ATL and left lateralised in the PTL and IFG&MFG. Amodal SF was predominantly right lateralised in the ATL and PTL and left in the IFG&MFG. VF was left lateralised for most subjects across all ROIs (Table 7.2).

Table 7. 2

Lateralisation of Subjects in Anatomical ROIs

Contrast	ROI		
	ATL	PTL	IFG&MFG
AN	–*	–	=
AN-R	+	+	+*
PN	–	–*	+
PN - Sp & Cfc	+	+	+
Prog Act to PN	–	–*	–
Prog Deact to PN	–*	–	–*
FF	–**	+	=
FF– RR	–	+**	+**

FF - Rest	–*	–*	+
FF - (RR & Rest)	–	=	+
Prog Act to FF	–*	–	–
Prog Deact to FF	–*	–*	–*
SF	–	+	+
SF– RR	–	–	+*
SF - Rest	–	–	+
SF - (RR & Rest)	–	+	+*
Prog Act to SF	–	+	+
Prog Deact to SF	–*	–*	–*
VF	+*	+*	+*
VF Deact	–*	–	–*

Note. Greater number of subjects left lateralised (+) vs right lateralised (–) or equal (=) left and right for contrasts in anatomical ROIs. * Number of lateralised subjects >50% and ** number of lateralised subjects >70% of total in group.

Correlation of amodal language lateralisation between the ATL and anatomical ROIs. Significant correlations ($p<0.05$; adjusted for multiple comparisons with permutation testing) was seen between the ATL and PTL for amodal SF ($r=0.55$, $p=0.02$) and between the PTL and IFG&MFG for amodal AN ($r=0.52$, $p=0.04$).

Lateralisation in the ICNs

Most lateralisations were evident in the DMN (task ICN 13) where activating contrasts were predominantly left lateralised. Deactivating contrasts were right lateralised for most subjects in all ICNs.

VF was the most lateralising contrast for ICNs. For most subjects, amodal AN was right lateralised in rest ICN 7, and task ICNs 5, 16 and 17. It was left lateralised for most subjects across all other ICNs. Amodal PN was predominantly left lateralised in the DMN (rest ICN 4 and task ICN 13). Amodal FF was left lateralised for most subjects in all ICNs but not in task ICN 1 and 5. Amodal SF was primarily left lateralised in ICNs but right lateralisations were predominant in task ICN 1, 5 and 16 (Table 7.3).

Table 7. 3.

Lateralisation of Subjects in ICN ROIs

Contrast	Rest ICN					Task ICN					
	4	**7**	**8**	**9&10**	**1**	**4**	**5**	**12**	**13**	**16**	**17**
AN	+	–*	+	–*	+	–	–*	+	+*	–	–
AN-R	+*	–	+	+**	+	+	–*	+	+*	–*	–
PN	+	–	+	–	+	+	–*	+*	+*	–*	+*
PN - Sp & Cfc	+	+	–	+	+	–	+	+	+	+	+
Prog Act to PN	+	–	+	–*	+	+	0	+*	+*	+	+*
Prog Deact to PN	–	–	–	–	–	–*	–	–	–*	–*	–**

FF	+	–	–	–	–	+	–	+	+*	–	+
FF– RR	+	+	+	+**	–	+	–	+	+*	+	+*
FF - Rest	+	–	–	–	–*	+	–*	+**	+*	–*	+
FF - (RR & Rest)	+	–	+	+	–	+	–	+	+**	–	+*
Prog Act to FF	+	–	–	–	–	–	–	+	=	–	=
Prog Deact to FF	–	–	–	–	–*	–	–	–	–	–	–
SF	+	+	+	+	+	+	–	+	+**	–	+**
SF– RR	+	+*	+	+*	–	+*	–	+	+*	–*	+
SF - Rest	–	–	–	+	+	+	–	+	+*	–*	+
SF - (RR & Rest)	+	–	–	+*	=	+*	–	+	+**	–*	+
Prog Act to SF	+	+	–	=	+	+	–*	+*	+*	+	+**
Prog Deact to SF	–	–*	–	–*	–*	–	–	–*	–	=	–*
VF	+*	+*	=	+**	+*	+	–**	+	+**	+*	+**
VF Deact	–	–*	–	–*	–*	–*	–	–	–*	–	–**

Note. Greater number of subjects left lateralised (+) vs right lateralised (–) or equal (=) left and right for contrasts in ICNs. * Number of lateralised subjects >50% and ** number of lateralised subjects >70% of total in group. No subject lateralised (0).

Correlation between lateralisation in the ATL and lateralisation in ICNs

Significant positive correlations between lateralisation in the ATL and lateralisation in ICNs were seen for amodal contrasts predominantly for temporal lobe ICNs - task ICN 1 and

16 and rest ICN 7 (Table 7.4). There was not a significant association between LI in the ATL and ICNs for FF.

Table 7. 4

Correlation between Lateralisation in the ATL and ICNs

Language task	ICN	R	P*
AN	rest ICN 7	0.48	0.004
AN	task ICN 1	0.74	<0.001
AN	task ICN 4	0.42	0.016
AN	task ICN 16	0.37	0.039
PN	rest ICN 7	0.36	0.047
PN	task ICN 1	0.66	<0.001
PN	task ICN 4	0.54	0.001
PN	task ICN 17	0.48	0.004
SF	rest ICN 7	0.47	0.005
SF	task ICN 1	0.72	<0.001
SF	task ICN 16	0.43	0.012
VF	rest ICN 7	0.39	0.029
VF	task ICN 1	0.41	0.018
VF	task ICN 4	0.39	0.027
VF	task ICN 16	0.41	0.017
Deactivating VF	task ICN 16	0.39	0.030
Deactivating VF	task ICN 1	0.73	<0.001

Note. Significant correlations between lateralisation in the ATL and lateralisation in ICNs**.**

*Adjusted for multiple comparisons with permutation testing.

Lateralisation of SF and Progressive activation to SF was anti-correlated with LI in task ICN 13.

For amodal activating contrasts there were significant correlations for AN between LI in the ATL and lateralisation in rest ICN9&10 as well as task ICN 4 and 16. PN showed significant correlations with task ICNs 4, 16 and 17, FF with task ICN 16 and 17, and SF with rest ICN 4 and task ICNs 4, 16 and 17. In the ATL, VF lateralisation correlated significantly with LI in task ICN 1 and 16.

Discussion

Results

Using a published atlasing approach we demonstrated repeatability and amodal processing in ICNs. Results supported a precedence for naming over fluency; as well as semantic over phonetically mediated fluency in temporal ICNs. A well-established bootstrap lateralisation method showed significant patterns of lateralisation and connectivity in ICNs selected for their relevance to ATL function.

Repeatability

We observed a trend of reduced activation between sessions, that have been attributed to increased neural efficiency in the majority of studies that have examined the effects of task practice (Kawakubo et al., 2018; Kelly et al., 2005; Miro-Padilla et al., 2018).

Our results demonstrated repeatability of task-based recruitment of ICNs. Whilst ICN reliability between resting state sessions have previously been observed (Damoiseaux et al., 2006; Kozak et al., 2017; Shehzad et al., 2009; Wisner et al., 2013; Zuo, Di Martino, et al., 2010; Zuo, Kelly, et al., 2010) and correspondence of the brain's functional architecture during activation and rest (Smith et al., 2009) imply consistency of language task recruitment of ICNs between sessions, it has not been explicitly demonstrated.

ICN engagement

Significant differences were seen in intensity of activation as well as spatial recruitment between modal and amodal contrasts demonstrated amodal language processing in ICNs. The difference between BOLD activation and deactivation have been related to attentional focus, (Golland et al., 2007) and the potential localising value understood as interruption of ongoing processes not engaged by the explicit task (Binder, 2012). However, across ICNs, we noted less variance in spatial recruitment, net engagement as well as density of deactivations - indicating that activations provide a finer grading towards localisation.

Fluency. Consistent with previous findings (Bonelli et al., 2012) fluency was mediated primarily by frontal ICNs. In temporal ICNs greater activation was seen for amodal SF than other fluency paradigms which reached significance in comparison with FF in temporal ICNs. It lends support for a greater role of temporal cortex in semantic based word retrieval compared to phonetic word retrieval - consistent with temporal lobe lesion studies that show greater semantic than phonemic fluency deficit (Baldo et al., 2006; Henry & Crawford, 2004).

Naming. Frontal networks showed higher densities compared to temporal networks for naming. However, comparison of fluency and naming contrasts in temporal lobe ICNs showed significantly greater activation for naming than fluency paradigms confirming that these naming paradigms are better candidates for prediction of language decline following ATLR than fluency paradigms (Gonzálvez, et al., 2016).

Selection of ICNs for language analyses

Structural connectivity was seen for rest ICNs 8 and 10, while rest ICNs 4, 7 and 9, and task ICNs 1, 16 and 4 showed greater overlap with the ATL. Hierarchical clustering of task networks showed that task ICN 5 consistently clustered with task ICN 1 and task ICN 17 clustered consistently with task ICN 16 for activations, net engagement and deactivations. The recruitment of task ICNs 12 and 13 featured prominently in fluency and naming

contrasts. Inclusion of task ICN 12 for further study was also supported by previous language studies that reflect correlation between language performance and functional connectivity in posterior temporal regions for both left and right medial TLE patients (Protzner & McAndrews, 2011), observation that posterior regions are sensitive to sentence-level semantic information (Griffiths et al., 2013; Wilson et al., 2014) and voxel based morphometry results that implicate left posterior temporal cortices in semantic and lexical naming mechanisms (Migliaccio et al., 2016).

Lateralisation

For deactivating contrasts, a greater number of subjects were consistently right lateralised across ICN and anatomical ROIs whilst contrasts that included non-linguistic components were robustly contra lateral to amodal processing. In amodal activating contrasts we observed predominance of left lateralised language networks, consistent with models in the functional imaging literature (Binder et al., 2009; Price, 2012). The IFG&MFG was the most lateralised ROI across tasks also reflecting most lateralisation power for VF compared to other paradigms which likely accounts for its sensitivity (Bonelli et al., 2012), and wide use in language lateralisation studies.

Task specific connectivity and potential predictive value were demonstrated for anatomical ROIs and ICNs. While a range of deactivating networks other than the DMN was observed, lateralisation of activating networks showed more variance than deactivating networks, indicating greater potential for prediction. It is especially relevant to ICNs with large structural overlap insofar the number of contrasts which evidenced task connectivity between ICNs and the ATL was robustly concordant with the extent of structural connectivity.

Conclusion

We conclude that the panel of paradigms as reflected in the study of ICNs can provide reliable indices of language function with potential for prediction. Their value in clinical settings is yet to be determined.

Strengths and limitations

Test-retest studies numbers were limited to 18 subjects. However we used a broad range of contrasts in the assessment of repeatability, including rest and active control conditions to address motor activations inherent in overt speech function (Gonzálvez et al., 2016). It was complemented by a retrospective method for removal of movement artefact and physiological noise (Tierney et al., 2016). We used unthresholded maps which facilitates interpretation of the full spectrum of BOLD activity. While the ICNs and ICN_atlas metrics represent somewhat novel measures we employed conventional anatomical ROIs and a well-established lateralisation method that will allow comparison to other studies.

Chapter 8

Language Activation in Temporal Lobe Epilepsy. An fMRI Study of Intrinsic Connectivity Network Engagement

Abstract

Background: Temporal lobe epilepsy has been associated with atypical language network patterns as well as impaired word retrieval in the context of naming and fluency function. Using fMRI, anatomical and intrinsic connectivity network recruitment and lateralisation in TLE patients and healthy controls were investigated to establish connectivity patterns and associated performance that may help to inform prediction of language decline following ATL resection.

Methods: An established lateralisation method and selected metrics of an atlasing approach to functional mapping that provided spatial, density and intensity characteristics in relation to a priori defined anatomical and intrinsic connectivity network ROIs as reflected in BOLD language maps were employed. BOLD maps of five language paradigms in 30 righthanded healthy controls were obtained and compared with the patterns and performance in 24 LTLE and 16 RTLE patients.

Results: Healthy controls had better language performance scores compared to patient groups. Task performance was associated with activation and deactivation in ICNs. Greater differences in recruitment of canonical networks relative to healthy controls were observed for patients with left TLE. Significant correlations with engagement of ICNs and anatomical ROIs were observed for naming and fluency tasks. Significantly different LI in the ATL compared to ICNs were seen with predominantly greater LI in the ATL compared to ICN ROIs.

Conclusions: Delineation of idiosyncratic recruitment of large-scale networks as well as anatomical areas were associated with atypical organisation of language networks. Disease features – age of disease onset, duration of disease, seizure frequency and number of antiepileptic drugs - may be associated with patterns of reorganisation. Presurgical assessments by a panel of paradigms may benefit from assessing ICN recruitment insofar ICNs of both naming and fluency tasks may play a role in prediction of language decline following ATLR but are unlikely to provide greater positive predictive value of language decline than are LI obtained in anatomically defined ROIs.

A significant proportion of individuals suffer cognitive difficulties after resection of a speech-dominant temporal lobe. While language fMRI can be used to determine expressive language dominance and the likelihood of language dysfunction after anterior temporal lobe resection (Duncan, 2010), prediction of post-surgical complications is compounded by the possibility of atypical language organisation (Loring et al., 1990). TLE has been associated with atypical language network patterns (Trimmel et al., 2018) and impaired word retrieval in the context of naming and fluency function (Bell et al., 2003; Hamberger, 2015).

A prerequisite to more accurate prediction is identification of fMRI tasks that consistently activate crucial networks as well as understanding the correlates of atypical patterns of activation and lateralisation. Large scale language networks have been implicated in speech production (Geranmayeh et al., 2014) and various elements (syntactic structure, prosody, combinatorial semantics, lexical-semantics) engage large frontal-temporal-parietal networks, that include the ATL (Hickok & Poeppel, 2007; Poeppel & Hickok, 2004).

In this chapter I investigate ICN recruitment and lateralisation in TLE patients and healthy controls with specific reference to networks that may impact clinical language performance in the context of ATL resection.

The studies in healthy subjects (Chapter 7) yielded specific patterns that may be used to better characterise language function in those with epilepsy. This study will compare typical recruitment patterns of 1) resting state and task derived ICNs; and 2) anatomical regions of interest, in groups of healthy controls, LTLE and RTLE patients.

The aim of this study was to (1) identify and characterise abnormal network recruitment in LTLE and RTLE groups relative to healthy controls, and (2) establish the association and predictive value of large-scale networks in clinical language performance in patients with refractory TLE. I hypothesised that:

1. Significantly better language performance will be seen for controls compared to patient groups, particularly those with LTLE.
2. Individual ICN ROIs will be significantly correlated with neuropsychological performance outside the scanner.
3. There will be significant connectivity between the ATL, anatomical ROIs and ICNs.
4. There will be significant differences in lateralisation power in the ATL, anatomical ROIs and ICNs.

Methods

Subjects

Forty TLE patients (38% females; age range 19–58 years) participated in the study, comprising 24 patients with left TLE (LTLE) and 16 patients with right TLE (RTLE). Patients with a confirmed diagnosis of TLE were consecutively recruited from those undergoing presurgical assessment at the National Hospital for Neurology and Neurosurgery (NHNN). Results of investigations and associated clinical details for patient groups were described in Chapter 5. Thirty healthy subjects (63.3% females, age range 22–59) were also studied. Exclusion criteria for all subjects were non-fluency in written and spoken English, pregnancy, any contraindication to MRI, and inability to give informed consent. TLE patients with a secondarily generalised tonic-clonic seizure (SGS) within 24h prior to the study were excluded. There was no significant difference in the distribution of age between the three groups (one-way ANOVA, $p > 0.05$; Table 1). Demographic and clinical data are summarised in Table 8.1.

Table 8. 1.

Demographic and Clinical Data for All Subjects

	Gender female/male	Handedness right /left	Age (years)	Naming score	IQ	Phonetic fluency score	Semantic fluency score
LTLE	8/16	20/4	38±	*14.1±	*94.1±	*13.1±	*17.8±
(n=24)			10.9	5.4	10.7	3.9	5.3
RTLE	7/8	13/3	40.1±	18.8±	102.6±	14.1±	*17.2±
(n=16)			9.9	5.6	10.1	5.7	6.2
CTR	19/11	30/0	39.1±	18.1±	106.8±	15.1±	23.2±
(n=30)			11.3	5.8	11	5.1	5.3

Note: CTR = control subjects; IQ = estimated intellectual level; IQR = interquartile range; LTLE = left temporal lobe epilepsy; RTLE = right temporal lobe epilepsy; SD = standard deviation; ** = LTLE<RTLE two sample t-test, p = 0.014; CTR = (29); *LTLE (n=23); *RTLE (n=15). Age, language scores and estimated intellectual level (IQ) are shown as mean ± SD.

Neuropsychological tests

All controls in this study completed the National Adult reading test, which derives a full-scale IQ from reading vocabulary. Patients' IQ were derived from full scale Wechsler test scores (Tulsky et al., 1997; Tulsky et al., 2003). All subjects completed the McKenna Graded Naming Test as well as a phonemic and semantic fluency test outside the scanner. These tests are described in the common methodology section (Chapter 5). Neuropsychological measures were obtained for 29/30 controls and all patients prior to functional imaging.

MR data acquisition

The MRI data acquisition and pre-processing was performed according to the common protocol for language studies as described in Chapter 5 – Common Methodology.

Language paradigms

Subjects in this experiment performed five language paradigms described in the common methods section for language studies in Chapter 5. Auditory naming could not be acquired in one healthy control due to technical difficulties with equipment and in two patients who suffered hearing impairment. Constraints on patients' time did not allow FF and SF to be obtained in one LTLE and one RTLE patient.

Statistical analysis

Details of statistical analyses described below were performed according to distribution. Adjustment for multiple comparisons employed Bonferroni correction and permutation testing and support for the alternative null hypotheses was investigated with Bayes factors, as described in Chapter 5.

fMRI data analysis

The creation of contrasts was described in the common methods section for language studies in Chapter 5.

ICN_atlas metrics

Estimated anatomical regions from Laird and colleagues (Laird et al., 2011) were described in Chapter 5. In this study twelve ICNs were selected based on the results of connectivity analysis described in Chapter 7 together with three anatomical regions. Greater anatomical reference for ICNs was obtained with the human Brainnetome Atlas (Fan et al, 2016), with 210 cortical and 36 subcortical subregions, as reported in the common methods section - Chapter 5.

Neuropsychological performances

Group differences in neuropsychological performance were investigated using one-way ANOVA and post hoc independent samples T tests, Bonferroni adjusted for multiple comparisons.

ICN recruitment: Correlation with performance

Kendall correlation adjusted for multiple comparisons with permutation testing as described in Chapter 5 was used to assess association between recruitment of individual ICN ROIs with neuropsychological performance outside the scanner. Significant observations were examined for intergroup differences using Fisher's *r*-to-*z* transformation after transforming Kendall tau to Pearson's R (Walker et al., 2003), Bonferroni adjusted for multiple comparisons.

Lateralisation

Calculation of LIs of statistic parametric maps (SPM[T] maps) to assess hemispheric dominance for language (Adcock et al., 2003) was described in Chapter 5. A bootstrapping approach (Wilke & Schmithorst, 2006) (Chapter 5) was employed in individual subjects on sixteen SPM[T] maps implementing anatomical ICN masks comprising five rest ICNs and seven task ICNs (see Table 8.2) that were seen to show language connectivity in healthy controls (Chapter 7) as well as anatomical masks described in the common methodology section.

Comparison of lateralisation in controls and patients

Differences in lateralisation between groups were investigated with Kruskal-Wallis ANOVA and post-hoc pairwise comparisons (Mann Whitney independent samples) with Bonferroni adjustment for multiple comparisons.

Lateralisation: Correlations with language performance.

Kendall correlation adjusted for multiple comparisons with permutation was used to assess association between subjects' LI within individual ICN and anatomical ROIs with language performance outside the scanner.

Lateralisation: Correlation between LI in the ATL, anatomical ROIs and ICNs

Correlational analysis adjusted for multiple comparisons with permutation testing was performed to identify association between LI in the ATL with lateralisation in anatomical ROIs and ICNs. Significant observations were further investigated for group differences using Fisher's *r*-to-*z* transformation after transforming Kendall tau to Pearson's R, Bonferroni adjusted for multiple comparisons.

Differences in lateralisation power in the ATL and ICNs

Lateralisation power in the ATL, and ICNs were investigated by changing all LI indices to positive values. Differences were investigated using Friedman ANOVA, Bonferroni corrected for multiple comparisons.

Results

Neuropsychological performance

Group differences. There was a significant difference between groups with respect to IQ (one-way ANOVA = 9.85, $p < 0.001$), naming scores ($F = 4.7$; $p < 0.05$) and semantic fluency ($F=9.07$; $p<0.001$). Groups did not differ significantly with respect to phonetic fluency. Post-hoc pairwise comparisons (independent samples two-tailed t-test; Bonferroni adjusted for multiple comparisons) showed no significant intergroup difference for naming. IQ was significantly higher in controls than LTLE patients ($T = 4.39$; $p<0.009$). Both RTLE ($T = -3.42$, $p = 0.009$) and LTLE ($T= -3.74$; $p=0.009$) performed significantly worse than controls in relation to semantic fluency.

fMRI results. Amodal ICN recruitment: Correlation with language performance. Kendal correlation showed that higher phonetic fluency scores were significantly correlated with greater VF activations in task ICN 16 ($r=0.21$, $p=0.032$) and task ICN 4 ($r=0.20$, $p=0.049$). Significant intergroup differences were not seen.

Lateralisation indices

Comparison of lateralisation in controls and patients. A higher proportion of subjects were left rather than right lateralised across amodal tasks (Tables 8.2 and 8.3). The proportion of highly lateralised (LI >+0.5/<−0.5) subjects typically followed a normal distribution seen for conventional lateralisation indices (>+0.2/<-0.2). A greater proportion of right lateralisation was seen for progressive activations and a greater proportion of left lateralisation for deactivations in all groups.

Intergroup comparison showed significantly different within group proportions of left compared to atypical lateralisation. Differences with controls were seen predominantly for LTLE. A greater number of differences were seen in anatomical rather than ICN ROIs: Kruskal Wallis ANOVA showed significant group differences for amodal FF in the ATL (Ht= 8.41; p=0.015) and task ICN 1 (Ht= 6.33; p=0.042) and for amodal PN in task ICN 5 (Ht=6.55 ; p=0.038). Post-hoc pairwise comparison (Mann-Whitney independent samples test, Bonferroni adjusted for multiple comparisons) showed a significantly greater proportion of LTLE left lateralised for amodal FF (p=0.048) in the ATL, compared to controls who were atypically lateralised.

Table 8. 2.

Percentage Lateralised Controls and Patients in ICNs

		Controls					LTLE					RTLE				
	Contrast	**Left**	**High**	**Right**	**High**	**Atypical**	**Left**	**High**	**Right**	**High**	**Atypical**	**Left**	**High**	**Right**	**High**	**Atypical**
Rest ICN 4	AN-R	65.5	37.9	10.3	3.4	34.5	68.2	45.5	4.5	0.0	31.8	56.3	31.3	12.5	0.0	43.8
	PN - ScP&Cfc	36.7	16.7	30.0	13.3	63.3	54.2	25.0	16.7	4.2	45.8	31.3	6.3	12.5	0.0	68.8
	FF-RR	56.7	30.0	10.0	6.7	43.3	62.5	20.8	8.3	0.0	37.5	40.0	6.7	33.3	0.0	60.0
	SF-RR	43.3	13.3	16.7	0.0	56.7	56.5	21.7	4.3	0.0	43.5	42.9	7.1	21.4	0.0	57.1
	VF	56.7	20.0	23.3	6.7	43.3	66.7	33.3	12.5	0.0	33.3	56.3	31.3	12.5	12.5	43.8
	VF Deact	13.3	0.0	23.3	3.3	86.7	12.5	0.0	41.7	0.0	87.5	43.8	6.3	37.5	6.3	56.3
Rest ICN 7	AN-R	31.0	13.8	34.5	31.0	69.0	50.0	27.3	27.3	18.2	50.0	37.5	18.8	12.5	6.3	62.5
	PN - ScP&Cfc	36.7	16.7	30.0	13.3	63.3	37.5	12.5	41.7	25.0	62.5	37.5	37.5	50.0	31.3	62.5
	FF-RR	50.0	33.3	26.7	13.3	50.0	58.3	54.2	20.8	12.5	41.7	53.3	40.0	33.3	6.7	46.7
	SF-RR	53.3	20.0	33.3	26.7	46.7	34.8	30.4	56.5	34.8	65.2	35.7	28.6	57.1	35.7	64.3
	VF	70.0	43.3	13.3	0.0	30.0	79.2	54.2	8.3	4.2	20.8	81.3	62.5	18.8	12.5	18.8
	VF Deact	23.3	10.0	56.7	20.0	76.7	37.5	8.3	45.8	29.2	62.5	50.0	18.8	31.3	6.3	50.0
Rest ICN 8	AN-R	31.0	3.4	24.1	0.0	69.0	31.8	4.5	13.6	0.0	68.2	31.3	0.0	25.0	0.0	68.8
	PN - ScP&Cfc	36.7	16.7	30.0	13.3	63.3	20.8	0.0	29.2	8.3	79.2	37.5	12.5	18.8	0.0	62.5
	FF-RR	40.0	6.7	23.3	3.3	60.0	25.0	8.3	16.7	8.3	75.0	13.3	6.7	33.3	6.7	86.7
	SF-RR	33.3	6.7	30.0	6.7	66.7	30.4	0.0	34.8	4.3	69.6	42.9	7.1	28.6	14.3	57.1
	VF	20.0	3.3	20.0	3.3	80.0	33.3	8.3	33.3	4.2	66.7	31.3	6.3	37.5	6.3	68.8
	VF Deact	13.3	0.0	30.0	3.3	86.7	20.8	8.3	37.5	0.0	79.2	12.5	0.0	43.8	0.0	87.5
Rest ICN 9&10	AN-R	82.8	55.2	10.3	10.3	17.2	77.3	59.1	9.1	9.1	22.7	87.5	68.8	6.3	0.0	12.5
	PN - ScP&Cfc	36.7	16.7	30.0	13.3	63.3	70.8	45.8	12.5	0.0	29.2	68.8	56.3	12.5	0.0	31.3
	FF-RR	73.3	53.3	13.3	6.7	26.7	62.5	33.3	29.2	0.0	37.5	60.0	40.0	40.0	13.3	40.0
	SF-RR	66.7	40.0	16.7	6.7	33.3	65.2	39.1	21.7	17.4	34.8	71.4	50.0	21.4	14.3	28.6
	VF	90.0	63.3	6.7	3.3	10.0	83.3	70.8	12.5	8.3	16.7	87.5	62.5	6.3	6.3	12.5
	VF Deact	13.3	0.0	53.3	30.0	86.7	16.7	4.2	54.2	25.0	83.3	25.0	0.0	56.3	31.3	75.0
Task ICN 1	AN-R	37.9	13.8	27.6	17.2	62.1	45.5	13.6	18.2	9.1	54.5	43.8	6.3	25.0	12.5	56.3
	PN - ScP&Cfc	36.7	16.7	30.0	13.3	63.3	41.7	20.8	29.2	4.2	58.3	43.8	25.0	25.0	12.5	56.3
	FF-RR	26.7	13.3	40.0	16.7	73.3	54.2	25.0	12.5	8.3	45.8	26.7	13.3	33.3	20.0	73.3
	SF-RR	36.7	13.3	40.0	20.0	63.3	34.8	13.0	52.2	34.8	65.2	28.6	0.0	64.3	35.7	71.4
	VF	56.7	20.0	23.3	6.7	43.3	33.3	25.0	37.5	8.3	66.7	56.3	43.8	6.3	6.3	43.8
	VF Deact	10.0	3.3	66.7	26.7	90.0	16.7	8.3	50.0	12.5	83.3	12.5	0.0	43.8	12.5	87.5
Task ICN 4	AN-R	48.3	17.2	13.8	6.9	51.7	59.1	40.9	13.6	4.5	40.9	56.3	37.5	12.5	6.3	43.8
	PN - ScP&Cfc	36.7	16.7	30.0	13.3	63.3	58.3	25.0	20.8	8.3	41.7	68.8	25.0	25.0	0.0	31.3
	FF-RR	43.3	26.7	20.0	6.7	56.7	50.0	20.8	12.5	8.3	50.0	40.0	33.3	33.3	26.7	60.0
	SF-RR	60.0	30.0	20.0	3.3	40.0	47.8	21.7	34.8	17.4	52.2	42.9	21.4	35.7	7.1	57.1
	VF	66.7	36.7	10.0	0.0	33.3	75.0	50.0	16.7	8.3	25.0	68.8	56.3	12.5	6.3	31.3
	VF Deact	10.0	3.3	63.3	33.3	90.0	12.5	8.3	66.7	41.7	87.5	6.3	6.3	87.5	56.3	93.8
Task ICN 5	AN-R	17.2	3.4	58.6	20.7	82.8	9.1	0.0	68.2	31.8	90.9	18.8	0.0	68.8	37.5	81.3
	PN - ScP&Cfc	36.7	16.7	30.0	13.3	63.3	16.7	0.0	62.5	20.8	83.3	6.3	0.0	75.0	37.5	93.8
	FF-RR	23.3	0.0	43.3	13.3	76.7	12.5	4.2	41.7	16.7	87.5	13.3	0.0	60.0	26.7	86.7
	SF-RR	26.7	0.0	36.7	6.7	73.3	8.7	0.0	52.2	8.7	91.3	14.3	0.0	57.1	21.4	85.7
	VF	13.3	3.3	76.7	40.0	86.7	12.5	4.2	54.2	33.3	87.5	6.3	0.0	75.0	31.3	93.8
	VF Deact	20.0	3.3	50.0	16.7	80.0	25.0	4.2	41.7	12.5	75.0	6.3	0.0	25.0	12.5	93.8
Task ICN 12	AN-R	31.0	6.9	24.1	0.0	69.0	22.7	0.0	4.5	0.0	77.3	31.3	6.3	25.0	0.0	68.8
	PN - ScP&Cfc	36.7	16.7	30.0	13.3	63.3	58.3	12.5	12.5	0.0	41.7	43.8	0.0	18.8	0.0	56.3
	FF-RR	36.7	10.0	20.0	0.0	63.3	50.0	12.5	8.3	0.0	50.0	26.7	6.7	26.7	6.7	73.3
	SF-RR	40.0	3.3	30.0	0.0	60.0	26.1	0.0	13.0	0.0	73.9	28.6	0.0	35.7	14.3	71.4
	VF	50.0	20.0	23.3	0.0	50.0	41.7	8.3	33.3	0.0	58.3	62.5	25.0	25.0	6.3	37.5
	VF Deact	3.3	3.3	46.7	0.0	96.7	29.2	8.3	50.0	12.5	70.8	12.5	12.5	37.5	25.0	87.5
Task ICN 13	AN-R	69.0	44.8	6.9	3.4	31.0	77.3	63.6	0.0	0.0	22.7	75.0	37.5	0.0	0.0	25.0
	PN - ScP&Cfc	36.7	16.7	30.0	13.3	63.3	66.7	37.5	8.3	0.0	33.3	56.3	37.5	18.8	12.5	43.8
	FF-RR	66.7	36.7	13.3	10.0	33.3	62.5	25.0	12.5	4.2	37.5	46.7	33.3	6.7	0.0	53.3
	SF-RR	66.7	36.7	10.0	0.0	33.3	43.5	26.1	17.4	8.7	56.5	78.6	21.4	7.1	0.0	21.4
	VF	83.3	66.7	6.7	3.3	16.7	70.8	58.3	8.3	4.2	29.2	68.8	56.3	6.3	6.3	31.3
	VF Deact	6.7	3.3	63.3	10.0	93.3	8.3	4.2	50.0	12.5	91.7	18.8	12.5	43.8	18.8	81.3
Task ICN 16	AN-R	31.0	20.7	58.6	24.1	69.0	40.9	18.2	36.4	13.6	59.1	25.0	18.8	50.0	25.0	75.0
	PN - ScP&Cfc	36.7	16.7	30.0	13.3	63.3	33.3	16.7	54.2	33.3	66.7	18.8	12.5	50.0	43.8	81.3
	FF-RR	50.0	30.0	36.7	23.3	50.0	58.3	45.8	29.2	20.8	41.7	53.3	33.3	20.0	20.0	46.7
	SF-RR	30.0	3.3	56.7	30.0	70.0	39.1	30.4	52.2	39.1	60.9	35.7	28.6	35.7	28.6	64.3
	VF	66.7	40.0	16.7	10.0	33.3	62.5	50.0	12.5	4.2	37.5	50.0	18.8	37.5	18.8	50.0
	VF Deact	33.3	20.0	43.3	16.7	66.7	29.2	4.2	45.8	20.8	70.8	37.5	25.0	31.3	6.3	62.5
Task ICN 17	AN-R	31.0	10.3	51.7	27.6	69.0	45.5	40.9	31.8	13.6	54.5	43.8	37.5	31.3	12.5	56.3
	PN - ScP&Cfc	36.7	16.7	30.0	13.3	63.3	45.8	25.0	29.2	16.7	54.2	68.8	43.8	12.5	0.0	31.3
	FF-RR	56.7	30.0	33.3	23.3	43.3	58.3	41.7	41.7	16.7	41.7	33.3	20.0	53.3	33.3	66.7
	SF-RR	43.3	26.7	30.0	16.7	56.7	39.1	8.7	43.5	30.4	60.9	42.9	21.4	42.9	14.3	57.1
	VF	86.7	60.0	3.3	0.0	13.3	79.2	66.7	16.7	8.3	20.8	87.5	68.8	6.3	6.3	12.5
	VF Deact	20.0	3.3	80.0	53.3	80.0	29.2	16.7	54.2	37.5	70.8	25.0	6.3	75.0	62.5	75.0

Table 8. 3.

Percentage Lateralised Controls and Patients in Anatomical ROIs

		Controls					LTLE					RTLE				
	Contrast	Left	High Left	Right	High Right	Atypical	Left	High Left	Right	High Right	Atypical	Left	High Left	Right	High Right	Atypical
ATL	AN-R	34.5	13.8	27.6	17.2	65.5	31.8	13.6	40.9	27.3	68.2	37.5	18.8	43.8	31.3	62.5
	PN - ScP&Cfc	36.7	16.7	30.0	13.3	63.3	25.0	16.7	50.0	16.7	75.0	31.3	12.5	50.0	12.5	68.8
	FF-RR	13.3	10.0	50.0	23.3	86.7	58.3	29.2	20.8	8.3	41.7	40.0	13.3	53.3	26.7	60.0
	SF-RR	26.7	6.7	46.7	20.0	73.3	30.4	13.0	60.9	34.8	69.6	28.6	7.1	71.4	57.1	71.4
	VF	53.3	30.0	10.0	3.3	46.7	50.0	33.3	16.7	4.2	50.0	68.8	31.3	0.0	0.0	31.3
	VF Deact	6.7	0.0	70.0	36.7	93.3	16.7	4.2	54.2	20.8	83.3	18.8	0.0	68.8	25.0	81.3
IFG&MFG	AN-R	58.6	31.0	17.2	6.9	41.4	31.8	59.1	40.9	4.5	68.2	56.3	43.8	12.5	12.5	43.8
	PN - ScP&Cfc	36.7	16.7	30.0	13.3	63.3	25	29.2	50	12.5	75	68.8	25.0	25.0	12.5	31.3
	FF-RR	66.7	33.3	20.0	13.3	33.3	54.2	37.5	20.8	25	45.8	46.7	33.3	20.0	13.3	53.3
	SF-RR	56.7	36.7	20.0	3.3	43.3	26.1	34.8	60.9	13	73.9	50.0	28.6	28.6	28.6	50.0
	VF	80.0	60.0	6.7	6.7	20.0	50	62.5	16.7	12.5	50	75.0	50.0	12.5	6.3	25.0
	VF Deact	20.0	0.0	56.7	30.0	80.0	16.7	8.3	54.2	37.5	83.3	0.0	0.0	68.8	37.5	100.0
PTL	AN-R	48.3	31.0	27.6	6.9	51.7	68.2	40.9	13.6	9.1	31.8	62.5	31.3	43.8	18.8	37.5
	PN - ScP&Cfc	36.7	16.7	30.0	13.3	63.3	54.2	12.5	16.7	4.2	45.8	31.3	31.3	12.5	6.3	68.8
	FF-RR	73.3	50.0	13.3	6.7	26.7	75	50	8.3	8.3	25	40.0	33.3	33.3	20.0	60.0
	SF-RR	33.3	13.3	36.7	13.3	66.7	60.9	26.1	30.4	21.7	39.1	28.6	71.4	14.3	21.4	71.4
	VF	66.7	20.0	20.0	3.3	33.3	41.7	16.7	25	4.2	58.3	50.0	37.5	25.0	6.3	50.0
	VF Deact	33.3	16.7	36.7	13.3	66.7	16.7	4.2	45.8	12.5	83.3	50.0	43.8	25.0	0.0	50.0

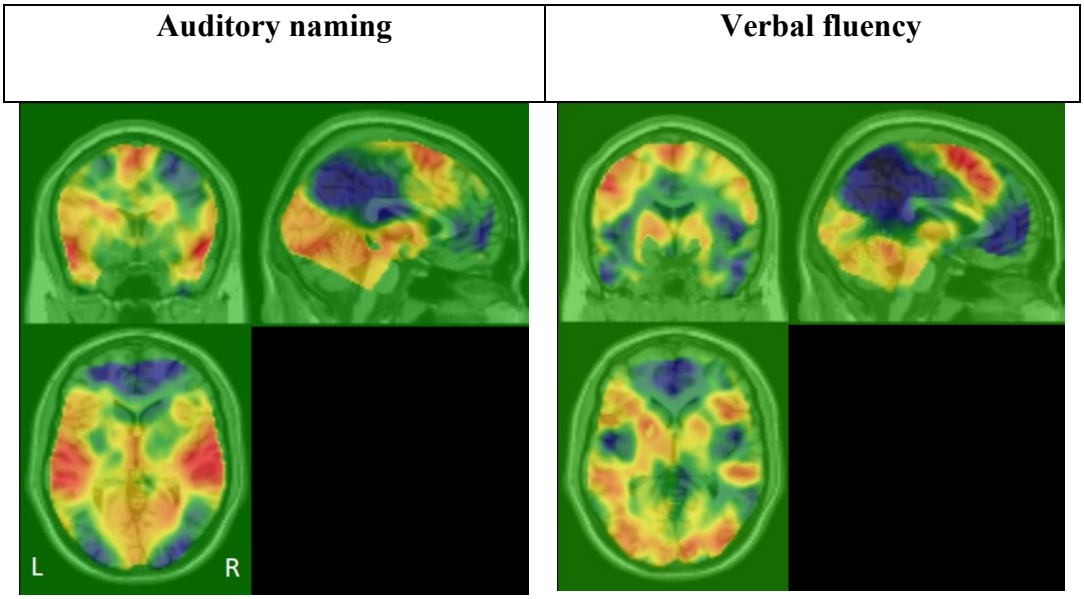
Amodal lateralisation: Correlation with language performance. There was no significant correlation between lateralisation and language performance.

Correlation of amodal language lateralisation between the ATL, anatomical ROIs and ICNs. Significant correlation of lateralisation, adjusted for multiple comparison with permutation testing, was seen for AN (r=0.33, p=0.002) and for PN (r=0.27, p=0.018) between the ATL and IFG&MFG. AN (r=0.25, p=0.034), FF (r=0.29, p=0.008) and SF (r=0.33, p=0.002) were significantly correlated between the ATL and PTL. No significant group differences were seen.

Task ICN 1 demonstrated the highest degree of connectivity with the ATL across all paradigms. SF showed more significant correlations between the ATL and ICNs compared to other paradigms. Deactivating VF show the least number of ICNs connected with the ATL. Task ICN 1 and 16 showed connectivity with the ATL across all paradigms. Task ICN 4 showed connectivity across activating paradigms. Significant intergroup differences were not seen for ATL-ICN connectivity. The different structure-function relationships for a fluency and naming paradigm observed in healthy controls participating in experimental studies in this thesis are demonstrated in Figure 8.1.

Figure 8.1.

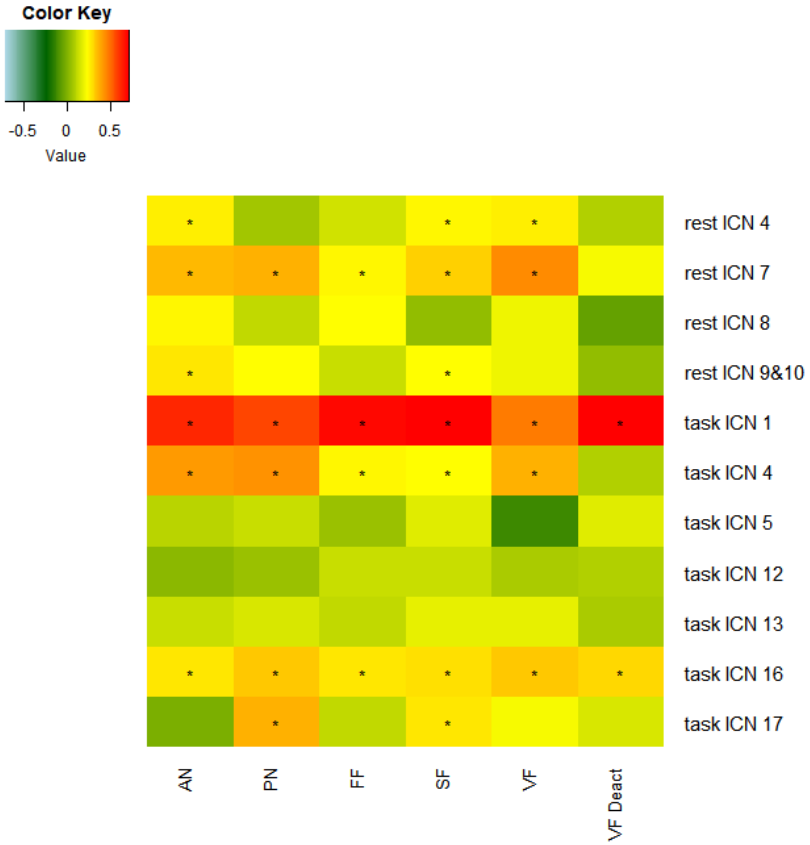
Verbal Fluency and Auditory Naming fMRI Activations



Note. fMRI findings in the healthy control subjects performing tasks of verbal fluency (*right*) and auditory naming (*left*) showing activations predominantly in the frontal lobe and temporal lobes, respectively: Statistical parametric maps overlaid on single subject T1 volumes shows intensities of activation (>red) and deactivation (>blue) shown in coronal, sagittal and axial planes in MNI standard space according to neurological convention (patient right is onscreen right). Anatomical-functional relationships shows specificity in relation to function using overt auditory naming and covert verbal fluency. The results confirms previous report (Gonzálvez et al., 2016) that have shown bilateral temporal activations for auditory naming and predominantly activation of the left inferior frontal gyrus for verbal fluency. Naming activated temporal lobe structures, which are resected during ATLR, more frequently than did verbal fluency rendering these paradigms more predictive of postoperative language decline than verbal fluency fMRI.

Figure 8. 2.

Correlations between LI in the ATL and ICNs



Note. Significant correlation between the ATL and ICNs as a function of the colour (light blue, dark green = negative correlation; light green, yellow, orange, red = positive correlation; starred squares, $p < 0.05$).

Language paradigms: Lateralisation power in the ATL and ICNs

There were no significant differences between LI achieved by paradigms in the ATL. Friedman ANOVA showed significantly different LI in the ATL compared to LI in ICNs for AN ($F=137.201$, $p<0.001$), PN ($F=69.53$, $p<0.001$), FF ($F=121.71$, $P<0.001$), SF ($F=104.35$, $p<0.001$), VF ($F=135.10$, $p<0.001$) and deactivating VF ($F=122.95$, $p<0.001$) across all subjects. Significant differences predominantly showed greater LI in the ATL compared to ICN ROIs. However, post hoc pairwise comparisons, Bonferroni corrected for multiple comparisons showed a significantly greater LI for AN in rest ICN 9&10 than LI in the ATL ($p< 0.001$).

Significantly greater LI was seen for VF in the rest ICN 9&10 ($p<0.001$), task ICN 13 ($p<0.001$) and task ICN 17 ($p<0.001$) compared to LI in the ATL, without significant greater LI for these ICNs compared to the ATL within groups.

Discussion

Summary of results

Using novel fluency and naming fMRI paradigms (Gonzálvez et al. 2016) as well as a widely employed phonetic fluency fMRI paradigm the results provide novel evidence for the association between ICNs and language performance in controls and patients suffering from refractory TLE. Significant connectivity was seen between the ATL and anatomical and ICN ROIs. Significantly different distribution of lateralisation and significant different connectivity patterns between groups suggest reorganisation in the context of disease characteristics.

There was not significant evidence for the selective influence of disease features. Consistent with observation of no significant intergroup differences for ATL-anatomical and ATL-ICN connectivity there was no evidence for significant group differences for lateralisation in the ATL compared to ICNs.

Language performance and association with subject characteristics

IQ was significantly higher in controls and higher in RTLE compared to LTLE patients and suggests a greater disruption of cognitive development (Farwell et al., 1985; Hermann et al., 2008; Rathouz et al., 2014) in LTLE associated with earlier age of onset seen in the LTLE group. Patient groups did not differ significantly in relation to semantic fluency but both patient groups performed significantly worse than controls which is consistent with language disruption in TLE patients. LTLE patients showed worse out-of-scanner naming performance compared to controls and to RTLE patients although the difference did not reach significance. These results suggest idiosyncratic impact of disease characteristic on language

performance. Disease affecting the temporal pole has been associated with semantic dementia, that include general semantic deficits manifest in the naming, categorisation and discrimination of objects (Compston, 2011; Mummery et al., 2000).

Higher IQ was significantly correlated with better naming, phonetic fluency and semantic fluency. It is consistent with findings which indicate that IQ predicts concurrent neuropsychological performance across the entire spectrum of intelligence (Diaz-Asper et al., 2004).

Differences in subject characteristics. Differences between patient groups and patient and controls that may have potential impact on results relate to assessment of IQ, the average IQ in the groups, and the gender composition.

Methodological differences in assessing IQ. While the IQ of patients were derived from full scale Wechsler test scores, the IQ of healthy controls was obtained using an estimate of full-scale IQ derived from the National Adult Reading test (un/corrected for educational attainment) which derives IQ from reading vocabulary. It has been suggested that reading tests may systematically under and overestimate IQ for the higher and lower IQ ranges respectively (Johnstone & Wilhelm, 1996). Furthermore, healthy individuals demonstrate a wide variation in performance across different cognitive domains (Taylor & Heaton, 2001) so that the use of one cognitive domain to determine the level of general intellectual functioning is debatable.

However, in studies exploring differences, between predicted IQ using reading tests and IQ obtained with full test batteries, two studies (Hart et al., 1986; Paolo et al., 1997) found either no effect or only a small difference. A further study (McCarthy et al., 2005) used the reading tests of the Revised and Third Editions of the Wide Range Achievement Test, that indicated a moderate difference; however there was no such difference found for the National Adult Reading test. Moreover a comparison of the raw data from the studies (Bright et al.,

2002; Crawford et al., 1988) where effect sizes could not be calculated, there appeared to be only negligible differences between reading-estimated and WAIS IQ.

Differences in controls and patients' IQ. Several standardisations of the GNT (McKenna, 1983; Murphy et al., 2020; Warrington, 1997) have reported a significant correlation between general intellectual ability and performance on the GNT. In our cohort healthy controls spanned the low average to superior range with the average IQ (106.8) upwardly skewed so that there was a significant difference with LTLE (see also Language performance and association with subject characteristics in Chapter 9). The potential mediating impact of IQ and disease features on pre- to post language changes after surgery are considered in Chapter 10.

Gender differences. For right sided lesions gender was well balanced (7 male/8 female) but not for left sided lesions (8 female/16 male) potentially impacting the findings: Gender differences in neuronal networks and brain connectivity in children (İçer et al., 2020) and adults (Gong et al., 2011), and task fMRI data have been observed (Saeidi et al., 2022). However, a recent meta-analysis of three decades of human MRI and post-mortem studies, show that connectome differences and gender prediction are largely based on brain size. While distortions in automated image processing, are greater for smaller structures and may, therefore, differentially affect the measurement of male versus female brain structures, the reported gender differences were not significant across diverse populations: It was concluded that task-based fMRI, has failed to find reproducible activation differences so that brain differences appear trivial (Eliot et al., 2021).

Main fMRI results and association with language performance

Studies have previously investigated the relevance of clinically applied language fMRI paradigms such as verbal fluency tasks to frontal lobe language areas (Bonelli et al., 2012; Szaflarski et al., 2008; Woermann et al., 2003) and temporal lobe locations (Thivard et

al., 2005). Recent studies employing novel naming paradigms (Gonzálvez et al., 2016; Trimmel et al., 2018) have demonstrated their potential utility to temporal lobe function. These observations were elaborated using naming and novel fluency paradigms in addition to a standard verbal fluency task for their relevance to ICN and ATL function and language performance. Connectivity was seen between the ATL and anatomical and ICN ROIs. Different patterns of connectivity and lateralisation achieved by paradigms between groups suggested reorganisation in the context of disease characteristics.

Amodal ICN recruitment: Correlation with language performance

Observation of an association between increased VF proficiency and greater activations in temporal and frontal ICNs (task ICN 16 and task ICN 4) are in line with the engagement of frontal regions (Bonelli et al., 2012) but also indicate a significant role of temporal regions in phonetic fluency which runs contrary to expectation that any individual brain networks is associated with a set of cognitive function. Rather it indicates that cognitive brain networks ultimately function in and depends on a multidimensional, that is, its situational and neural context (Bressler & McIntosh, 2007).

Lateralisation

Lateralisation across anatomical ROIs, and ICNs. A higher proportion of subjects were left rather than right lateralised across amodal tasks consistent with a left lateralised language network, as previously reported (Price, 2012). The proportion of highly lateralised subject typically followed a normal distribution seen for conventional lateralisation indices (>+2/<-2).

A significant difference in lateralisation seen for FF in the ATL where LTLE showed significantly greater left lateralisation compared to healthy controls, and a different representation of left compared to atypical lateralisation in our patient groups compared to controls suggests reorganisation, more so for LTLE than RTLE.

Increased atypical language organisation in patients compared to controls for VF and SF in the IFG&MFG and deactivating VF is concordant with previous fMRI studies, that reflect increased atypical language organisation in patients compared to controls: A previous study showed 94% of 100 right-handed healthy subjects to be left hemisphere dominant and 6% had bilateral representation. In comparison of 50 right-handed epilepsy patients with a probable focal onset, 78% showed left hemisphere dominance, 16% symmetric activation, and 6% showing right hemisphere dominance. In the group that proceeded to surgery (41/50), 93% had a temporal and 7% an extratemporal focus and 56% were left and 44% right lateralised for surgery (Springer et al., 1999).

Correlations with performance. There was no significant correlation between lateralisation and language performance. It is likely that lateralisation across more elaborate networks, that represent a combination of the individual ICN ROIs undergird performance.

Correlation of amodal language lateralisation between the ATL and ICN ROIs

Naming and semantic deficits have been observed after ATLR (Drane et al., 2009; Emerton et al., 2014) with the severity of decline correlated with the extent of lateral temporal neocortex resected (Hermann et al., 1999). Resection involving the left inferior temporal gyrus, fusiform gyrus, middle temporal gyrus and parahippocampal gyrus are associated with naming deficits (Wilson et al., 2015). These areas overlap anatomically with the task ICN 1 and 16 which have shown ATL connectivity across all paradigm contrasts and with task ICN 4 and rest ICN 7 which have shown ATL connectivity across all paradigms for all activating contrasts. It indicates a potentially crucial role for these ICNs in language function mediated by the ATL. Greater relevance of naming as opposed to fluency tasks for temporal areas (Gonzálvez et al., 2016; Trimmel et al., 2018) indicate that these ICNs may provide greater specificity in prediction.

Significant intergroup differences were not seen for ATL-ICN or ATL connectivity with anatomical ROIs. These findings are not consistent with reports of altered network dynamics specific to epilepsy syndromes: Reduction in functional connectivity has been seen in TLE patients within the language network (Vlooswijk et al., 2010; Waites et al., 2006), and reduced connectivity demonstrated in the left hemisphere (Pravata et al., 2011). Increased functional connectivity correlated with language performance has been reported in posterior temporal regions for both left and right medial TLE patients (Protzner & McAndrews, 2011).

Lateralisation power in the ATL and ICNs

Pre-surgical fMRI investigation contends with the fact that the ATL is functionally diverse. It has modality-specific sub regions (Skipper et al., 2011) and integrates semantic information from different modalities (Visser et al., 2010; Wong & Gallate, 2012). It is considered to be predominately bilateral and highly overlapping in function although it has been held to be left lateralised when the input is a written word or when word retrieval is required (Rice, Hoffman, et al., 2015; Rice, Ralph, et al., 2015) which is consistent with reports of a high proportion of TLE patients that have suffered naming decline after resection of the dominant temporal pole (Binder et al., 2011; Middlebrooks et al., 2017).

Functional imaging studies have indicated that the ATL is engaged by a variety of lexical and semantic tasks, including categorisation, naming, lexical decisions, and semantic knowledge decisions (Noppeney & Price, 2002; Peelen & Caramazza, 2012), that it is closely associated with semantic memory (Simmons et al., 2009). In our cohort a significant difference was not seen between paradigms in the ATL which suggests that it is not individually specialised for any of these naming or fluency functions. Significant differences within paradigms predominantly showed greater LI in the ATL compared to ICN ROIs which reiterate the crucial role of the ATL in language function relative to ICNs.

Our results demonstrated connectivity with the ATL and implicated a role for selected ICNs (see Chapter 7) for prediction of fluency and naming performance. It was seen for VF in task ICN 17 which typically show lateralisation within cerebellar networks that is generally crossed with respect to the other ROIs (Tailby et al., 2017), in task ICN 13 and rest ICN 9&10 - consistent with higher lateralisation indices in frontal than temporal lobe areas (Bonelli et al., 2012; Friedman et al., 1998). It was seen for AN in rest ICN 9&10 - particularly relevant in the context of its demonstrated ATL connectivity. It reiterates a role for frontal networks in prediction of naming decline following ATLR (Bonelli et al., 2012). It follows previous observations that inferior frontal lobe activations are implicated in the semantic naming network (Binder et al., 2009; Bookheimer, 2002; Middlebrooks et al., 2017) and for naming performance in TLE (Bonelli et al., 2012). Our results indicate that activations in ICNs are unlikely to provide greater accuracy or sensitivity to reduce the effects of TL resection on language, compared to LI obtain in anatomically defined ROIs.

Strengths and limitations

An atlasing method and naming paradigms recently shown to be more specific to temporal lobe activations as well as novel overt fluency paradigms were employed. Recruitment by non-linguistic cognitive processes were controlled for using active control conditions. ROIs associated with motor cortex activations caused by overt speech production were excluded from the analysis. Analyses were conducted in unthresholded maps in large ROIs capturing information that may not be accounted for in thresholded maps. Retrospective noise and movement artefact methods shown to significantly improve signal to noise ratio in fMRI language maps were employed (Tierney et al., 2016). Bivariate task specific correlational analyses based on individual statistical parametric maps were performed to retain specificity with out-of-scanner performance. Bonferroni adjustment and permutation testing as described in the common methods section were used to limit Type 1

and Type 2 errors in the context of multiple comparisons. Patient groups were small. To increase power, sample size was maximised by testing relevant hypotheses across patient groups and healthy controls. Support for the alternative null hypotheses was investigated with Bayes factors. There was not an out of scanner correlate for FF.

Performance indicators were based on single assessments not accounting for measurement variance. While there was a disparity in the gender makeup of the LTLE group, it is unlikely to be significant in task-based fMRI connectivity analyses.

Clinical implications

Seizure freedom has been reported in up to 80% of patients following resection of the anterior temporal lobe (de Tisi et al., 2011) although it is associated with a risk of postoperative naming and verbal fluency deficits. Language fMRI patterns, specifically VF LI have been shown to be sensitive but not specific predictors of language decline following temporal lobe resection (Bonelli et al., 2012). Significant ATL connectivity was shown for AN and PN for the IFG& MFG and for AN, FF and SF between the ATL and PTL. Significant ATL connectivity was seen with task ICN 1 and 16 for all paradigms and for task ICN 4 and rest ICN 7 for all activating contrasts. While the ATL predominantly showed higher LI than ICNs, it suggests that ICNs may provide additional information in the presurgical workup rather than take precedence relative to anatomical indices. Performance was not significantly correlated with lateralised activation but insofar these ROIs represent crucial nodes in language networks, higher fMRI activations in these regions ipsilateral to seizure onset and the focus of resection may be associated with a greater risk of naming and word finding difficulties following ATLR.

Cross lateralisation seen within and between language tasks in controls and patient groups suggests that comprehensive preoperative assessment towards prediction of naming and word finding deficits may benefit from a panel of tasks aimed at identifying recruitment

of temporal ROI and functionally connected networks. For patients that are multi-lingual the use of a panel of tasks are likely to benefit investigation of localisation insofar unique and overlapping sites for languages have previously been demonstrated (Lucas et al., 2004; Polczynska et al., 2016; Walker et al., 2004).

Conclusions

Language performance is associated with ICN recruitment. Language networks, across anatomical ROIs and ICNs are reorganised in TLE patient groups. ICNs of both naming and fluency tasks may play a role in prediction of language decline following ATLR but are unlikely to provide greater positive predictive value for language decline compared to LI obtained in anatomically defined ROIs. A relationship with disease features and identification with associated risk factors are investigated and reported in Chapter 9.

Chapter 9

Temporal Lobe Epilepsy. Correlation of disease features with fMRI patterns of Intrinsic Connectivity Network engagement

Abstract

Aim: Temporal lobe epilepsy is associated with atypical language network patterns and impaired word retrieval. The correlates of atypical patterns of activation and lateralisation are not entirely understood. The correlation of age of onset, duration of epilepsy, number of AEDs and seizure frequency with language performance and fMRI activation patterns were investigated.

Methods: An established lateralisation method and selected atlasing metrics were used to study anatomical ROIs and intrinsic connectivity networks. BOLD maps of five language paradigms in 30 righthanded healthy controls were compared with 24 LTLE and 16 RTLE patients. Simple correlations were used to assess associations between disease features and performance with fMRI activations across patients and in three data derived subgroups that represented homogenous fMRI patterns.

Results: Patient groups showed higher indices of depression with a significant difference between RTLE and controls. There was a significant association between a greater number of AED and poorer phonetic fluency across subjects. Seizure frequency and number of AEDs were significantly correlated with task induced deactivation in three ICNs: Across both patient groups a lower monthly seizure frequency was significantly correlated with greater AN deactivation in task ICN 13, and a higher number of AEDs was significantly correlated with reduced VF activation in task ICN 1 and rest ICN10. Significant task specific correlations between neuropsychological performance and LI in ICN ROIs were not seen. An earlier age of onset was significantly correlated with greater atypically lateralised deactivating VF in task ICN 5. Significant differences in task activations between subgroups that represented homogenous fMRI patterns was not associated with to age, handedness, IQ, clinical scores, or disease characteristics or with performance.

Conclusions: Delineation of the association of disease features with fMRI patterns and recruitment of language networks may identify risk and help to inform prediction of language outcome following temporal lobe resection. Specifically, the number of AEDs is associated with a cost to neuronal network function and level of language performance. It reiterates the need to account for effects of AED when fMRI patterns are clinically interpreted at the single subject level.

Language fMRI has been used to help predict decline in language function following epilepsy surgery (Bonelli et al., 2012; Duncan, 2009). Evaluation is made more difficult by the possibility of atypical language organisation (Loring et al., 1990). The spectrum of influences on language organisation can be divided into fixed factors, such as underlying pathology and variable factors such as mood and side effects of AEDs (Baxendale & Thompson, 2010) and seizures (Meador, 2002; Thompson & Duncan, 2005). Age of onset of the seizure disorder is also relevant, affecting the severity of neurocognitive impairments (Baker et al., 2011).

In view of the observed different patterns of connectivity in those with epilepsy and healthy controls, the study will compare recruitment patterns of 1) resting state and task ICNs; and 2) anatomical regions of interest, in groups of healthy controls, LTLE and RTLE patients.

The aim was to characterise association of disease characteristic with network recruitment in LTLE and RTLE groups relative to healthy controls with a view to identify risk factors for language decline after ATLR. I hypothesised that:

1. Greater seizure frequency, an earlier age of onset, longer disease duration and a higher number of AEDs will be associated with a greater decrement in performance.
2. Disease features will be associated with fMRI patterns more for LTLE than RTLE.
3. Temporal regions and ICNs will show greater correlation with disease features and atypical organisation than frontal ROIs.
4. Greater reorganisation associated with disease features will be seen in the temporal ROIs than frontal ICNs or the DMN.

Methods

Subjects

Clinical data and results of electro-clinical and imaging investigations were described in Chapter 5 and are summarised in Table 9.1.

Table 9. 1.

Demographic and Clinical Data for Patients and Controls

	Gender female/male	Handedness right /left	Age (years)	Age onset (years)	Disease duration (years	CPS monthly	SGS monthly	Number AED	Naming score	IQ	Phonetic fluency score	Semantic fluency score
LTLE	8/16	20/4	38±	**15.7±	22.5 (22.5)	6.5 (8.5)	0 (0)	2 (2)	14.1±	94.1±	*13.1±	*17.8±
(n=24)			10.9	8.8					5.4	10.7	3.9	5.3
RTLE	7/8	13/3	40.1±	24.4±	13.5 (9.5)	4.5 (6.75)	0 (0)	2 (1)	18.8±	102.6±	14.1±	*17.2±
(n=16)			9.9	12.7					5.6	10.1	5.7	6.2
CTR	19/11	30/0	39.1±	n.a.	n.a.	n.a.	n.a.	n.a.	18.1±	106.8±	15.1±	23.2±
(n=30)			11.3						5.8	11	5.1	5.3

Note. Age, age of onset of epilepsy, language scores and estimated intellectual level (IQ) are shown as mean ± SD. Disease duration, seizure frequency (CPS, SGS) and number of AED are shown as median and IQR.

AED = antiepileptic drugs; CPS = complex partial seizures; CTR = control subjects; IQ = estimated intellectual level; IQR = interquartile range; LTLE = left temporal lobe epilepsy; RTLE = right temporal lobe epilepsy; SD = standard deviation; SGS = secondarily generalised seizures; ** = LTLE<RTLE two sample t-test, p = 0.014; *LTLE (n=23); *RTLE (n=15)

There were no significant differences in the ages of the three groups (Table 1). RTLE had a significantly later mean age of onset than left TLE (two samples two-tailed T-test; Table 1). The two patient groups did not differ for disease duration, seizure frequency or number of AEDs (Mann-Whitney independent sample test). Controls had a significantly higher average IQ than LTLE patients (see Chapter 8).

Neuropsychological tests

Neuropsychological measures were as reported in Chapters 5 and 8. All controls completed the National Adult reading test, while patients' IQ was obtained from their Wechsler Full scale scores. All subjects completed the McKenna Graded Naming Test as well as a phonemic and semantic fluency test outside the scanner. These tests are described in the common methodology (Chapter 5) and further discussed in Chapter 8. Neuropsychological measures were obtained prior to functional imaging.

MR data acquisition

The MRI data acquisition and pre-processing was performed as in Chapter 5.

Language paradigms

Subjects in this experiment performed five language paradigms as described in Chapters 5 and 8.

Statistical analysis

Statistical analyses and alpha adjustment for multiple comparisons were performed as described in Chapter 5 - Common methods. Analyses unique to this chapter are described below.

Group difference in disease features

Differences in disease features between patient groups were investigated with independent samples t tests, Bonferroni adjusted for multiple comparisons. Differences in anxiety and depression between groups were investigated with Kruskal-Wallis ANOVA and post-hoc pairwise comparisons (Mann Whitney independent samples) with Bonferroni adjustment for multiple comparisons.

Correlations between disease features and language performance

Kendall correlation was used to assess association between subjects' neuropsychological performance and disease features. Permutation tests as described in the common methods section were used to adjust significance for multiple comparisons.

fMRI data analysis

The creation of contrasts was described in the common methods section for language studies in Chapter 5.

ICN_atlas and metrics

ICN_atlas metrics were described in Chapter 5 and selection of ICNs in Chapter 7.

Amodal ICN recruitment: Correlation with clinical features

Kendall correlation between ICN recruitment and disease features for activations, deactivations and net engagement were tested and adjusted for significance by permutation testing. Significant observations were examined for intergroup differences using Fisher's *r*-to-*z* transformation after transforming Kendall tau to Pearson's R (Walker et al., 2003), Bonferroni adjusted for multiple comparisons.

Greater anatomical reference for ICNs was obtained with the human Brainnetome Atlas (Fan et al, 2016), with 210 cortical and 36 subcortical subregions, as reported in the common methods section - Chapter 5.

Lateralisation

Calculation of LI was described in Chapter 5.

Lateralisation: Correlation with disease features. Kendall correlation between lateralisation achieved by each language paradigm and age of onset, number of AEDs, disease duration and seizure frequency were tested and adjusted for significance by permutation testing as described in Chapter 5. Significant observations were examined for intergroup differences using Fisher's *r*-to-*z* transformation after transforming Kendall tau to Pearson's R (Walker et al., 2003), Bonferroni adjusted for multiple comparisons.

Association of disease features with fMRI patterns in ICNs

Principal component analysis (PCA) and hierarchical clustering as described in Chapter 5 was performed on fMRI data. It aimed to reduce the number of variables of the data set, while preserving sufficient information deemed to meaningfully summarize and visualize the multiple inter-correlated quantitative variables. The scree test (Cattell, 1966) that identifies the maximum curvature in the plot of eigenvalues, was used to indicate a sufficient number of principal components (PCs) to retain. PCA provided a new lower-dimensional space of variance across ICNs and language tasks.

Hierarchical clustering using Ward's criterion was performed on the selected principal components aimed at distinguishing homogeneous groups of subjects based on fMRI patterns of lateralisation rather than seizure focus. K-means clustering was performed to improve the initial partition obtained from hierarchical clustering.

Language performance, clinical features and involved brain regions were analysed with respect to the resulting clusters of subjects: To delineate differences between groups, Kruskal-Wallis ANOVA were performed for each variable. Significant results were investigated with Mann Whitney independent samples tests, Bonferroni corrected for multiple comparisons.

Kendall correlations were performed to identify the most characteristic clinical and subject features and the most typically involved brain regions in each group and adjusted for significance by permutation testing as described in Chapter 5. Clusters were further depicted by the patient most characteristic of each cluster - identified by their maximum distance in fMRI space from other subjects in the other groups.

Results

Neuropsychological performance

Intergroup differences were described in Chapter 8.

Disease features

Group Differences. Patient groups did not differ with respect to number of AEDs, disease duration, or seizure frequency. LTLE showed a lower age of onset than RTLE although the difference did not reach significance (Table 9.1). Anxiety scores were not significantly different between the three groups. There was a significant difference (Kruskal-Wallis ANOVA; Ht = 10.55, p=0.005) between groups for depression. Patient groups showed higher indices of depression compared to controls. RTLE showed significantly higher indices of depression than controls ($p<0.05$, Dunn Bonferroni corrected for multiple comparisons).

Correlation between disease features and language performance. Both patient groups performed significantly worse on semantic fluency than controls and LTLE patients showed significantly worse out-of-scanner naming performance compared to controls and to RTLE patients (Chapter 8). There was a significant association (r= -313, p=0.0047) between a greater number of AEDs and poorer phonetic fluency across subjects, without a significant intergroup difference.

fMRI results. Amodal ICN recruitment: Correlation with clinical features

Lower monthly seizure frequency was significantly correlated with greater AN deactivation in task ICN 13 (r=0.35 p=0.026). A higher number of AEDs was significantly correlated with reduced VF activation in task ICN 1 (r=0.35, p=0.027) and rest ICN 10 (r=0.32, p= 0.042) adjusted for multiple comparisons by permutation testing. There were no significant intergroup differences.

Lateralisation indices

As previously shown (Chapter 8) significant task specific correlations between neuropsychological performance and LI in ICN ROIs across groups were not seen.

Correlation with disease features. An earlier age of onset was significantly correlated (r=0.41, p=0.01) with greater atypically lateralised deactivating VF in task ICN 5. Bayes factors provided strong support for an association between atypically lateralised naming and longer duration in rest ICN 8 and higher number of AEDs in temporal ROIs (Table 9.2). Significant intergroup differences were not seen.

Table 9. 2

Correlation of Number of AED with Activation in ROIs

Disease feature	Paradigm	ROI	r	BF_{10}
AED	AN	rest ICN 8	-.318	19
AED	PN	Task ICN 12	-.306	18
AED	AN	PTL	-.375	*87
AED	AN	Task ICN 16	-.327	24

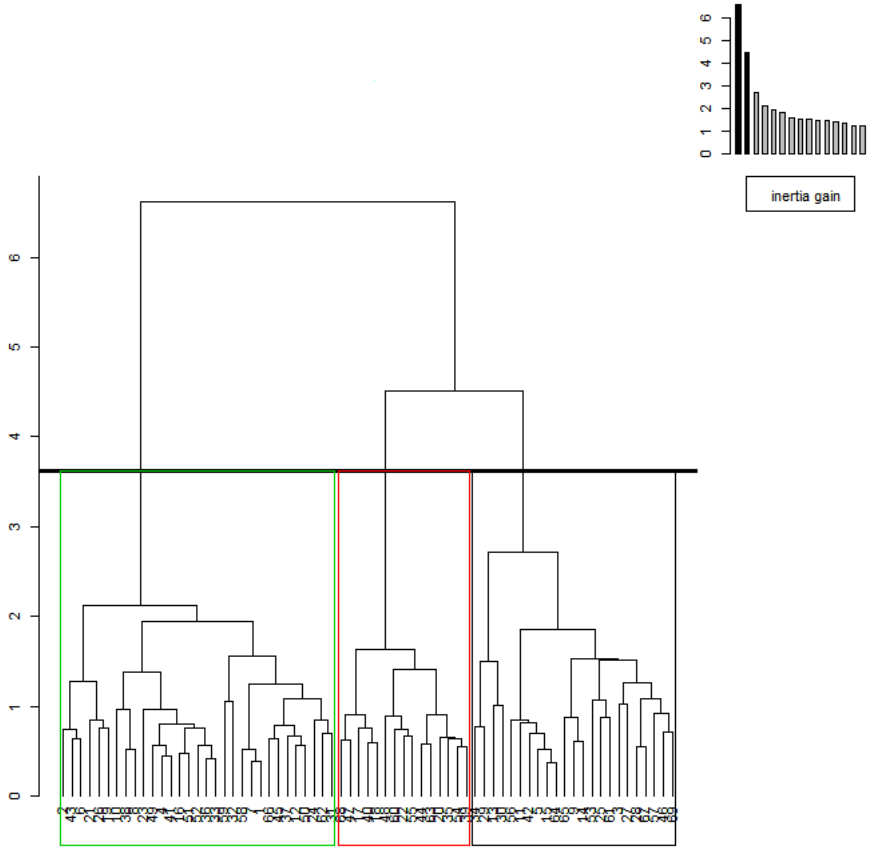
Note. Bayes factors showing strong and *very strong support for association between disease characteristics and lateralisation across all patients.

The association of disease features with fMRI patterns in the ATL and ICNs

The maximum curvature of the scree plot for PCA across LI for 69 subjects yielded three principal components accounting for 28% of total variance which was deemed insufficient. Ten principal components were selected, accounting for 59% of variance, across

LI indices for all subjects. Hierarchical classification resulted in three clusters of subjects with homogeneous fMRI activations (Figures 9.1 and 9.2).

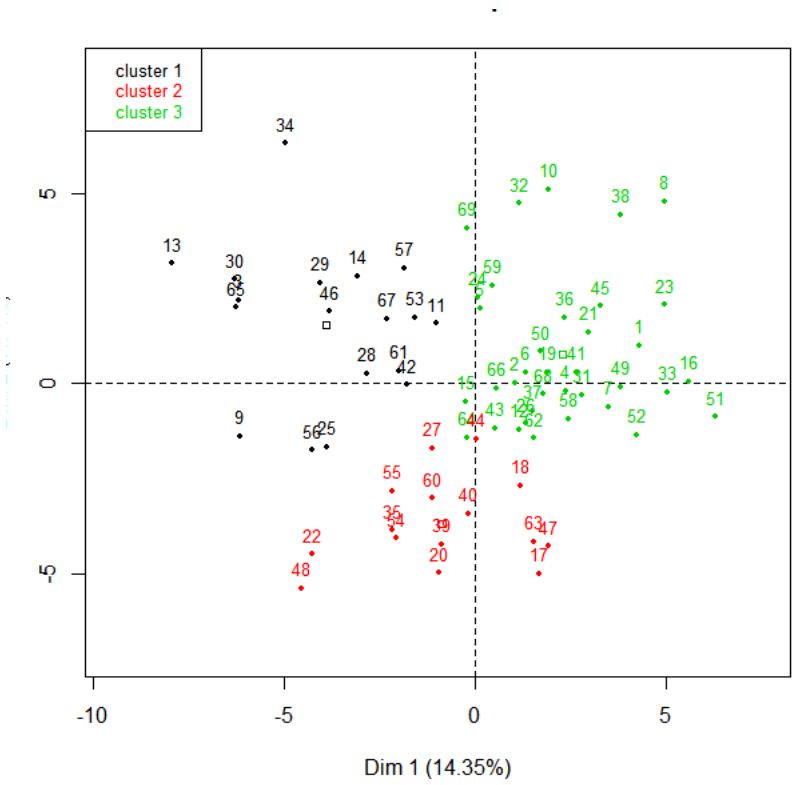
Figure 9. 1. *Hierarchical Clustering of Lateralisation Indices*



Note. The classification is based on the first 10 principal classification and shows three clusters of subjects with homogeneous fMRI activations

Figure 9. 2.

Distances Between Subjects in Clusters of Homogenous fMRI Patterns



Note. Three clusters of subjects are shown on the first two principal components. Cluster 1: 8 controls, 4 LTLE (1 lefthanded), and 4 RTLE (1 lefthanded) patients. Cluster 2: 11 controls, 6 LTLE (1 lefthanded), and 4 RTLE (1 lefthanded) patients. Cluster 3: 10 controls, 10 LTLE (2 lefthanded), and 5 RTLE (1 lefthanded) patients.

Subgroup characteristics and differences in fMRI patterns of lateralisation. The three patients most characteristic of each cluster in fMRI space, differed markedly with respect to handedness, seizure frequency, pathology, age of onset, duration as well as number and type of AED (shown in Appendix A). Kruskal-Wallis analysis of variance, however, showed no significant intergroup differences in relation to age, handedness, IQ, clinical scores, or disease characteristics. The drug profile of 20% of patients in subgroup *one* contained either Zonisamide, Topiramate and Carbamazepine, 50% in subgroup *two*, and 44% in subgroup *three*.

Subgroup *one* was predominantly atypically lateralised across the ATL and ICNs. Subgroup *two was* significantly right lateralised across all ROIs for deactivating VF. Subgroup *three* was predominantly left lateralised across the ATL and all ICNs. AN and deactivating VF showed the greatest number of significant intergroup differences. Subgroup *one* showed atypical FF lateralisation in rest ICN 9&10. For all other language tasks and ROIs, all three groups were left lateralised in the frontal ICNs. Kruskal-Wallis analysis of variance and Mann Whitney independent samples tests, Bonferroni adjusted for multiple comparisons showed a high number of significant intergroup differences (Table 9.3).

Table 9. 3.

Significant Differences between fMRI Subgroups

	ROI	Group (1)	Group (2)	Group (3)	Z	*P =
AN	rest ICN 4	(3)		(1)	4.007	P = 0.015
AN	rest ICN 7	(3)		(1)	3.826	P = 0.015
AN	rest ICN 7	(3)	(2)		4.193	P < 0.015
AN	rest ICN 9_10	(3)		(1)	3.928	P = 0.015
FF	task ICN 4	(3)		(1)	4.04	P = 0.015
FF	rest ICN 8	(3)		(1)	4.277	P < 0.015

PN	ATL	(3)		(1)	3.725	P = 0.031
PN	task ICN 4	(3)		(1)	3.86	P = 0.015
PN	rest ICN 9_10	(3)		(1)	3.601	P = 0.046
SF	ATL		(3)	(2)	3.601	P = 0.015
SF	task ICN 1		(3)	(2)	3.588	P = 0.046
SF	task ICN 17		(3)	(2)	3.947	P = 0.015
VF	ATL		(2)	(1)	3.757	P = 0.031
VF	task ICN 1		(2)	(1)	3.849	P = 0.015
VF	task ICN 13		(2)	(1)	4.23	P < 0.015
VF	task ICN 17	(3)		(1)	3.827	P = 0.015
VF	task ICN 4		(2)	(1)	4.782	P < 0.015
VF	task ICN 4	(3)		(1)	5.098	P < 0.015
VF	rest ICN 7		(2)	(1)	4.098	P < 0.015
VF	rest ICN 7	(3)		(1)	4.411	P < 0.015
VF	rest ICN 9_10		(2)	(1)	3.941	P = 0.015
VF	rest ICN 9_10	(3)		(1)	4.322	P < 0.015
Deactivating VF	task ICN 16	(3)	(2)		3.871	P = 0.015
Deactivating VF	rest ICN 4		(2)	(1)	3.809	P = 0.015
Deactivating VF	rest ICN 9_10		(2)	(1)	4.295	P < 0.015

Note. Differences between fMRI subgroups are Bonferroni adjusted for multiple comparisons.

No significant correlations were seen between lateralisation in subgroups and seizure frequency, age of onset, disease duration or a number of AEDs. There was no support for an association between LI and performance in subgroups.

Discussion

Summary of results

Using novel fluency and naming fMRI paradigms (Gonzálvez et al., 2016) as well as a widely employed phonetic fluency fMRI paradigm we provide novel evidence for the association between ICNs and disease features in patients with refractory TLE. We found significant correlation between disease features – greater seizure frequency and a higher number of AEDs - with intensities of ICN activation and deactivation. A significant correlation was also seen with lateralisation, specifically between earlier age of onset and greater atypical, lateralised deactivating VF in task ICN 5.

Language performance and association with disease characteristics

An association between disease features and language has been indicated by subjective reports of seizure frequency on cognitive function (Feldman et al., 2018) and by network abnormalities thought to undergird cognitive dysfunction (Holmes, 2015). In our cohort a relationship between disease and performance was indicated by significantly worse semantic fluency for patient groups and significantly lower IQ for LTLE (see Chapter 8) which could be attributed to a greater disruption of cognitive development in patients (Hermann et al., 2008; Rathouz et al., 2014), particularly an earlier age of onset in LTLE (see Chapter 8). There was a significant association between a greater number of AED and poorer phonetic fluency across patients, which is consistent with adverse effect of a higher drug load on cognition (Feldman et al., 2018; Witt et al., 2015) and reduced VF activations in task ICN 1 and rest ICN 10 in LTLE (see below). A higher number of AEDs was significantly correlated with reduced VF activation in task ICN 1 ($r=0.35$, $p = 0.027$).

Disease features and IQ. In our cohort the average IQ of healthy controls (106.8) was skewed into the high average range. As previously noted IQ was significantly higher in controls and higher in RTLE compared to LTLE patients and suggests a greater disruption of cognitive development in LTLE associated with earlier age of onset seen in the LTLE group which is consistent with the literature (Farwell et al., 1985; Hermann et al., 2008; Rathouz et al., 2014). The potential impact of disease features on pre- to post language changes are discussed in Chapter 10.

Main fMRI results and association with language performance

Patterns of ICN recruitment: Correlation with disease features and performance.

Significant correlations between ICN recruitment and disease features were observed across paradigms in frontal (rest ICN 10), temporal (task ICN 1) ROIs, and the DMN (task ICN 13).

AED. While several studies have focused and found varying effects of drugs on the balance between default mode network and language networks (Helmstaedter et al., 2008; Szaflarski & Allendorfer, 2012; Wandschneider et al., 2014; Xiao et al., 2018; Yasuda et al., 2013) we found that a higher number of AEDs was significantly correlated with reduced VF activations in task ICN 1 and rest ICN 10: It is consistent with a significant association between a greater number of AED and poorer phonetic fluency across subjects consistent with the adverse effect of a higher drug load on cognition reported in previous studies (Feldman et al., 2018; Witt et al., 2015). It, furthermore, reiterates the relevance of clinically applied language fMRI paradigms such as verbal fluency tasks to frontal lobe (Bonelli et al., 2012; Szaflarski et al., 2008; Woermann et al., 2003) and temporal language areas.

While a potential differential effect of medication on fMRI activations in LTLE and RTLE patients was not accounted for, the drug load was comparable in LTLE and RTLE patients (median AEDs = 2 in both groups).

Different AEDs have been associated with differential effects on neuropsychological performance (see Chapter 2) and Topiramate and Zonisamide may affect language fMRI activation patterns (Wandschneider et al., 2017; Yasuda et al., 2013). There was, however, no statistically significant difference (Fisher's exact test: p-value = 0.083) between LTLE and RTLE in the number of patients treated with Topiramate (LTLE 0 patient, RTLE 2 patients) or Zonisamide (LTLE 5/24 patients, RTLE 0/16 patients) or the mean daily doses (Topiramate: Mann-Whitney U = 168, p = 0.079; Zonisamide: Mann-Whitney U = 161.5., p = 0 .175.).

Seizure frequency. An impact of recent or underlying seizure activity (Jayakar et al., 2002) on fMRI patterns has previously been articulated. In our cohort lower monthly seizure frequency was significantly correlated with greater AN deactivation in task ICN 13. Although deactivation of task-negative areas has previously been associated with successful performance (Raichle et al., 2001; Seghier & Price, 2012) a significant association with performance was not seen across participants.

Lateralisation

Significantly different patterns of lateralisation between groups and across tasks (Chapter 8) in the ATL and ICN ROIs, potentially provide informed markers in the prediction of decline in the study of language decline following ATLR.

Amodal lateralisation in the ATL and ICNs: Correlation with disease characteristics. Although there was very strong support for an association between a higher number of AEDs and atypical lateralised AN in the PTL, a significant correlation between features of disease and lateralisation was not seen for anatomical ROIs. Rather than this lack of correlation (Duke et al., 2012) we observed a significant association in task ICN 5 that incorporates substantial extra temporal areas. An earlier age of onset was significantly correlated with greater atypically lateralised deactivating VF in task ICN 5 across patients. The results are partly concordant with findings in LTLE that have associated language reorganisation with the duration of epilepsy (Wellmer et al., 2009) as well as age of injury particularly in LTLE (Springer et al., 1999) and with reports of a correlation of atypical lateralisation with earlier age of onset and prolonged disease duration (Miro et al., 2014; Yuan et al., 2006) and with effects of longer disease duration on language networks (Duke et al., 2012; Trimmel et al., 2018).

The findings here are not compatible with a greater effect on language regions close to the seizure focus (Kurthen et al., 1992; Spreer et al., 2002; Thivard et al., 2005): While different findings may be accounted for by different language paradigms and smaller ROIs, our results did not distinguish the ATL to have greater association with disease features than other ROIs. While a comparable association between LI and disease features was not seen in anatomical ROIs there was limited spatial sampling compared to ICNs.

Bayes factors suggested an association between lateralised naming and higher number of AEDs in temporal lobe ICNs and the PTL, which should be addressed in future studies: Insofar a higher number of AEDs represent more seizure related activity and associated disruptive effects it is compatible with shifts in laterality (Janszky et al., 2003; Janszky et al., 2006) and a greater degree of right hemisphere language dominance in right-handed patients with seizures originating from the left hemisphere (Rausch & Walsh, 1984) and partly with the conclusions that only left-handedness and a left seizure focus predicted atypical language lateralisation (Stewart et al., 2014).

Lateralisation patterns in homogeneous subgroups: Correlations with disease characteristics and performance. Cross dominance was observed between and within tasks. This finding supports previous observations (Bonelli et al., 2011) that disease characteristics effecting patterns of recruitment in both LTLE and RTLE are not necessarily expressed in cross hemisphere reorganisation and that intra-hemispheric shifts are idiosyncratic rather than typically associated with seizure focus.

Although there is a body of evidence that attest to the influence of different disease characteristics including AEDs (Feldman et al., 2018; Helmstaedter et al., 2008; Szaflarski & Allendorfer, 2012; Wandschneider et al., 2014; Witt et al., 2015; Xiao et al., 2018; Yasuda et al., 2013), seizure frequency (Berl et al., 2005; Hamberger & Seidel, 2009; Rosenberger et al., 2009), age of onset (Miro et al., 2014; Yuan et al., 2006) and disease duration (Binder et al., 2009; Bookheimer, 2002; Duke et al., 2012; Middlebrooks et al., 2017; Trimmel et al., 2018) on activation and lateralisation, our results did not show a significant association with disease features or out-of-scanner performance for subgroups distinguished by significantly different fMRI lateralisation patterns. The results suggest that fMRI patterns alone are not sufficiently specific and that fMRI results require interpretation in the context of idiosyncratic clinical complexity at a single subject level.

Strengths and limitations

Strengths and limitations were described in Chapter 8 and are elaborated in relation to this study: Bivariate task specific correlational analyses based on individual statistical parametric maps were performed to retain specificity with out-of-scanner performance and the individual roles of disease characteristics. ICN ROIs represented greater and unique spatial sampling compared to anatomically defined ROIs.

Performance measures reflected single assessments that are subject to measurement error. Patient groups were small. To increase power, sample size was maximised by testing relevant hypotheses across patient groups and healthy controls. Nevertheless, the analyses of homogenous fMRI patterns and associated disease features suggest relatively insensitivity to disease features at a group level.

Measures of seizure frequency obtained from patient history may not be accurate. High number of AEDs can be a marker for more seizure activity and while Bayes factors provided strong support for an association between higher number of AEDs and atypically lateralised auditory and picture naming in temporal lobe networks it warrants further study.

Different AED have been associated with differential effects on neuropsychological performance. The drug load was comparable in LTLE and RTLE patients. While Topiramate or Zonisamide have greater effects (see section on AED above) and was not accounted for in the analysis, the number of patients taking Topiramate or Zonisamide and their daily doses were comparable between patient groups.

Clinical implications

The high proportion of reported seizure freedom following resection of the anterior temporal lobe (de Tisi et al., 2011) is in many cases associated with the cost of post-operative naming and word finding difficulties. Language fMRI patterns have been shown to be predictors of language decline following temporal lobe resection (Bonelli et al., 2012). The

results of the current study suggest that fMRI patterns are associated with disease characteristics.

While crucial involvement for language function can be surmised from both connectivity (Chapter 8) and vulnerability to disease features in frontal (rest ICN 10), temporal (task ICNs 1 and 5) ROIs, and the DMN (task ICN 13) the role of reorganisation in the context of higher disease burden and its influence on fMRI activation in the prediction of language outcome after ATLR is to be determined.

The significance of changes in intra and interhemispheric patterns associated with disease features need to be evaluated in a clinical context. Given proven stability of these networks in patient groups higher fMRI activations in these regions ipsilateral to seizure onset and the focus of resection are likely to be associated with a greater risk of naming and word finding difficulties following ATLR.

The main clinical implications are that features of disease can impact significantly on intensity of BOLD activations and task performance. Specifically, the number of AEDs or drug load is associated with a cost to neuronal network function and level of language performance. It reiterates the need to account for effects of AED when fMRI patterns are interpreted in patient BOLD language maps.

While cognitive modularity (i.e., impairment in specific language function with other language and cognitive functions intact) is best studied by group design, through converging evidence from different populations (Robertson et al., 1993) the benefit of group study was potentially limited by small group size as well as heterogeneity with the priori patient classification of LTLE and RTLE. The results in relation to disease features and fMRI patterns suggest idiosyncratic clinical complexity (see Appendix A for marked individual patient differences) that requires investigation at the single subject level. It has been argued that the case study approach is the most promising method for providing information and

inferences on the functional organisation of cognitive subsystems (Caramazza & McCloskey, 1988; Nickels et al., 2011; Shallice, 1979; Sokol et al., 1991). It will allow for in depth study of phenomena including subtle features that may be clinically significant.

Cross lateralisation seen within and between language tasks in controls and patient groups and illustrated in individual cases, suggests that comprehensive preoperative assessment towards prediction of naming and word finding deficits may benefit from a panel of tasks aimed at identifying recruitment of temporal ROI and functionally connected networks.

Conclusions

A higher number of AEDs, earlier age of onset, and more seizures were associated with changes in language networks affecting activations in the DMN, temporal and frontal ROIs. A significant correlation was also seen with lateralisation, specifically between earlier age of onset and greater atypical, lateralised deactivating VF in task ICN 5. It reiterates the need to account for effects of AED and age of onset when fMRI patterns are clinically interpreted at the single subject level.

Appendix A

Profiles of Individual Patients most Characteristic of fMRI LI Subgroups

Subgroup 1: Subject #34

47 yr old, lefthanded, female RTLE patient. She suffered cryptogenic, bilateral complex partial seizures with an average of 20 seizures per month with a greater number of seizures on the right than left. There were no SGS. Her medication comprised PRG 150, LTG 700, TOP 500. Age of onset was 41 with a duration of 6 years. IQ fell in the high average range (111). Clinical language performance for naming (21) was high average, phonetic fluency (14) fell in the normal range. Semantic fluency (11) fell below the 10th percentile and was below average. HADS scores for anxiety (7) fell in the normal range whereas the indices for depression (10) was clinically elevated. Cross dominance was seen across language tasks in the ATL and ICNs. She was left dominant for PN but atypical for other paradigms in the ATL. She was atypically lateralised for AN, FF, SF, VF and deactivating VF but highly atypically lateralised for PN in the ATL. She was left dominant for AN in rest ICN 7 and 9&10, task ICN 4 and 13 and atypical in rest ICN, 4 and 8, and task ICNs 16, and 17. She was atypical for FF across ICNS but was highly left dominant in rest ICN 7 and task ICN 16. She was highly left lateralised for PN across ICNs but not in rest ICN 9&10 which was atypical. SF was atypical in ICNs but not in rest ICN 7 and task ICN 17 which was left dominant. VF was highly atypically lateralised across ICNs. Deactivating VF was left dominant but not in task ICN 1 and 4 that showed atypical indices.

Subgroup 2: Subject #20.

41 yr old righthanded, male LTLE patient with left temporal DNET and an average of 3 seizures per month. There were no SGS. Onset was at age 3 with a duration of 38 yrs. Medication comprised LEV 3000, LTG 100, PHT 300. IQ fell in the average range (91). Clinical language performance for naming (15), phonetic (15) and semantic fluency (17) fell in the normal range. HADS scores for anxiety (9) and depression (9) were mildly clinically elevated. Cross dominance was seen across the ATL and ICNs. Left lateralised for AN and PN and atypically lateralised for other language tasks in the ATL. Atypical lateralisation was seen across tasks in the ATL and ICNs: He was left dominant for AN, FF and VF in the ATL and atypically lateralised for PN, SF and deactivating VF in the ATL. AN was highly left lateralised in ICN 13 and rest ICN 4. It was atypical in task ICN 4 and highly atypical in rest ICN 7, task ICNs 16 and 17. FF was atypical in rest ICN 8 and task ICN 4 and highly atypical across other ICNs. PN was highly left dominant in ICNs but atypical in rest ICN 4 and highly atypical in task ICN 16. SF was left dominant in task ICN 4, but atypical and highly lateralised across ICNs. VF was atypical in rest ICN 8 but highly left lateralised in all other ICNs. Deactivating VF was atypical across ICNs.

Subgroup 3: Subject #8

20 yr old, righthanded, female LTLE patient with left hippocampal sclerosis. She suffered an average of two left complex partial seizures per month. There were no SGS. Medication comprised OXC 2400. Age of onset was 20 with a duration approaching 1 year. IQ (95) fell in the average range. Clinical language performance for naming (13) was low average. Phonetic fluency (13) was average whereas semantic fluency (13) was below average.

HADS scores for anxiety (16) fell in the severe range whereas depression (8) was clinically elevated into the mild range. She was atypically lateralised for in AN in ATL and predominantly left lateralised for other tasks in the ATL and ICNs. She showed atypical lateralisation for AN, PN and VF and deactivating VF and left lateralisation for FF and SF in the ATL. She was left and predominantly highly left lateralised for all tasks in ICNs but not for AN in rest ICN 4, PN in task ICN 1, SF in task ICN 4. She was atypically lateralised for VF across ICNs but not in task ICNs 1 and 17 where she was left dominant.

HADS = Hospital Anxiety and Depression Scale

PRG = *Pregabalin*, LTG= *Lamotrogine*, OXC= *Oxcarbazepine*, PHT = *Phenytoin*, TOP = *Topiramate*

Chapter 10

Prediction of Language Decline after ATLR

Abstract

Aim: To determine what role large network and anatomical areas with ATL connectivity and involvement in the specialised function for word retrieval, required in naming and fluency tasks, may have in the prediction of language decline after ATLR.

Methods: We obtained BOLD maps of five language paradigms in 26 TLE patients who underwent anterior temporal lobe resection. An established lateralisation method and selected metrics of an atlasing approach to functional mapping were employed to quantify engagement of anatomical and ICN ROIs that have shown functional connectivity with the ATL. Reliable Change Indices (RCI) for naming and fluency measures were calculated in four-month retest data of 18 Controls. Presurgical fMRI patterns and performance were compared with post-surgical naming and fluency performance in 26 patients (17 LTLE, 9 RTLE). To identify the sensitivity of ROIs to post-operative language change simple correlations were used to test an association between change in performance with preoperative activations in ROIs. Multiple linear regression was used to assess the significance between pre-operative activation in the identified ROIs and change in language scores. Logistic regression was conducted for significant results and the predicted probabilities quantified by the Area under the Receiver Operator Characteristic curve. Dose-response curves were fitted to describe the relationship between LI and the likelihood of significant decline. Repeated language fMRI was obtained post-operatively at four-months for 17 patients (13 LTLE, 4 RTLE). Multiple linear regression was used to identify networks significantly associated with ATL activation in seven LTLE patients with significant decline. It was compared to networks in LTLE patients without significant decline: Students t tests, and connectivity graphs based on correlational analysis were used to distinguish network differences and changes relevant to significant naming decline.

Results: Following surgery both LTLE patients and RTLE patients performed significantly worse than controls in relation to semantic fluency and LTLE patients showed significantly worse naming compared to controls. For individual patients significant clinical decline as defined by scores greater than the RCI for each measure was seen for naming in 53% of LTLE (9/17) and 22% of RTLE (2/9) patients, for semantic fluency in 11 % of RTLE (1/9) and for phonetic fluency in 22 % (2/9) of RTLE patients. Lateralisation in anatomical ROIs and ICNs for picture naming and fluency paradigms correlated significantly with post-operative decline. Linear regression showed significant association between pre-operative LI in anatomical and ICN ROIs and magnitude of predicted post-operative language change. Significant association between changes in language function and disease features were not seen. Compared to preoperative connectivity LTLE patients with significant post-operative decline showed greater ipsilateral ATL - PTL connectivity and patients without significant decline showed greater contralateral ATL - PTL connectivity.

Conclusions: There is a greater risk of naming decline after ATLR compared to fluency. Activation in temporal lobe networks serve as a predictor for naming and fluency decline and the intensity of pre-operative activation is associated with the magnitude of post-operative decline. Significant naming decline was associated with pre-operative activation of posterior temporal networks (the PTL and task ICN 12) whereas decline in semantic fluency showed greater association with networks that encompass posterior as well as anterior temporal regions, specifically limbic and medial temporal areas that include parahippocampal gyri (PTL, ATL and task ICN1). Phonetic fluency decline was associated with preoperative activation in a network that encompass the transverse temporal gyri including the primary auditory cortices (task ICN 16). Left lateralised PN in the PTL and task ICN 12 showed 80% PPV for significant naming decline after ATLR. Left lateralisation in both the PTL and the ATL and both task ICN 1 and the PTL showed 24 % PPV for significant decline in semantic fluency. Left lateralised VF in task ICN 16 provided a PPV of 14% for significant decline in phonetic fluency. The methods employed to predict postoperative decline in individual subjects used a lateralisation index in the anatomically and ICN defined ROIs that can readily be applied in a clinical setting.

Peak fMRI BOLD activity in anatomical structures have been employed to provide structure-function mappings studies of language function (Bonelli et al., 2012a; Centeno et al., 2014; Szaflarski et al., 2008; Woermann et al., 2003). While language fMRI has provided a non-invasive means to assess language laterality in relation to the epileptic focus in neurosurgical candidates it has to date not provided reliable and specific localisation of crucial language sites and failed to engage some of the regions such as the ventral and anterior temporal regions often compromised by surgery. Localisation of crucial language sites in the workup for ATLR resection, has been improved by tasks that are more specific (Gonzálvez et al., 2016). However, the value of these tasks in identifying risks posed by surgery has not been investigated.

ICNs appear to link patterns of resting state and task-related connectivity. Given demonstrated stability of ICNs in healthy controls, ATL connectivity and association with disease features, the idiosyncrasies of language organisation that are apparent in TLE patients, these canonical networks may assist prediction of post-operative language function. In this study we investigate the relevance of large regions of interest that have previously been shown to function as ICNs as well as anatomical areas in language function.

ROIs were previously identified in controls (Chapter 7): Five paradigms with contrasts that distinguish language processes that involve perceptual, motor and executive function from those supra-modal areas that involve processing of abstracted (i.e., amodal) information, were employed.

Specifically, we 1) correlated the recruitment of ICNs that have shown functional naming and fluency task connectivity with the ATL with post-operative language function. We also investigated correlation of activations in the anterior temporal lobe (ATL), the posterior temporal lobe (PTL) as well as the inferior and medial frontal gyrus (IFG&MFG) with post-operative naming and fluency performance.

The aim of this study was to investigate (1) the association of anatomical ROIs, large-scale resting state and task activation networks, and (2) the mediating impact of effect of presurgical language proficiency and disease features; on pre- to post-operative changes in clinical language performance in patients with refractory TLE.

We hypothesised that:

1) Recruitment of the ATL and temporal lobe ICNs will have a significantly greater predictive value for naming decline than frontal ROIs and networks.
2) Frontal ROIs and networks will have significantly greater predictive value for fluency tasks than temporal ROIs and networks.
3) Disease features will be predictive of language decline.
4) Pre to post-surgical network changes will be associated with prediction of decline.

Methods

Subjects

Results of electro-clinical and imaging investigations and associated clinical details for patient groups were described in Chapter 5. Demographic and clinical data relevant to the current study are summarised in Tables 10.1 and 10.2.

Measures of mood and handedness (Edinburgh handedness questionnaire) phonetic fluency, semantic fluency and naming were described in the common methods section (Chapter 5).

Table 10. 1.

Demographic and Clinical Data for Patients and Control Subjects

	Gender female/male	**Handedness right/left**	**Age (years)**	**CPS/mo**	**SGS/mo**	**AEDs**	****Age of onset**	**Disease duration**
HC	6/12	18/0	42±	na				
(n=18)			11.4					
LTLE	5/12	14/3	38±	5	0	3 (1)	15.1	23.4
(n=17)			10.3	9.2	0			14.6
RTLE	3/6	3/6	43.7±	4	0	2 (1)	25.1	18.7±
(n=9)			8.4	17.5	0			15.6

Note. Age, age of onset of epilepsy, language scores and estimated intellectual level (IQ) are shown as mean ± SD. Disease duration, seizure frequency (CPS, SGS) and number of AED are shown as median and IQR.

AED = antiepileptic drugs; CPS = complex partial seizures; HC = control subjects; IQ = estimated intellectual level; IQR = interquartile range; LTLE = left temporal lobe epilepsy; RTLE = right temporal lobe epilepsy; SD = standard deviation; SGS = secondarily generalised seizures; ****** = LTLE<RTLE two sample t-test, p = 0.021.

Table 10. 2

Performance Data for Patients and Control Subjects

		Session 1/Pre-surgical performance			Session 2/Post-surgical performance		
	IQ	**Naming**	**Phonetic fluency**	**Semantic fluency**	**Naming**	**Phonetic fluency**	**Semantic fluency**
HC	110.2	20.2±	17.7 ±	*25.6 ±	21.2 ±	18.6 ±	25.5 ±
(n=18)	10.34	4.3	4.39	4.7	4.85	5.15	4.71
LTLE	93.9	13.4 ±	13.07 ±	16.9 ±	12.2 ±	14.0 ±	15.38 ±
(n=17)	11.6	5.22	3.75	4.43	7.08	4.76	5.03
RTLE	104.5	19.4 ±	15.9 ±	17.2 ±	18.1 ±	13.2 ±	17.0±
(n=9)	10.64	4.88	4.91	5.39	5.21	5.52	5.07

Note. Language scores and estimated intellectual level (IQ) are shown as mean ± standard deviation.

In the LTLE group there were eight patients with hippocampal sclerosis, six with dysembryoplastic neuroepithelial tumour one cavernoma and one with focal cortical dysplasia. In the RTLE group there were four cases with hippocampal sclerosis, three with dysembryoplastic neuroepithelial tumour, one cavernoma and one non-lesional case. There were no significant differences in the distribution of age between the three groups (one-way ANOVA, $p > 0.05$; Table 1a). RTLE had a significantly later mean age of onset than left TLE (two samples two-tailed T-test; $t=2.461$, $p = 0.021$) (Table 10.1). The two patient groups did not differ for disease duration, seizure frequency or number of AEDs (Mann-Whitney independent sample test). There was no significant difference in anxiety and depression scores between the groups.

The study was approved by the National Hospital for Neurology and Neurosurgery and the UCL Queen Square Institute of Neurology Joint Research Ethics Committee. Written informed consent was obtained from all participants.

Neuropsychological tests

Neuropsychological measures were obtained for all subjects prior to functional imaging as reported in Chapters 5 and 8. All subjects in this study completed the National Adult Reading test, the McKenna Graded Naming Test as well as phonemic and semantic verbal fluency tests outside the scanner as described in the common methodology section (Chapter 5). The performance indicator was the number of items correctly named or produced. Reliable change indices (RCI) were calculated for each test from the test-retest results of 18 healthy controls. In all language tasks a change score that exceeded the RCI was considered significant.

MR data acquisition

The MRI data acquisition and pre-processing was performed according to the common protocol for language studies as described in Chapter 5 – Common Methodology.

Language paradigms

Subjects in this experiment performed five language paradigms described in the common methods section for language studies in Chapters 5 and 8.

Disease features

Measures of anxiety and depression described in the common methods were obtained for all controls and patients prior to functional imaging. The number of AEDs, monthly seizure frequency, age of onset and disease duration was obtained from patient history and clinical reports as described in the common methods section

Statistical analysis

Details of statistical analyses and alpha adjustment for multiple comparisons were described in the common methods section for language studies in Chapter 5. Analyses unique to this chapter are described below.

Group differences in language performance

Group differences in IQ and language performance at session *one* and at session *two* were assessed using one-way ANOVA with post hoc independent samples t-tests, Bonferroni adjusted for multiple comparisons. Test-retest differences in language performance for all subjects (controls, LTLE and RTLE) were assessed by the Wilcoxon test (paired samples), Bonferroni adjusted for multiple comparisons.

Individual change in language performance

The Reliable Change Index statistic (RCI) (Chelune et al., 1993) that provided a measure of how large an individual's change in scores between two assessments must be to exceed random variation was computed for each language task using Cronbach's alpha as the measure of reliability and 1.96 times the standard error of change in healthy controls (Evans, Margison & Barkham, 1998). Accordingly, the SE of measurement of a difference (SE_{diff})

was calculated as $SD_1 \sqrt{2} (S_E)^2 \sqrt{r-1}$ where SD_1 is the standard deviation of the baseline observations and, *r* is the reliability of the measure (Jacobson & Truax, 1991).

Correlations between change scores and presurgical proficiency

Correlations between presurgical levels of proficiency and changes in pre-to post-surgical performance were assessed with Kendall correlation, adjusted for multiple comparison with permutation.

Correlations between change scores and disease features

Correlations between changes in pre-to post-surgical performance and disease features were assessed with Kendall correlation, adjusted for multiple comparison with permutation testing in 26 patients who had pre- and post-operative neuropsychometric testing.

Difference in disease features between patients with and without significant decline

Difference in disease features between patients with and without decline in the group of 26 who had pre- and post-operative neuropsychometric testing was assessed by Mann Whitney independent samples test. The chi-squared test was used to determine whether there was a significant difference between the proportion of subjects with hippocampal sclerosis that suffered decline compared to the proportion without decline.

fMRI data analysis

The creation of contrasts was described in the common methods section for language studies in Chapter 5.

ICN_atlas and metrics

ICN_atlas metrics were described in Chapters 5 and selection of ICNs in Chapter 7. Estimated anatomical regions from Laird et al (2011) were described in Chapter 5 together with voxel membership for greater anatomical specificity as per the human Brainnetome Atlas (Fan et al., 2016).

Lateralisation

Calculation of LI to assess hemispheric dominance in anatomical and ICN ROIS were described in Chapter 5. Kendall correlation was used to assess association between subjects' LI within individual ICN and anatomical ROIs, with disease features and language performance outside the scanner.

Correlational analysis: Identification of ROIs that are sensitive to post-operative language change

Pre to post naming and fluency performance was compared in each of the 26 patients. A vector of pre to post difference in performance was established for each patient that contained a positive sign for increase in scores (an improvement in function), a zero (no change) and a negative sign for a decrease (decline in function) in scores.

To select ROIs with association between activation and change in pre- to post-surgical performance Kendall correlations, adjusted for multiple comparison with permutation testing were performed to quantify the strength of any relationship between activation, with changes in pre- to post-operative language performance. Bayes factors as described in the common methods section, for a one-sided alternative hypothesis that the population correlation between activation in any ROI and change scores in language performance was higher than zero were tested.

Regression analysis: Prediction using pre-operative activations and pre- to post-operative change scores

Linear regression was used to assess the strength and significant of relationship between pre-operative activation in ROIs and pre- to post-operative change in language scores for ROIs. A Variance Inflation Factor of ≥ 3 was used to indicate multicollinearity for multiple linear regression. Logistic regression evaluated with the Hosmer-Lemeshow test for goodness of fit was conducted for significant results and the predicted probabilities of

significant decline provided ranking that was quantified by the Area under the Receiver Operator Characteristic (ROC) curve (AUC) to ascertain whether LI can reliably distinguish between patients with and without significant decline. A probit dose-response curve was used to obtain a series of probabilities that described the relationship between the intensity of activation, lateralisation in individual ROIs and the likelihood of significant decline.

Diagnostic utility of prediction indices

Sensitivity and specificity to significant decline. The diagnostic utility of indices was obtained by calculating sensitivity and specificity.

Probability of significant language decline. The pre-test probability of significant language decline as defined by a negative pre-to-post change test score ≥ RCI and a correspondent LI > .2 and the likelihood that a patient will not suffer a significant decline given specific fMRI patterns was obtained using a pre-test probability of language decline that comprised an estimate of the base rate proportion of language decline following ATLR. Base rates were estimated from the observed data and the accuracy informed by a previously published study (Davies et al., 1998) that used a 90^{th} centile RCI and showed significant naming decline in 53% of males and 31% of females and a decline of 2% for verbal fluency six to eight months postoperatively**.**

A standard logit confidence intervals method (MedCalc Statistical Software version 18.10.2, 2018) suited to case control studies (Mercaldo et al., 2007) was employed to obtain positive predictive value (PPV) and negative predictive values (NPV).

Pre and postoperative naming networks in left TLE

Of the 26 patients who had pre- and post-surgical neuropsychometric assessment, fMRI was obtained pre-operatively for 26 patients and repeated post-operatively for 17 patients (13 LTLE, 4 RTLE). In the group of 13 LTLE patients, disease characteristics and networks were compared in patients with and without significant naming decline.

Association with disease features and pathology

Mann Whitney independent sample tests Bonferroni adjusted for multiple comparisons, were conducted to ascertain significant group differences in disease features. The proportion of subjects with hippocampal sclerosis that suffered decline were compared to the proportion without decline using Fisher's exact test.

Association of performance with network recruitment

The association of performance with network recruitment was obtained by Kendall correlation of pre-surgical scores with presurgical activations, adjusted for multiple comparison with permutation testing.

Effectiveness of pre- to post-operative network changes in LTLE

Changes in lateralisation. Student's t tests, for the comparison of means, Bonferroni adjusted for multiple comparisons, were conducted to assess differences between lateralisation in individual ROIs between groups with and without significant decline before and after surgery.

Changes in connectivity. Connectivity changes in the group of patients that suffered significant naming decline were observed by selecting networks that significantly covaried with activation in the ATL. Backwards multiple regression was performed with ATL activation as the dependent variable and preoperative LIs in other ROIs as the covariates. Accordingly, all covariates were entered simultaneously, and then removed in a sequence of ANOVA tests to identify a significant and optimal model. Connectivity networks involving the identified ROIs were constructed from unthresholded Pearson correlation maps. Differences and changes were observed pre and post operatively in the decline and no decline groups.

Results

Neuropsychological performance

Group differences prior to surgery. Intergroup comparison of psychometric performance showed a significant difference of IQ between groups (one-way ANOVA = 10.805, $p < 0.001$), phonetic ($F=4.801$; $p=0.014$) and semantic fluency ($F=19.968$; $p<0.001$) as well as naming ($F=10.378$; $p < 0.001$). Post-hoc pairwise comparisons (independent samples two-tailed t-test, Bonferroni adjusted for multiple comparisons) showed that IQ was significantly higher in controls than LTLE patients ($T = 4.586$; $p=0.001$). Post-hoc pairwise comparisons (independent samples two-tailed t-test) showed significantly lower semantic fluency ($T= -5.607$; $p < 0.001$) for LTLE and RTLE ($T= -4.190$; $p=0.004$) compared to controls. LTLE showed significantly lower phonetic fluency ($T= -3.318$; $p=0.024$) compared to controls. LTLE showed significantly lower naming ($T= -4.225$; $p=0.024$) compared to controls.

Group differences following surgery. Intergroup comparison of psychometric performance at follow-up for controls and following surgery showed a significant difference for semantic fluency (One-way ANOVA; $F=19.968$; $P < 0.001$), phonetic fluency ($F=4.801$; $P = 0.014$) and naming ($F=10.378$; $p<0.0001$). Post-hoc pairwise comparisons (Independent samples two-tailed t-test; $p>0.05$, Bonferroni adjusted for multiple comparisons) showed that patient groups did not differ significantly in relation to semantic fluency. Compared to controls both LTLE patients ($T = 6.06$; $p = P < 0.001$) and RTLE patients ($T = 4.15$; $p = 0.004$, Table 1) performed significantly worse. No significant group differences were seen in relation to phonetic fluency. LTLE patients showed significantly worse naming compared to controls ($T=4.40$; $p = 0.0009$).

Within group test-retest changes. Wilcoxon test (for paired samples) showed that there were no significant differences in performance for naming, semantic or phonetic fluency in session two compared to session one.

Postoperative language changes in individual patients. One LTLE patient did not complete post-operative phonetic and semantic fluency tasks and one RTLE patient did not complete the semantic fluency task post-operatively.

Reliable change criterion (RC) for naming was observed as 2.73 and provided an index of ≥ 3 as an indicator of significant change. The RC for semantic fluency was 5.01 which provided a critical value of ≥ 6 as indicator of significant change. The RC for phonetic fluency was 7.64 with a critical value of ≥ 8 that reflected significant pre- to post-operative change. Eleven of 17 LTLE patients showed a decline in naming following surgery (median change for all LTLE patients = -3; range -10 to 18). The decline was significant in 52% of all LTLE patients. Nine LTLE patients showed a decline in semantic fluency (median change for all LTLE patients = -1.5; range -5 to 3). It was not significant in any of the LTLE cases. Six LTLE patients showed a decline in phonetic fluency (median change = 0; range -5 to 8) with no cases showing a significant decline.

Five RTLE patients showed a decline in naming (median change for all RTLE patients = -2; range -7 to 5). Decline was significant in one left and one right-handed patient, that is 22% (2/9) of all RTLE cases. Three RTLE patients showed a decline in semantic fluency (median change = 5; range -11 to 5) which was significant for (1/9) 11 % of all RTLE cases. Five cases showed a decline in phonetic fluency (median change for all RTLE patients = -2; range -12 to 7) which was significant for (2/9) 22 % of all RTLE patients.

Nine LTLE and two RTLE (42%) of all TLE patients suffered significant decline in clinical naming. 4% of all TLE patients (1 RTLE) suffered significant decline in semantic fluency. 8% of all patients (2 RTLE) patients showed a significant decline in phonetic fluency.

In two RTLE and one LTLE patient naming scores remain unchanged. In four LTLE and one RTLE patient semantic fluency remained unchanged. In three LTLE and one RTLE phonetic fluency scores were unchanged.

Nineteen percent of all TLE patients (one RTLE and three LTLE patients) showed significant improvements in naming. Four percent (one RTLE patient) showed a significant improvement in semantic fluency. Four percent of all TLE patients (one LTLE patient) showed significant improvement in phonetic fluency.

Correlations between change scores and presurgical proficiency. Significant task specific correlations between presurgical levels of proficiency and changes in pre-to post-surgical performance were not seen for any of the tasks.

Correlations between change scores and disease features. A significant association between changes in language function and disease features were not seen.

Difference in disease features between patients with and without decline. There was no difference in disease features between patients with and without decline. There was not a significant difference in the proportion of subjects with hippocampal sclerosis that suffered decline compared to the proportion without decline.

fMRI results

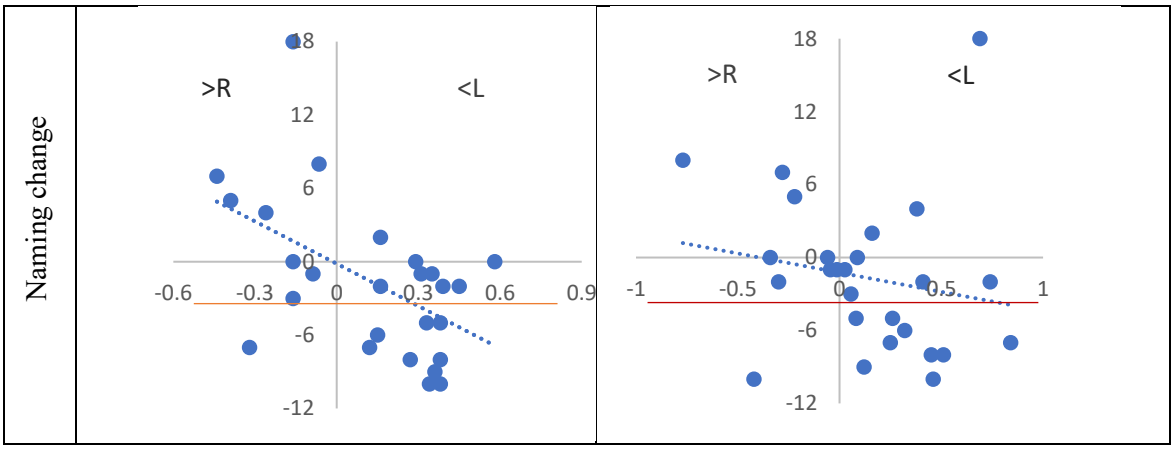
Identification of ROIs sensitive to post-operative language change

Correlation between preoperative fMRI activations and change scores in all patients identified several ROIs that are sensitive to changes in language function.

Naming. There was moderate support (BF_{10} = 3.83) for an association between naming decline and left lateralised PN in the PTL (r=0.29) and for the association (r=0.33) between naming decline and left lateralised PN in task ICN 12 (BF_{10} = 6.87). The correlations are depicted in Figure 10.1.

Figure 10. 1.

Correlation between Preoperative fMRI and PN Change Scores

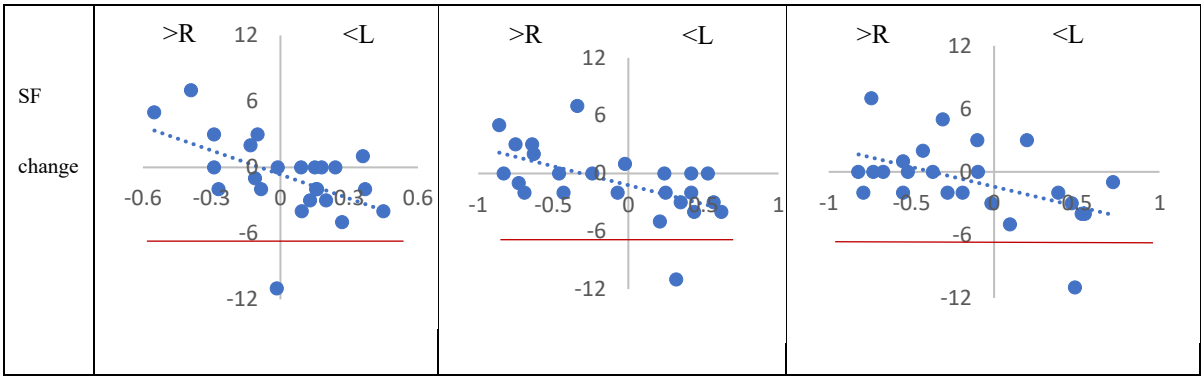


Note. Left: Task ICN 12 (r=0.29). Right: PTL (r=0.33). The red line shows the RCI score for significant decline (≥ -3). >R, <L = direction of greater or lesser right or left LI.

Semantic fluency. Significant correlation, adjusted for multiple comparison with permutation testing, was seen for a greater decline in semantic fluency with greater left activations in task ICN 1 (r=0.37, p= 0.047), task ICN 12 (r=0.38, p= 0.041) and the PTL (r=0.46, p=0.01). Significant correlations are depicted in Figure 10.2. There was moderate support (BF_{10}=6.2) for a correlation (r=- 0.333) between change in SF performance and atypical (bilateral or right) lateralised activation in the ATL.

Figure 10. 2.

Correlations between Preoperative fMRI and SF Change Scores

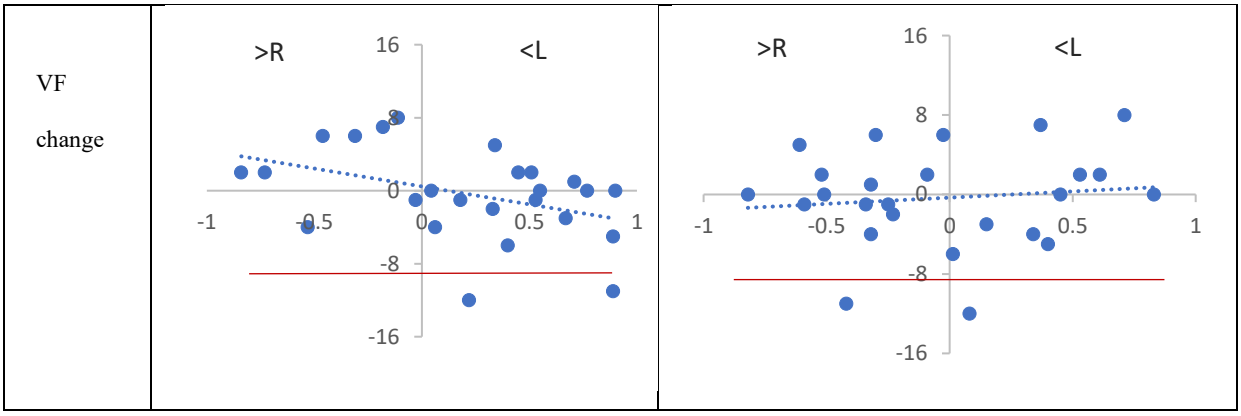


Note. Left: Task ICN 12 (r=0.38). Middle: PTL (r=0.46). Right: Task ICN 1 (r=0.37). The RCI score for significant decline (≥ -6) is denoted by the red line. >R, <L = direction of greater or lesser right or left LI.

Phonetic fluency. There was no support for an association or significant task specific correlations between activations and phonetic fluency change scores. There was anecdotal support for an association between decline in phonetic fluency and left lateralised (BF_{10} = 2.33, r=2.57) and atypically lateralised deactivating VF (BF_{10} = 2.782, r=-0.27) in task ICN 16 (Figure 10.3).

Figure 10. 3.

Correlations between Preoperative fMRI and VF Change Scores



Note. Left: Activations in task ICN 16. Right: Deactivations in task ICN 16. The RCI score for significant decline (≥ -8) is denoted by the red line. >R, <L = direction of greater and lesser right or left LI.

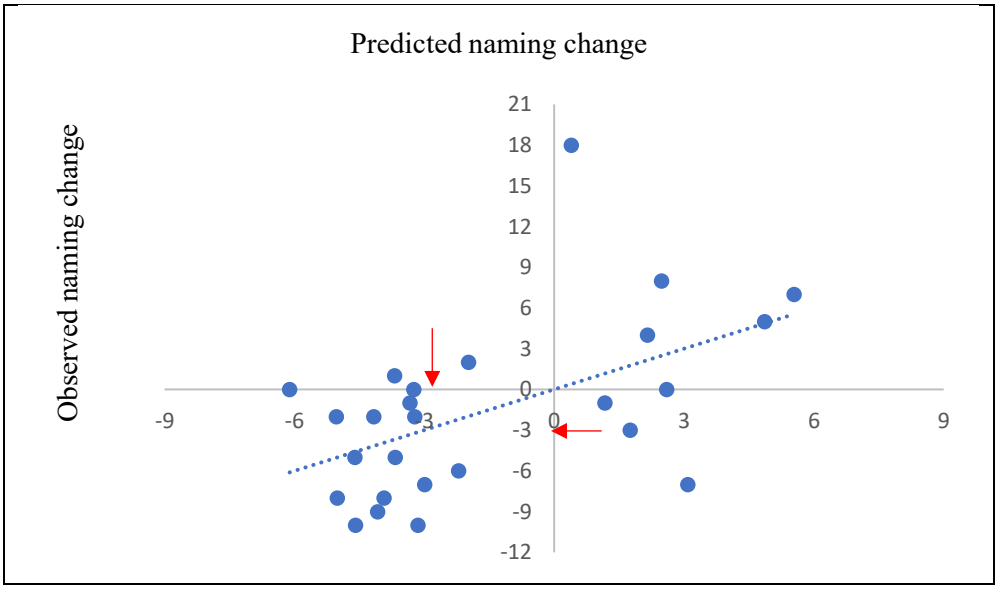
Regression analysis: Prediction of change scores

Linear regression showed significant predictive correlation between activation in ROIs and change scores for all patients.

Naming. Significant correlation between naming change and pre-operative activation was seen in task ICN 12 (R^2=0.262, p=0.007). A significant correlation between naming change and pre-operative activation in the PTL was not seen. Multiple linear regression based on pre to post change in naming scores, checked for multi-collinearity, in both the PTL and task ICN 12 (R^2=0.278, p= 0.024; Figure 10.4), showed significant correlation between pre-operative activation and change in naming.

Figure 10. 4.

Correlation between Predicted and Observed Naming Change



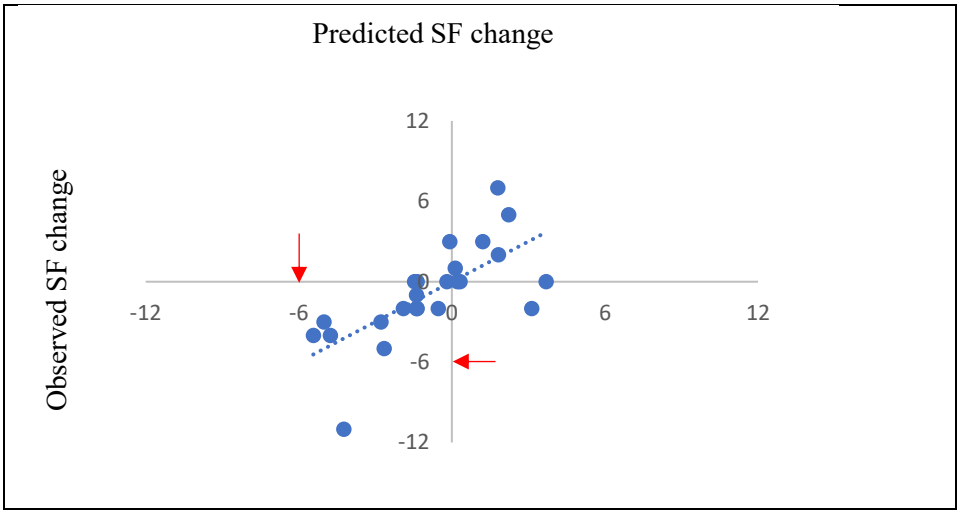
Note. Correlation of predicted and observed naming change used preoperative activation in both task 12 and the PTL (R^2=0.278) in patients with left and right TLE. The RCI index (≥ 3) for significant decline is depicted by a red arrow on the axes.

Semantic fluency. Significant correlations were seen between SF change scores and pre-operative activation in the PTL (R^2=0.315, p=0.004), task ICN 1 (R^2=0.257, p=0.012), task ICN 12 (R^2= 0.249, p=0.010) and the ATL (R^2= 0.227, p=0.019).

Multiple linear regression of pre to post change in SF scores, checked for multicollinearity, showed significant correlation between activation in both the PTL and task ICN 1 (R2=0.483, p<0.001; Figure 10.5), both the PTL and the ATL (R2=0.413, p<0.001) and both task ICN 12 and the PTL (R^2=0.342, p=0.012) with SF change scores.

Figure 10. 5.

Correlation of Predicted and Observed Change in Semantic Fluency



Note. Correlation of predicted and observed change in semantic fluency used preoperative activation in both the PTL and task ICN 1 (R^2=0.257) in patients with left and right TLE. The RCI index (≥ -6) for significant decline is depicted by a red arrow on the axes.

Phonetic fluency. Linear regression showed significant correlation between VF change and pre-operative activation in task ICN 16 (R^2=0.315; p=0.047).

Sensitivity and specificity of all LI to significant language decline after ATLR

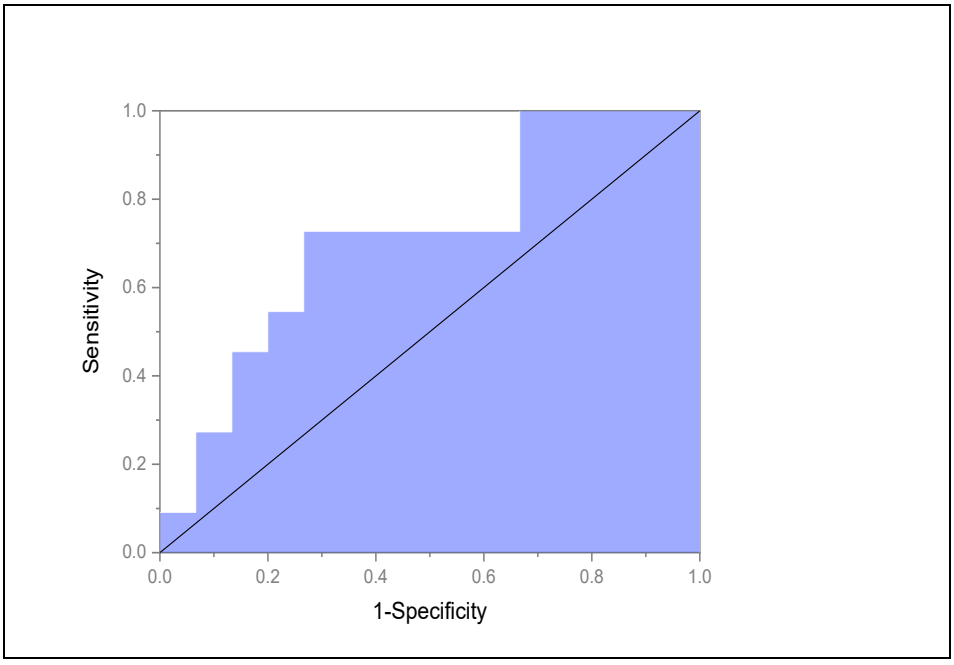
Chi-squared results (Hosmer-Lemeshow goodness of fit test; p > 0.05) showed good logistic regression model fits and binary classification of significant and no significant decline of naming, semantic fluency and phonetic fluency. Predicted probabilities of

significant decline based on all LI values obtained with logistic regression showed high classification accuracy for patients without significant decline. Correct classification of patients with significant SF and VF decline was not seen.

Naming. Goodness of fit was seen for logistic regression ($\chi 2=5.49$, $p=0.60$) that compared significant with no significant naming decline for all patients based on LI in both task ICN 12 and the PTL. It showed a correct classification of 65%. Classification was correct for 45% of patients with significant decline and 80% for patients without significant decline. An AUC ROC of 0.72 (95% CI 0.51 to 0.87) was significant (Area=0.5; Z = 2.028, p=0.024) with sensitivity of 82% and specificity of 47%.

Figure 10. 6.

ROC of Predicted Naming Decline



Note. ROC (AUC=0.72, p=0.024) of predicted significant naming decline based on logistic regression of left and atypical LI in task ICN 12 and PTL.

Semantic fluency. Goodness of fit was seen for logistic regression that compared significant with no significant SF decline for all patients based on LI in both the PTL and task ICN ($\chi2$=5.49, p=0.60), both the PTL and ATL ($\chi2$ =5.78, p=0.57) and both the PTL and ICN 12 (goodness of fit; $\chi2$=2.22, p=0.95). It showed a correct classification of 96%. Correct classification was 0% for significant decline (one patient) and 100% for non-significant decline (25 patients). ROC AUC models were not significant.

Phonetic fluency. For all patients the results of logistic regression (goodness of fit; $\chi2$=6.82, p=0.45) based on LI in task ICN 16, showed a correct classification for VF of 92.31%. Correct classification was 0% for significant decline (two patients) and 100% for non-significant decline (24 patients). The ROC AUC was not significant.

Diagnostic utility

The diagnostic test for significant decline in each language paradigm constituted a negative pre-to-post change test score ≥ RCI and a correspondent LI >.2.

Sensitivity and specificity of left lateralisation to the presence of significant language decline after ATLR

Naming. The greatest sensitivity (64%) for significant naming decline for all TLE cases was seen for PN in the PTL with a specificity of 73%. A left index of > .2 in the PTL predicted significant naming decline in one left-handed RTLE patient while left activation in task ICN 12 predicted significant decline in one right-handed RTLE patient. Low sensitivity (36%) but high specificity (93%) to significant decline was shown when left lateralised PN in both the PTL and task ICN 12 constituted the test.

Semantic fluency. A 100% sensitivity for significant fluency decline was shown for SF in task ICN 1 with a specificity of 72%. When left lateralised SF in both the PTL and the ATL or task ICN 1 constituted the test, high sensitivity (100%) and specificity (87%) was seen.

Verbal fluency. A 100 % sensitivity for significant phonetic fluency decline was shown for left lateralised VF in task ICN 16 with a specificity of 47.82%. A 100 % sensitivity for significant phonetic fluency decline was shown for atypically lateralised deactivating VF in task ICN 16 with a specificity of 33.33%.

Sensitivity and specificity for significant correlations between left lateralised presurgical activation and decline in language performance are reported in Table 10.3.

Table 10. 3.

Sensitivity and Specificity of Left LI to Significant Language Decline

task	ROI	Total number: significant decline	True positive	Absence of significant decline	True negative	Sensitivity%	Specificity%
PN	PTL	11	7	15	10	64	73
PN	task ICN 12	11	7	15	9	63	60
PN	PTL & task ICN 12	11	4	15	14	36	93
SF	PTL	1	1	24	13	100	57
SF	task ICN 1	1	1	24	17	100	74
SF	ATL	1	1	24	5	100	22
SF	PTL & task ICN 1	1	1	24	20	100	87
SF	PTL & ATL	1	1	24	20	100	87
SF	Task ICN 12	1	0	24	19	0	76
VF	Task ICN 16	2	2	23	11	100	48

Note. Left LI (> .2). PN 95% RCI = 2.73: Significant naming decline ≥3; SF 95% RCI =5.01: Significant semantic fluency decline ≥6; VF 95% RCI =7.64: Significant phonetic fluency decline ≥8

Probability of naming decline

A percentage base rate of 42% indicating the prevalence of naming decline four months after ATLR was estimated from the data and previous studies (Bell et al., 2003; Davies et al., 1998; Loring et al., 1994). The predictive value of two tests, namely left dominant and atypical lateralisation in specific ROIs in the form of point estimates and 95% confidence intervals are reported in Table 10.3. The PTL showed the highest predictive value and in combination with task ICN 12 showed a higher post-test probability (.80) of significant naming decline given left lateralisation in both ROIs.

Table 10. 4.

Posterior Probability of Decline

		Left lateralisation		Atypical lateralisation	
task	ROI	*Presence of decline	95% CI	**Absence of decline	95% CI
PN	PTL	63	40 to 82	74	55 to 87
PN	task ICN 12	54	35 to 71	69	48 to 84
PN	PTL & task ICN 12	80	34 to 97	67	56 to 76
SF	task ICN 1	14	7 to 24	100	
SF	PTL	9	6 to 13	100	
SF	ATL	5	4 to 6	100	
SF	PTL&ATL	24	10 to 48	100	
SF	PTL& task ICN 1	24	10 to 48	100	
VF	task ICN 16	14	10 to 20	100	

Note. *Positive Predictive Value; ** Negative Predictive Value

Probability of fluency decline

For phonetic fluency 2 of 25 (8%) and semantic fluency 1 of 25 (4%) patients showed a decline that exceeded the respective reliable change index (RCI) 95th centile. Low observed prevalence for VF (8%) and SF (4%) informed low predictive values. The greatest

PPV for SF was seen in task ICN 1. Left lateralisation in both the PTL and the ATL and both task ICN 1 and the PTL showed greater PPV (24%) for SF than individual ROIs. The PPV for left lateralised VF in task ICN 16 was 14% and the PPV for atypically lateralised deactivating VF 12%.

Pre and postoperative naming networks in left TLE

A significant difference or strong support for difference in disease burdens in LTLE patients with and without significant naming decline in the 13 LTLE patients who had post-surgical scanning, was not seen (Table 10.5).

Table 10. 5.

Data for Patients with and without Naming Decline

	Gender female/male	**Handedness right /left**	**Age (years)**	**CPS/mo**	**SGS/mo**	**AEDs**	**Age of onset**	**Disease duration**
Decline	2/5	6/1	36.1±	10	0	3 (0)	18	18.1±
(n=7)			(10.9)	(16)	(0.3)		(9.7)	(16.9)
No decline	2/4	6/0	39.8±	5.5	0	2.5 (2)	13	26.8±
(n=6)			(7.5)	(8)	(0)		(7.4)	(10.6)

Note. Age, age of onset of epilepsy, clinical naming scores and estimated intellectual level (IQ) are shown as mean ± standard deviation. Disease duration, seizure frequency (CPS, SGS) and number of AED are shown as median and Inter quartile range.

Association of performance with network recruitment

A significant association between performance and network recruitment was not seen across the 13 LTLE patients.

Effectiveness of pre- to post-operative network changes

Changes in lateralisation. Assessment of networks in 13 left TLE patients for whom post-surgical fMRI were obtained, showed that compared to the no decline group who were atypically lateralised, the decline group was left dominant pre and post operatively for PN in task ICN 12, the PTL and rest ICN 4. In the group with significant decline 5/7 patients (71%) were atypically lateralised in the ATL preoperatively and in the group without decline 5/6 patients (83%) were atypically lateralised in the ATL. In the group with decline 5/7 patients (71%) were left lateralised in the PTL. In the group without decline 6/6 patients (100%) were atypically lateralised in the PTL. Mean pre- and post-operative LI for both groups are shown in Table 10.6.

Table 10. 6.

Mean LI in LTLE Groups with and without Naming Decline

		Significant decline*		No significant decline**	
task	ROI	Pre	Post	Pre	Post
PN	ATL	0.01	0.02	-0.14	-0.04
PN	task ICN 1	0.19	0.2	-0.01	0.13
PN	task ICN 12	0.25	0.28	0.08	-0.03
PN	task ICN 13	0.3	0.12	0.33	0.21
PN	task ICN 16	-0.19	0.24	-0.54	-0.49
PN	task ICN 17	0.06	0.44	-0.12	-0.12
PN	task ICN 4	0.15	0.06	0.15	-0.17
PN	task ICN 5	-0.25	-0.15	-0.09	-0.08
PN	IFG_MFG	0.25	0.12	0.09	-0.37
PN	PTL	0.31	0.4	-0.16	-0.23
PN	rest ICN 4	0.36	0.21	-0.08	0.02
PN	rest ICN 7	-0.01	0.24	-0.48	-0.39
PN	rest ICN 8	0.04	-0.11	-0.04	-0.19
PN	rest ICN 9&10	0.5	0.44	0.24	-0.16

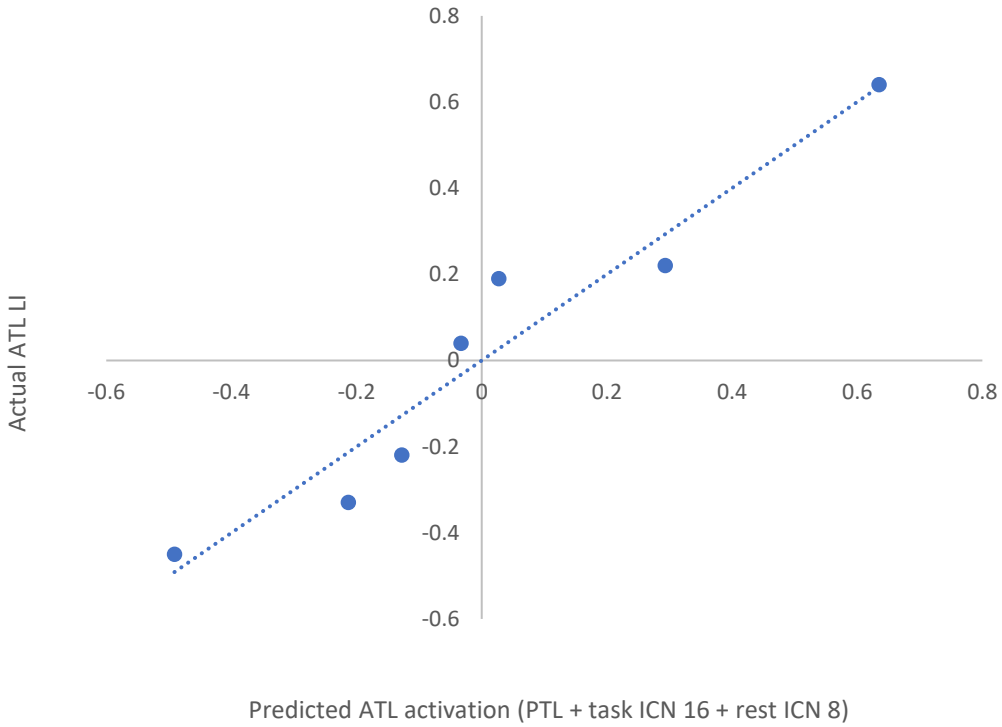
Note. *n=7; **n=6

There were no significant differences between groups. The greatest differences were seen pre- and post-op in the PTL and post operatively in task ICN 16, rest ICN 7 and rest ICN 9&10.

Changes in connectivity. Of the 26 patients that had pre and postoperative neuropsychometric testing, post-surgical fMRI in 13 LTLE patients allowed for comparison of connectivity changes in groups with and without significant naming decline: ROIs (a model comprising the PTL, task ICN 16, and rest ICN8) that covaried significantly (F=13.007, p=0.032) with preoperative ATL activations in the decline group were identified with multiple linear regression. The correlation is shown in Figure 10.7.

Figure 10. 7.

The Correlation between Predicted and Actual ATL LI

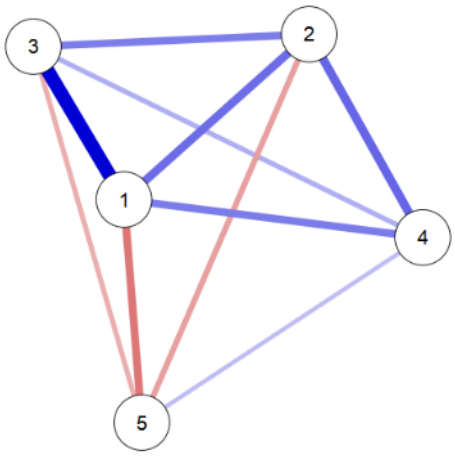
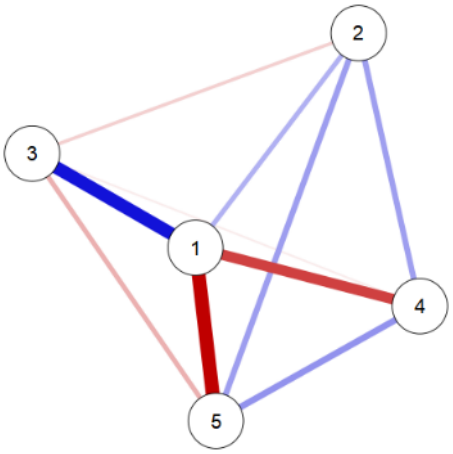


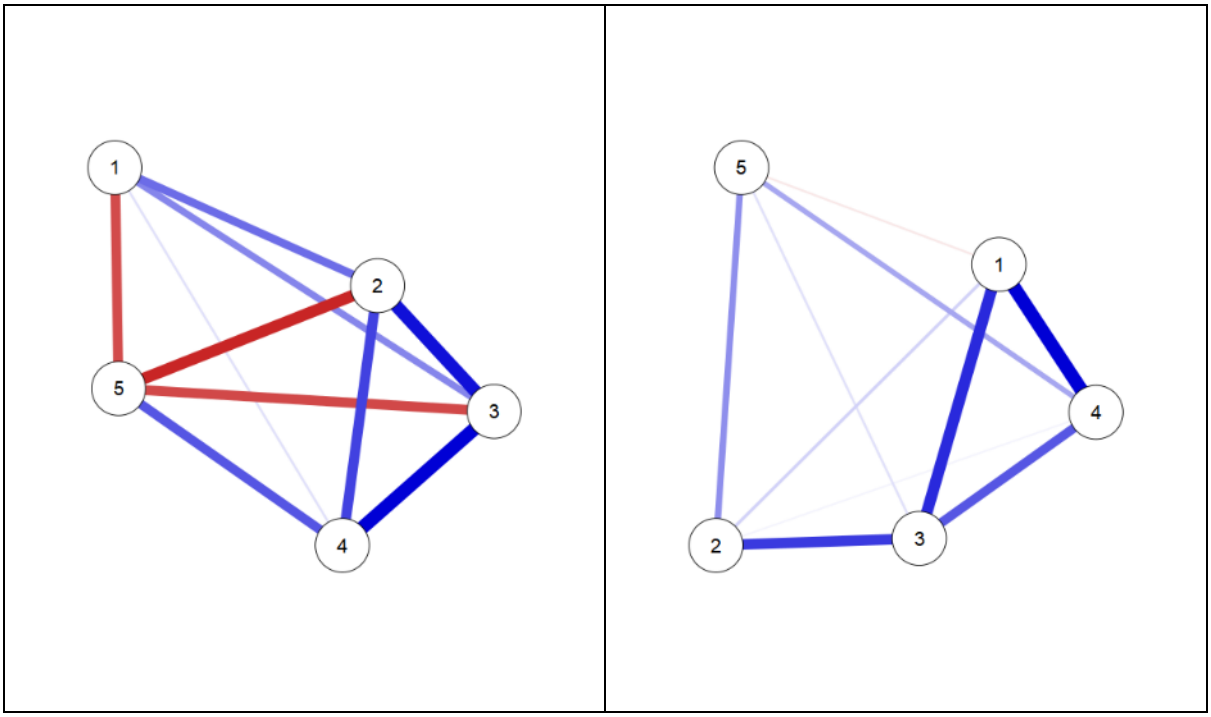
Note. The correlation is based on the linear combination of activations in the PTL, task ICN 16 and rest ICN 8 in seven patients with significant naming decline.

Task ICN 12 was included in descriptive network graphs based on significant ATL covariates (ROIs) and showed that the greatest difference between the groups related to ATL connectivity with the PTL (Figure 10.8). Both groups were preoperatively predominantly atypically lateralised for PN in the ATL with different connectivity patterns with task ICNs 16, 12, the PTL and rest ICN 8. Post operatively the remnant of the ATL showed greater connectivity with the PTL for both groups; the decline group with the left lateralised PTL and the no decline group with the atypically lateralised PTL.

Figure 10. 8.

PN Connectivity with the ATL described by Unthresholded Correlation Networks

pre-operative	post-operative
	



Note. Top: Decline group; Bottom: No decline group.
Networks: 1. ATL; 2. task ICN 12; 3. task ICN 16; 4. PTL; 5. rest ICN 8. Blue is positive correlation indicating ipsilateral connectivity. Red is a negative correlation indicating contralateral connectivity. The width of edges is indicative of the strength of correlation

Discussion

Summary of main findings

Language fMRI was used to identify engagement of anatomical and ICN ROI in TLE patients preoperatively and four months after ATLR. Activation in sensitive ROIs predicted post-operative language change. Positive predictive value for significant decline was seen in temporal lobe ROIs for naming and fluency tasks. Greater positive predictive value was seen where ROIs were employed to provide joint probability:

A greater decline in semantic fluency was significantly correlated with greater left activations in the ATL, the PTL, task ICN 1 and 12. Left activation in both the PTL and ATL, and both the PTL and task ICN 1, provided greater predictive indices of significant fluency decline. PPV for significant decline in phonetic fluency was associated with left activation in task ICN 16. Prediction based on a left lateralised index in both the PTL and

task ICN 12, compared to prediction based on LI in one or the other ROI provided greater predictive indices of significant postoperative naming decline after left ATLR.

There was a significant association between pre-operative LI and magnitude of predicted post-operative language change. Observed effects showed an increasing likelihood of significant decline with greater magnitude of left LI for naming, VF and SF.

Difference in organisation of language involving multiple ROIs was seen between LTLE patients prior to surgery: Multiple ROIs that significantly accounted for ATL activation in the LTLE group with significant naming decline were not seen in the group without naming decline and unthresholded connectivity graphs showed pre to post changes in connectivity involving ROIs with positive predictive value.

Prediction

Prediction was seen for naming and fluency in temporal ROIs. While greater activation was not predominantly seen in ICNs compared to the ATL (see Chapter 8), ICN activation contributed to predictive sensitivity and specificity of naming and fluency decline, indicating a crucial role for support networks in retaining language competence following ATLR.

Our results are not concordant with a correlation between higher preoperative performance and greater decline (Davies et al., 2005). Consistent with positive predictive values identified for the PTL and task ICN 12, clinically significant differences in lateralisation were seen: Patients that suffered significant decline were left lateralised in these ROIs whereas patients who did not suffer decline were atypically lateralised.

Dose-response analyses showed that LI =.2 in task ICN 12 alone, corresponded to a 45%, and LI =.2 in the PTL alone to a 44% probability of significant naming decline. An association between pre-operative LI and magnitude of predicted post-operative naming

decline is consistent with effects reported for a larger cohort that included patients groups in which the current results were obtained (Trimmel et al., 2019).

Left activation in the PTL predicted significant naming decline in one left-handed RTLE (non-lesional) patient, and left activation in task ICN 12 predicted significant decline in one right-handed patient with hippocampal sclerosis. The lateralised activations are consistent with Wada test results seen in a cohort of 100 MTLE patients that showed left-sided speech for 76% of the left-sided and 100% of the right-sided MTLE patients (Janszky et al., 2003). The results are in line with postoperative evaluations conducted at median of 6 months of 454 left and 421 right TLE patients, in a retrospective study that excluded left-handed patients: It showed that 5% (CI ± 2%) of RTLE patients who were left-hemisphere dominant for language on fMRI or Wada testing demonstrated clinically meaningful declines in confrontation naming compared to 38% (90% confidence interval [CI] ± 4%) who had left sided surgeries (Busch et al., 2016). Seizure related activity and associated disruptive effects are compatible with shifts in laterality (Janszky et al., 2003; Janszky et al., 2006). Cross dominance was seen in individual patients (Chapter 9). The likely influence of disease factors, indicated by handedness, and suggested by disease duration (43yrs) and a high average number of monthly seizures (120) in the right-handed RTLE case, are likely to account for interhemispheric shifts and greater contralateral connection with posterior temporal lobe networks that support crucial naming functions. It is akin to the mechanism postulated for a small group of LTLE who had post-surgical scanning and significant decline (see below) which showed greater and functionally ineffective contralateral ATL connectivity with the PTL - as opposed to the functionally effective ipsilateral connectivity seen in patients without decline.

The hypothesis that greater disease burden and right lateralised activation in posterior temporal networks constitute lesser vulnerability to decline after left ATLR in LTLE whereas

greater disease burden and left activation confer a greater risk of decline in RTL should be investigated in further studies.

Significant decline in naming was not accompanied by decline in either VF or SF, and significant decline in both SF and VF was seen only in one RTLE patient. Our results undergird requirement for comprehensive evaluation of language function to achieve clinically relevant prediction.

IQ and pre-operative language proficiency

While disease features are likely to have contributed to lower preoperative IQ and language scores particularly in the LTLE group (see Chapter 9), there was not a significant impact for disease features or presurgical language proficiency (and by proxy IQ), on the extent of pre to post clinical language after ATLR. It is consistent with available data (Chelune et al., 1993) that indicate more frequent positive Full Scale IQ changes for LTLE compared to RTLE patients following surgery, (whereas negative changes general and verbal memory indexes were more common for the LTLE patients compared RTLE) (Chelune et al., 1993).

Acute, short- and longer-term post operative language impairment

Comparison of surgery outcomes in children and adults with medically refractory epilepsy have shown that both left-resected groups displayed a significant decline in neuropsychological status at three months post-surgery. While children reached their preoperative level one year after surgery, the left-resected adults were still significantly worse than at the time of their preoperative examination (Gleissner et al., 2005). These results suggest that adults are with deficits at four months are likely to retain significant deficits one year after surgery.

Pre- and post-operative network changes

Although clinically different patterns of lateralisation were evident between two small groups of LTLE patients with (n=7) and without significant decline (n=6) for whom post-surgical scanning was obtained, statistically significant differences between groups were not seen pre- or post-operatively. Multiple ROIs that significantly correlated with ATL activation in the LTLE group with significant naming decline was not seen in the group without naming decline and unthresholded connectivity graphs showed pre to post changes in connectivity, primarily involving the PTL and task ICN 12 that held PPV for naming decline. Postoperative language reorganisation has been observed in a number of studies (Backes et al., 2005; Bonelli et al., 2012b; Helmstaedter et al., 2006; Hertz-Pannier et al., 2002; Pataraia et al., 2005; Wong et al., 2009). While there was observation of sustained pre to-post operative patterns of lateralisation in most ROIs, pre- to post-operative interhemispheric shifts were seen for PN from atypical to left dominance (in rest ICN 7 and task ICN 16) for the decline group and left to atypical lateralisation (in rest ICN 9&10) for the no decline group.

These results are consistent with reorganisation to support function seen in the context of stroke (Saur et al., 2006), disease (Chapter 9), and after surgery but does not provide support for a greater likelihood of postoperative interhemispheric reorganisation in patients with pre-operative atypical language representation (Pataraia et al., 2005).
relevant prediction.

Pre to post-operative connectivity changes. PPV seen for SF in the ATL, PTL, and task ICN 1 and for VF in task ICN 16 was consistent with significant ATL connectivity seen for these paradigms (see Chapter 8).

Weak ATL connectivity for task ICN 12 and the PTL was reflected in unthresholded correlation graphs in patients that underwent ATLR which is consistent with the pattern seen

across patients and healthy controls (Chapter 8). Groups with and without naming decline showed greater post operatively connectivity with the PTL. This reorganisation towards better naming performance is partly in line with an association between better clinical naming and functional connectivity of left posterior temporal lobe networks in TLE (Trimmel et al., 2018).

Patients with decline, showed a stronger and functionally ineffective shift toward greater contralateral ATL connectivity with the PTL as opposed to the functionally effective ipsilateral connectivity seen in patients without decline. Post operatively preoperative patterns were retained and the remnant of the ATL showed weaker connectivity with task ICN 12 for both groups.

Neurobiological implications

The results are consistent with a greater risk of naming decline after ATLR compared to other aspects of language function (Davies et al., 1998; Saykin et al., 1995).

While verbal fluency tasks have been associated with frontal lobe language areas (Bonelli et al., 2012; Szaflarski et al., 2008; Woermann et al., 2003) predictive values for fluency paradigms were seen only in temporal ROIs. Although inferior frontal lobe activations have previously been implicated in naming performance in TLE (Bonelli et al., 2012) and showed involvement in the semantic naming network (Middlebrooks et al., 2017) only temporal networks were predictive of naming decline which is consistent with direct cortical stimulation studies that showed a predominant role for the temporal lobe in naming (Corina et al., 2010).

Naming deficits have been reported after language dominant hemisphere ATLR (Davies et al., 1998; Davies et al., 2005; Hermann et al., 1999; Seidenberg et al., 1998; Szaflarski, 2019; You et al., 2019). Although a role for verbal learning and memory has been established for the speech dominant hippocampus (Squire, 1992) it has also been implicated

in naming: A greater probability of atypical language representation has been observed for patients with left hippocampal sclerosis than for other pathologies (Weber et al., 2006) and a paediatric study that a hippocampal lesion was associated with a greater likelihood for reorganisation of language function (Liégeois, et al., 2004). A more recent study of 93 TLE patients confirmed a negative impact of hippocampal atrophy on language networks and naming performance regardless of hemisphere but an association with the frequency of atypical lateralisation was not seen (Lopes, 2019).

Descriptive data showed stronger connectivity between the ATL and PTL post operatively for both groups with greater activation but ineffective recruitment of the left PTL in decline patients and greater activation and effective recruitment of the right PTL in those that did not decline. For LTLE patients, regardless of pathology, pre-operative reorganisation to the left or right PTL determined naming outcome after ATLR.

Both groups were predominantly atypically lateralised for PN in the ATL which is a pattern that was seen in controls. Our results suggest that persistent naming impairment at four months is consistent with reorganisation and that prediction of naming such decline from preoperative levels is determined by preoperative interhemispheric reorganisation and post-operative intra-hemispheric reorganisation to posterior temporal networks – the PTL and task ICN 12. The results are partly in line with preservation of naming in patients with hippocampal sclerosis after ATLR which has been attributed to intra-hemispheric reorganisation, in particular to the posterior and inferior temporal regions (Hamberger, McClelland, et al., 2007).

In the group without decline efficient naming function was supported predominantly by the right ATL and the left PTL, preoperatively. Postoperatively, these patients relied on the recruitment of the right ATL and PTL for word retrieval, while patients with decline showed greater reliance on the left PTL. The results are consistent with the larger cohort

(Trimmel et al., 2019) in which activation of left fusiform gyrus during picture naming was related to greater postoperative naming decline in left TLE patients. While both the PTL and task ICN 12 demonstrated PPV, the greatest structural overlap between these posterior networks were seen in the left medioventral fusiform gyrus (see Appendix B) which implicate it as a crucial role in prediction (Trimmel et al., 2019). Cortico-cortical evoked potential results have in fact demonstrated bidirectional connection between anterior and posterior language areas in TLE patients with typical language distribution (Matsumoto et al., 2004). The relevance of posterior temporal language regions was demonstrated by stimulus interrupted object naming that also identified atypical posterior language regions (Trimmel et al., 2013). These included the area anterior to the junction of the rolandic and sylvian fissures, ITG, angular gyrus and temporo-occipital junction. The results indicated that reorganised language areas may involve shifts to cortex beyond the anterior—posterior language connection (Trimmel et al., 2013) which is consistent with diffusion tensor imaging results which show at least 20% of essential language processing sites were outside white matter fibre terminations from the Broca's area (Ellmore et al., 2009).

Our results did not identify mechanisms for preoperative reorganisation: A significant association between an earlier age of onset (Chapter 8) and atypical lateralisation was seen for VF in task ICN 5 as well as shifts in laterality compatible with underlying seizure related activity (Janszky et al., 2003; Janszky et al., 2006) suggested by a higher number of AEDs (Chapter 8) in ROIs with predictive value for naming decline (the PTL and task ICN 12) conflicts with comparison of disease burdens that showed no difference between LTLE patients with and without decline. We demonstrated post-operative naming deficits in right handed patients with right TLE (one case with hippocampal sclerosis and one non-lesional) which may result from crossed lateralisation in the context of preoperative reorganisation (Gaillard et al., 2004). Both cases were strongly right lateralised for AN in the ATL and PTL

which indicate the potential value of this paradigm in prediction. The non-lesional case was atypically lateralised in task ICN 12 but highly left lateralised for PN in the ATL and PTL. The hippocampal sclerosis case was atypically lateralised for PN in the ATL and PTL but left lateralised in task ICN 12. Individual difference not represented in groups observations (see Chapter 9) and the post-operative naming deficits seen in righthanded patients with right TLE indicate the clinical value of patient specific profiles in neuroimaging analysis for the prediction of both seizure and language outcomes following surgical interventions.

Conclusion

In this chapter I elaborated patterns of connectivity in TLE patients discussed in Chapter 8 and the impact of disease features in Chapter 9 in reorganisation and prediction of language decline following ATLR. We showed the pre-eminent role of preoperative reorganisation and lateralisation in predicting naming decline after ATLR. The engagement of the contralateral posterior temporal regions defined by the PTL and ICN 12 following surgery was crucial to maintaining proficient naming following surgery whereas pre- and post-operative ipsilateral engagement of these regions predicted significant decline. The implication is that reorganisation prior to and within four months of speech dominant ATLR to the ipsilateral hemisphere is less effective. A further implication is that an earlier age of onset determines effective reorganisation to the contralateral hemisphere.

Five language paradigms and neuropsychological assessment pre- and postoperatively were employed to investigate the predictive utility in relation to language decline following ATLR. We showed PPV and NPV for anatomical and ICN ROIs. PPV of 80% was demonstrated for employing both the PTL and task ICN 12 as predictors of naming decline. Considering previous studies, the results suggest a significant role for preoperative reorganisation in the context of disease features, that is, relative lack of reorganisation

mediated by lower seizure frequency, later age of onset and shorter disease duration render greater risk of naming decline.

Clinical implications

Our results are consistent with findings (Sabsevitz et al., 2003) that support a crucial role for temporal lobe regions in predicting postoperative naming and fluency deficits after ATLR.

Cross paradigm sensitivity to significant language decline was not seen: Risk of either fluency or naming decline can be achieved with task specific paradigms and indices in multiple ROIs improved prediction. Given the PPV and the prevalence of naming decline, the use of naming paradigms in the presurgical work is essential.

The methods employed to predict postoperative decline in individual subjects used a lateralisation index in the anatomically defined ROIs and ICNs which can readily be applied in a clinical setting. The prominence of anatomical ROIs in prediction implies that the relevant language paradigms can be utilised in native space. Patients that were left lateralised in these ROIs were at risk of suffering a clinically significant naming and fluency decline after left ATLR. The results indicated that language activation in the nondominant hemisphere in some patients with epilepsy may contribute to language decline. Employing a combination of preoperative performance on the naming test and language lateralisation indices we were able to predict a clinically significant naming decline in all our patients with a positive predictive value of 80% at four months post-surgery.

While we observed significant language impairment postoperatively, four months after ATLR, the decline and subsequent recovery of other cognitive abilities such as memory has been found to stabilise within a two year window after surgery (Alpherts et al., 2006). Thus, decision on risks should take account of the fact that reorganisation and functional changes may continue over a longer time.

Strengths and limitations

This study has the advantage of comparing fMRI data and neuropsychological assessment before and four months after left or right ATLR employing task specific indices. This allowed study of the effects of surgery on function and task specific networks. Retrospective noise and movement artefact correction allowed for more accurate identification of language signal. We included healthy controls for repeat measures in relation to potential network changes and changes in performance. Overt task performance in the scanner allowed for observation of performance. Task specific analyses allowed for greater specificity. We considered preoperative performance, pathology and disease features in preoperative reorganisation and outcome. The predictive indices investigated are applicable to all patients having ATLR, regardless of language dominance and aetiology.

This study was limited by small numbers, heterogeneous pathologies and a priori defined region of interest analysis so that possible compensatory mechanisms in other brain areas were not assessed.

Assessment of clinical language changes among the surgical groups is complicated insofar it is potentially compounded by masked practice effects (Chelune et al., 1993) and in the absence of published practise effects and reliable change indices for TLE patients RC indices obtained in healthy controls were applied to patients groups. The range of scores obtained by a neurological population is likely to be different from that obtained by healthy adults (Bird & Cipolotti, 2007). However, practice effects in controls and patients are not inevitable: Test–retest reliability and practice effects in the British population for various verbal fluency tests, and specifically those employed in this thesis - for SF, the category animals , and for VF, the four categories (the letters ‘F’, ‘A’, ‘S’ and ‘B’), have shown that only around 60% of participants showed improvements in performance at second assessment (Harrison et al., 2000). For the naming test, practice effects of approximately one point have

previously been noted across participants independent of both age and estimated intelligence quotient (IQ) over a 1-month retest interval (Bird et al., 2004; Roberts, 2003). It is uncertain that this effect holds over a much longer interval of four months in controls – so that the practise effects for naming are likely to be less than one, particularly in patients with TLE. While the RCI for naming employed is consistent with the index used in comparable studies of language impairment after ATLR (Bonelli et al., 2012), the calculated RC indices employed are likely to be accurate insofar practise effects for the fluency tests are not inevitable and practise effects for naming are likely to have exhausted at four months.

Consideration of language decline did not include the impact of margins of ATL resection. Statistical power was particularly limited for network analysis insofar pre and post-operative fMRI was obtained in only 17 of the group of 26 patients who had pre and post-operative neuropsychometric testing. Quantification of decline using a visual confrontation task is not necessarily synonymous with a clinically significant decline. Auditory naming may be a more accurate measure of everyday and subjective naming difficulties. The AN task did not have a direct out of scanner analogue. The distinction was evident insofar AN activation was different from that seen for PN.

While observation of significant impairment in language function at a relatively early post operative period is likely to significant impact on social and occupation function and provide guidance to clinicians and patients, language reorganisation and recovery of function may continue well beyond a four-month period at which our patients were assessed postoperatively. That is, four months might be too early for compensatory responses to become fully functional and studies at a two-year window are likely to yield a comprehensive picture.

Preoperatively, we observed an association between greater drug load and poorer VF performance, and insofar there was a change in drug load in the pre-to post operative

assessment window it may have impacted VF scores and should be considered in future studies.

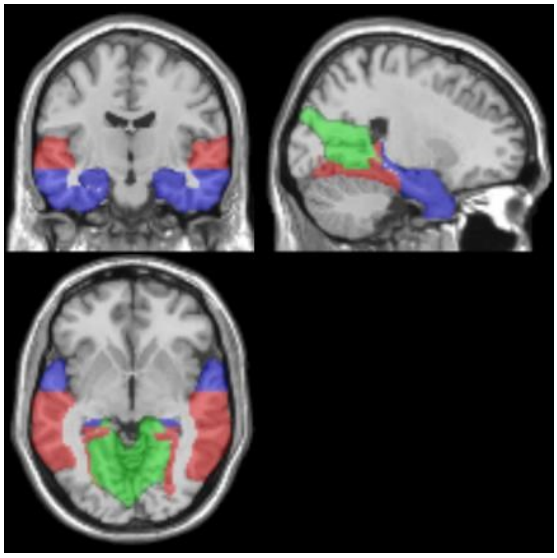
Findings were based on the analysis of left and atypical lateralisation as opposed to left, bilateral and right lateralisation. Results were obtained in standardised rather than native space. Thus, prediction based on group studies is compounded by single subject idiosyncrasies.

Appendix B

Anatomical overlap and differences between the PTL and task ICN12

Figure B.1

Anatomical coverage of the ATL, PTL and Task ICN 12



Note. ATL (blue), PTL (red) and Task ICN 12 (green), masks overlaid on single subject T1 volume according to neurological convention in MNI standard space.

Table B.1.

Anatomical overlap between the PTL and task ICN 12

	Anatomical and modified Cyto-architectonic descriptions	PTL voxels		Task ICN 12 voxels	
		Left	Right	Left	Right
PrG, Precentral Gyrus	*A4tl, area 4(tongue and larynx region)*	7	0		
STG, Superior Temporal Gyrus	*A41/42, area 41/42*	462	357		
	TE1.0 and TE1.2	457	231		
	A22c, caudal area 22	492	479		
	A22r, rostral area 22	189	188		
MTG, Middle Temporal Gyrus	*A21c, caudal area 21*	494	629		
	A21r, rostral area 21	8	1		
	A37dl, dorsolateral area37	495	715		
	aSTS, anterior superior temporal sulcus	544	684		
ITG, Inferior Temporal Gyrus	*A20iv, intermediate ventral area 20*	166	10		
	A37elv, extreme lateroventral area37	277	213		
	A20il, intermediate lateral area 20	179	73		
	A37vl, ventrolateral area 37	351	329		
	A20cl, caudolateral of area 20	487	395		
	A20cv, caudoventral of area 20	384	473		
FuG, Fusiform Gyrus	*A20rv, rostroventral area 20*	314	312	1	0
	A37mv, medioventral area37	677	673	139	13
	A37lv, lateroventral area37	721	752		
PhG, Parahippocampal Gyrus	*A35/36r, rostral area 35/36*	0	1		
	A35/36c, caudal area 35/36	106	64		
	TL, area TL (lateral PPHC, posterior parahippocampal gyrus)	149	127		

	A28/34, area 28/34 (EC, entorhinal cortex)	25	5		
	TH, area TH (medial PPHC)	69	92	44	41
posterior Superior Temporal Sulcus	*rpSTS, rostroposterior superior temporal sulcus*	289	324		
	cpSTS, caudoposterior superior temporal sulcus	343	281		
IPL, Inferior Parietal Lobule	*A39c, caudal area 39(PGp)*	2	451	46	0
	A40c, caudal area 40(PFm)	32	56		
	A39rv, rostroventral area 39(PGa)	494	592		
	A40rv, rostroventral area 40(PFop)	234	131		
PoG, Postcentral Gyrus	*A1/2/3tonIa, area 1/2/3(tongue and larynx region)*	100	30		
INS, Insular Gyrus	*G, hypergranular insula*	74	21		
	vId/vIg, ventral dysgranular and granular insula	13	0		
	dIg, dorsal granular insula	1	0		
CG, Cingulate Gyrus	*A23v, ventral area 23*	1	3	232	197
MVOcC, MedioVentral Occipital Cortex	*cLinG, caudal lingual gyrus*	8	2	225	127
	rLinG, rostral lingual gyrus	37	148		
LOcC, lateral Occipital Cortex	*V5/MT+, area V5/MT+*	104	551		
	iOccG, inferior occipital gyrus	73	82		
Hipp, Hippocampus	*rHipp, rostral hippocampus*	7	12	9	15
	cHipp, caudal hippocampus	219	153	137	104
Tha, Thalamus	*rTtha, rostral temporal thalamus*	19	0		
	Otha, occipital thalamus	6	0	29	38

Note. Human Brainnetome Atlas (Fan et al., 2016) - Anatomical reference of the PTL and task ICN 12

Chapter 11

ICN correlates of seizure networks and semiology: An EEG-informed fMRI Study

Abstract

Aims: The objective was to investigated the relationship between ictal semiology and the most involved brain areas (anatomical and ICN ROIs) in relation to seizure type and onset aetiology.

Methods: Ictal maps were normalised to MNI space in SPM12. A published atlasing approach to functional mapping that provides a range of metrics to capture variance in EEG-fMRI ictal BOLD maps was employed to assess network recruitment. T contrasts generated in a block design analysis of seizures were prepared and also allowed for assessing net recruitment (activations + deactivations) of ICN ROIs. An overall semiology score was established for each patient, with values of 0 (absence of sign), 1 (sign not always present) and 2 (sign always present). Thus, a matrix of clinical signs, encompassing 21 clinical signs scored 0–1–2 for each of the 18 patients, were obtained. A matrix of fMRI BOLD activation in 10 ICN ROIs (brain areas) and another comprising the fMRI BOLD activation in 246 cortical and subcortical ROIs (brain areas) for each of the 18 patients, constituting the EEG-informed haemodynamic activation during the ictal established phase were obtained. In a first analysis the significance of patient classification as defined by seizure type and aetiology were respectively investigated by hierarchical clustering of clinical signs. In a second analysis Kendall correlation was performed respectively on signs and ICN ROIs. These correlation matrices were used to compute dissimilarity matrices and to perform automatic hierarchical cluster analysis of correlated ROIs and clinical signs respectively. Kendall correlation was used to assess association between signs and individual ICN ROIs. In a third analysis, the contribution of multiple ICN ROIs to clinical signs was investigated: Principal component analysis (PCA) was performed on a matrix of clinical signs and ICN ROIs and elaborated with hierarchical clustering and value tests to identify groups of homogenous patients, their distinguishing clinical features and the associated ICN ROIs. In a fourth analysis, principal component analysis (PCA) and hierarchical clustering was performed on a matrix of clinical signs, ICN and anatomically defined ROIs to identify the involvement of ICN ROIs relative to anatomical areas in the context of associated clinical features. Finally, multiple factor analysis was employed to investigate the relationship between impairment of awareness and groups of ROIs.

Results: Large movement artefacts were observed in two cases (patients #6 and #10 in Chaudhary et al 2012) for which high resolution EPI images were not acquired. These cases were excluded and provided a total of 18 patients for analyses. Classification of patients by seizure type was significantly associated with the broad spectrum of clinical signs and with deactivation in brain areas. ICN ROIs were less prominent than anatomically defined ROIs and were recruited along an anterior-posterior axis. Clinical signs were associated with seizure networks that showed varying levels of haemodynamic activation and deactivation involving multiple ICN and anatomically defined ROIs, including cortical and subcortical areas that showed varying degrees of connectivity.

Conclusions: Impairment of consciousness and GTCS are significant distinguishing features in classifying patients based on clinical signs. Seizure type is significantly associated with deactivation of brain areas. Beyond its practical importance, impairment of awareness serves as a significant classifying feature of clinical expression with a neural basis associated with the inhibition of normal brain functions. Canonical ICNs including the DMN are not a meaningful framework for the study of seizure spread and ictal semiology. Clinical signs are associated with transient networks that comprise varying degrees of activation, deactivation and idiosyncratic connectivity across cortical and subcortical areas. Characterisation of seizure networks and semiology with EEG-fMRI is possible and may be an important tool in the presurgical workup.

Treatment of patients with epilepsy relies on the sensitivity and specificity of methods that characterizes the nature of epileptic networks together with the location of epileptic discharges. EEG-fMRI has been used to map haemodynamic networks in the context of cognitive function, resting state networks as well as interictal and ictal discharges-related activity such as seizure semiology. In this chapter I report investigation of haemodynamic correlations of typical seizure patterns in a group of 18 patients and report on its relationship with typical semiology.

Classification of the epilepsy syndrome together with the aetiology, determines treatment and prognosis, including the choice of pharmacological treatment (Benbadis & Luders, 1996). Ictal semiology appears to result from ictal propagation in areas both close to and remote from its origin (Chauvel et al., 1995) and represents an important behavioural data source providing clues to cerebral organization of the seizure network (McGonigal, 2020) which has long been used to classify epileptic seizures and epileptic syndromes. It represents a cost effective tool that allows localization of the symptomatogenic zone which either overlaps or is in close proximity of the epileptogenic zone (Tufenkjian & Luders, 2012) that plays an important role in the pre-surgical workup for patients with severe, drug-resistant epilepsy (Luders et al., 1993) (see overview in Chapter 1) particularly when analysed independently of other pre-surgical tests such as EEG monitoring and neuroradiology (Luders et al., 1993).

Localisation of the epileptogenic zone is critical for successful surgical intervention but substantial difficulties have been encountered in attempts to reliably localise seizures on clinical grounds (Manford et al., 1996), insofar the relationship between observed patterns of semiological and sub lobar localisation remains somewhat unclear (Bagla & Skidmore, 2011; Bonelli et al., 2007; Kotagal et al., 2003; O'Muircheartaigh & Richardson, 2012). Seizures with similar semiology could involve neuronal activity in the same brain networks

(O'Muircheartaigh & Richardson, 2012), although semiology patterns may not consistently relate to seizure onset in a specific region (O'Muircheartaigh & Richardson, 2012; So, 2006) or could result from idiosyncratic propagation pathways (Bonini et al., 2014).

In this work, I sought to identify networks, specifically ICNs, that are associated with semiology. The main aim of this study was to explore the role of canonical ICNs in seizure semiology and classification: An EEG-FMRI dataset comprised of patient with seizures onset in different regions as previously determined by EEG was employed to investigate ictal patterns associated with typical semiology. Analyses were conducted to investigate the relationship between typical semiology and ictal discharge as reflected in EEG informed haemodynamic correlates of activation (i.e., the BOLD signal – see Chapter 4), during the appearance of clinical signs in 1) intrinsic connectivity network areas, and 2) anatomically defined cortical and subcortical areas.

The main questions aimed to: (1) establish whether there is a relationship between classification by seizure type and/or seizure onset aetiology and the broad spectrum of clinical signs; and to (2) characterise the nature of ICN ROI involvement in the seizure network and clinical signs arising from it.

Methods

Participants

Images and clinical data of 20 patients with drug resistant epilepsy aged 18 – 60 years, who had participated in a study that mapped preictal and ictal haemodynamic networks using video-electroencephalography and fMRI (Chaudhary et al., 2012) were analysed. All 20 patients were reported to have 'typical seizures' during scanning: In 9/20 cases, semiology that were deemed to be unusual or potentially atypical were noted and described. Data from two patients were excluded (see Image normalisation below).

Acquisition of data

Of the 20 cases that were studied, six had frontal lobe epilepsy, four had focal reflex, four had multifocal, two had temporal lobe, two had parietal lobe and two had hypothalamic seizures. The seizures were identified on video-EEG in 15 of 20 patients (75%), on EEG only in two of 20 patients (10%, technical video failure) and on video only in three of 20 patients (15%, no ictal EEG change or EEG obscured by myogenic artefact). All 20 cases were reported to have 'typical seizures' during scanning: Specifically, 16 cases had spontaneous seizures and in four cases the seizures were triggered. In 13 of 20 patients (65%), distinct ictal phases could be identified, and the remainder had a single ictal phase. In 9/20 cases, the investigator noted and described semiology that were deemed to be unusual or potentially atypical. Subsequently, video-EEG recorded during video-EEG–functional MRI was reviewed jointly by the investigator and three experienced neurophysiologists to identify IEDs and ictal rhythms and semiology and compared with long-term video-EEG monitoring (Chaudhary et al., 2012). The authors proposed that the availability of synchronous video (Chaudhary et al., 2010) helped to identify and model the fMRI changes associated with non-epileptic physiological activities. Thus, a range of activities, including spontaneous eye movements and blinks, head jerks, voluntary chewing and speech, facial twitches, swallowing, coughing, yawning and brief hand or foot movements were differentiated from ictal semiology by comparing them with the patient's habitual seizure semiologies recorded during the long-term video-EEG recordings. These activities were included in the fMRI design matrix to explain a greater amount of nuisance variance in the functional MRI data, with consequent increased sensitivity to the effects of interest (i.e., seizures).

Semiology

While different types of seizure patterns have been identified (Wendling et al., 1996), the patient's habitual clinical seizure type out of the hospital have the most importance

in determining diagnosis, and aiding presurgical planning (Britton et al., 2016): Out of scanner clinical history, specifically semiology associated with typical seizures, was identified in patients' clinical records and relevant research protocols by a neurologist, Dr Jacopo Fantini. The signs were translated to correspondent labels and semiological categories that were employed in a previous study (Bonini et al., 2014) in which FLE patient groups were identified according to semiological features and anatomical seizure localisation correlates. Two descriptions of observations that could not be represented in the Bonini taxonomy were not included in the analysis ("wiping nose with left hand" and "may evolve automatism with vacant expression"). Conversely, two new categories of signs observed in patients (namely "gelastic seizure" and "loss of tone") that were not represented in the Bonini study were included. Analysis was conducted on a seizure phase that was defined by the manifestation of clinical signs (see below).

Data processing

MRI acquisition, video-EEG and data processing was described in the relevant study (Chaudhary et al., 2012): A range of methods for identification (Glover et al., 2000; Liston et al., 2006) and removal (Perlbarg et al., 2007) of physiological compounds and respiration related signals, (Birn et al., 2006; van Houdt et al., 2010) have been employed and EEG-fMRI studies of IEDs (Glover et al., 2000; Liston et al., 2006) and alpha rhythms (van Houdt et al., 2010) have shown that inclusion of these additional regressors as confounds improves sensitivity. In addition, cardiac effects have also been modelled in fMRI analysis of seizures (Thornton et al., 2010). Thus, as noted above Chaudhary and colleagues included as thorough a model as possible. It included the effects of motion, and physiological confounds such as pulse on the fMRI signal to avoid false positive findings and to optimise specificity of the observed BOLD signal changes in relation to neural activity.

Chaudhary and colleagues separated seizure onset related BOLD changes from those during propagation by comparing seizures recorded during vEEG-fMRI with the seizures recorded during long-term video-EEG monitoring. In turn, these were partitioned into phases based on spatiotemporal evolution of electrophysiological changes on EEG and ictal semiology on video. The ictal phases were defined as follows: *Ictal onset*: build-up of ictal-EEG-pattern preceding clinical features. *Ictal established*: onset of the clinical manifestations along with regional/generalised EEG changes or emergence of myogenic artefact on EEG. *Late ictal*: subsequent EEG slowing following the *Ictal established* phase. *Pre-ictal phase*: comprising the 30 seconds that immediately precede electrical onset.

In the relevant study (Chaudhary et al., 2012), seizures that did not have a specific electrographic signature and for which the ictal phases could not clearly be separated were labelled as a single *Ictal* phase. Seven patients' seizures were labelled as a single ictal phase. These were seizures for which the ictal phases could not be separated because of myogenic artefact on EEG, or for cases where seizures did not have an electrographic signature (e.g., simple partial seizures; Smith, 2005).

Contrasts and thresholds for assessment of activation in ROIs

SPM[T]-maps. Chaudhary (2012) prepared and obtained results using SPM [F]-maps in native space based on regressors convolved with the HRF and its time and dispersion derivatives for the early, established and late ictal phases, respectively. Insofar SPM [F]-maps provide activations suited to analysis of thresholded maps I defined T contrasts for onset, ictal established and late ictal phases within the SPM framework using the canonical HRF convolved with seizure phases marked on EEG to allow assessment of ICN deactivations. This allowed for the observation of both activation and deactivation as well as calculation of net recruitment of ICN in the resultant statistical image.

Image normalisation

Insofar atlasing analysis is conducted in MNI space I normalised the EPI time series (Collins et al., 1994). To obtain optimal correspondence with activations in native space I normalised the statistical images that were obtained in native space using the unified segmentation algorithm in SPM8 and employing the patient's own anatomy or an high resolution EPI as an input parameter (Crinion et al., 2007) since normalising EPI to EPI template matches the course anatomical brain shape but does provide a detailed account of local morphology. Unified segmentation based normalisation (Ashburner & Friston, 2005) provides greater precision but requires a good anatomical reference scan. In this regard, different strategies were employed for normalisation of the time series. First, the structural image (T1) was co-registered to the mean EPI 2) and normalisation parameters were determined for the T1 (via unified segmentation) which was then applied to the EPI time series (statistical maps). The advantage of this procedure is that accuracy is improved since the T1 provides much more spatial details (good contrast between grey matter, white matter and cerebrospinal fluid) which improve the normalisation. Segmentation and normalisation results were checked manually for every subject. The results showed that this approach, in some cases, led to the identification of substantial EPI deformations in the entire image - especially in temporal and orbitofrontal areas. Thus, the distortions of the two modalities (T1 weighted images vs. T2* weighted images) are different so that normalisation parameters from the structural image do not provide optimal accuracy for transforming EPI images into standard MNI space. In these cases unified segmentation was used on the mean EPI directly, using the available high resolution EPIs to separate grey matter and white matter in an approach akin to that used in other studies (Neggers et al., 2012). Accordingly, the unified segmentation procedure was applied directly to the mean EPI which provided normalisation parameters for the time series. fMRI images were normalised to MNI template space using

these parameters. In this procedure rigid body co-registration of the fMRI time series images to the 'whole brain EPI scan' is optimal because the whole brain EPI scan has the same spatial distortions as the fMRI images acquired during acquisition. Normalisation includes non-linear local transformations and is thus well able to correct for these spatial distortions when transforming the fMRI images to MNI space. Thus, new MNI space images with 2x2x2mm resolution for use with the ICN_atlas script were written preserving concentrations and using a trilinear interpolation. The largest movement artefact in the series was observed in two cases (patients #6 and #10 in Chaudhary et al 2012) for which high resolution EPI images were not acquired. These cases were excluded from analyses and provided a total of 18 patients for analyses.

Table 11. 1

Patients' Clinical Features

ID #	***ID #**	**Seizure type and (seizure onset aetiology)**	**Focal seizure onset on scalp-EEG**	**Structural MRI findings**	**Seizure onset zone**	**Typical semiology**
1	18	FIAS (Reflex)	Left fronto-temporal	Non-lesional	Left fronto-temporal	non-localised aura; vocalization; distal stereotypies. elementary motor signs; impairment of consciousness
2	12	FIAS (Reflex)	Regional fronto-central with left emphasis	focal cortical dysplasia: left paracentral lobule	Left frontal lobe	ipsilateral versive signs; elementary motor signs; rictus/asymmetric facial contraction; distal stereotypies;

						Loss of tone; manipulation/utilisation; impairment of consciousness
3	1	FIAS (PLE)	Regional right parieto-occipital	Multiple tubers: largest right parietal	Right parieto-occipital	non-localised aura, speech arrest; autonomic signs, staring/behavioural arrest, impairment of consciousness
4	14	FAS (Hypothalamus)	Non-localisable/lateralisable	Hypothalamic hamartoma	Hypothalamus	gelastic seizure
5	17	FAS (FLE)	Regional right centro-parietal	focal cortical dysplasia: right MFG + precentral gyrus	Right frontal lobe	contralateral versive signs; proximal/distal contralateral tonic posture; rictus/asymmetric facial contraction; elementary motor signs
6	20	FIAS (Hypothalamus)	Non-localisable/lateralisable	Hypothalamic hamartoma	Hypothalamus	non-localised aura; rictus/asymmetric facial contraction; autonomic signs; impairment of consciousness

7	19	FAS (PLE)	Regional right parieto-central	focal cortical dysplasia: right parietal-angular gyrus	Right parietal lobe	somesthetic localised aura; proximal/distal contralateral tonic posture; contralateral versive signs; symmetric proximal/axial tonic posture; elementary motor signs
8	16	FIAS (FLE)	Regional left fronto-central	focal cortical dysplasia: left posterior SFG + MFG	Left frontal lobe	contralateral versive signs; elementary motor signs; impairment of consciousness
9		FIAS (Multifocal)	Non-lateralised fronto-central	MCD: left frontal + parieto-temporal	Left frontal and parietal	somesthetic localised aura; proximal/distal contralateral tonic posture; vocalization; asymmetric tonic posture; contralateral versive signs; elementary motor signs; distal stereotypies; positive emotional/affective

						expression; impairment of consciousness
10	13	FIAS (FLE)	Max. right fronto-central	Non-lesional	Right frontal lobe	staring/behavioural arrest; impairment of consciousness; symmetric proximal/axial tonic posture; asymmetric tonic posture
11	2	FAS (Reflex)	Regional left centro-parietal	Non-lesional	Left centro-parietal	proximal/distal contralateral tonic posture; elementary motor signs
12	4	FIAS (TLE)	Regional left temporal	Non-lesional	Left temporal lobe	non-localised aura; staring/behavioural arrest; distal stereotypies; manipulation/utilization; proximal/distal contralateral tonic posture; impairment of consciousness
13	8	FIAS (Multifocal)	Multi-regional	Right polymicrogyria and schizencephaly	Right hemisphere	elementary motor signs; symmetric proximal/axial tonic posture; contralateral versive

						signs; impairment of consciousness
14	3	FIAS (Multifocal)	Lateralised left hemisphere	focal cortical dysplasia: left parieto-occipito-temporal	Left parieto-occipito-temporal	non-localised aura; proximal/distal contralateral tonic posture; contralateral versive signs; vocalization; asymmetric tonic posture; impairment of consciousness
15	15	FIAS (TLE)	Lateralised left max. fronto-temporal	Non-lesional	Left temporal lobe	ipsilateral versive signs; elementary motor signs; distal stereotypies; staring/behavioural arrest; negative emotional/affective expression; proximal/distal contralateral tonic posture; impairment of consciousness
16	11	FIAS (FLE)	Max. right frontal	Ischaemic damage: right hemisphere	Right frontal lobe	staring/behavioural arrest; contralateral versive signs; impairment of consciousness

17	7	FIAS (FLE)	Max. fronto-central	Non-lesional	Midline fronto-central	staring/behaviour arrest; impairment of consciousnes; asymmetric tonic posture
18	9	GTCS (Reflex)	Non-lateralised (fronto-central)	Non-lesional	Medial hemisphere	somesthetic localised aura; proximal/distal contralateral tonic posture; elementary motor signs; contralateral versive signs; asymmetric tonic posture; ispilateral versive signs; generalised tonic-clonic seizure; impairment of consciousness; elementary motor signs

Note. Table adapted and elaborated from *Chaudhary et al. 2012.

FLE = Frontal lobe epilepsy, PLE = Parietal lobe epilepsy, TLE = Temporal lobe epilepsy. Multifocal = multifocal, Reflex = Reflex seizure. FAS = Focal aware seizure, FIAS= Focal impairment of awareness seizure, GTCS = Generalised tonic clonic seizure.

Measures of BOLD engagement

Selection of ICN_atlas metric**.** Factor analysis as described in the chapter on common methodology (Chapter 5) was conducted across all ictal phases for all patients and reported in Chapter 6. It was conducted separately for activations, and deactivations as well as the net engagement of ICN ROIs and used to identify the most informative ICN_atlas metric.

Quantification of ROI engagement. The level of activation within each ICN ROI (region of interest) and anatomical ROI as quantified using ICN_atlas was summarised respectively by the selected metric.

ROIs and electroclinical features**.** Clinical features, namely, type of epilepsy, focal seizure onset on scalp-EEG, structural MRI findings as well as seizure onset zone as reported by Chaudhary (2012) are listed in Table 11.1.

In addition, to the details provided by Chaudhary and colleagues, and to analyse the clinical features associated with ictal activity on EEG in the a priori defined ROIs, that is, the ictal clinical signs associated with ROIs, each patient's clinical history, contained in reports and letters, together with records of semiology during simultaneous EEG-fMRI recording of seizures in the scanner were examined (as described in Chapter 5). Review of the patient history allowed for assessment of reproducibility of the clinical pattern for each patient's seizures, so that an overall semiology score, was established for each patient, with values of 0 (absence of sign), 1 (sign not always present) and 2 (sign always present). A list of typical ictal signs and the seizure type for each patient (Table 11.1) was compiled as described in Chapter 5 – common methods: Seizure type, namely, focal seizures with no impairment of awareness, focal seizures with impairment of awareness, focal to bilateral tonic clonic, was identified by the range of typical signs in each case**.** A matrix of clinical signs, encompassing 21 clinical signs and scored 0–1–2 (the columns in the matrix) for each of the 18 patients (the rows in the matrix), was obtained.

Secondly, matrices, comprising the fMRI BOLD activation and deactivation in ICN ROIs constituting the EEG-informed haemodynamic activity during the ictal established phase (defined by the onset of the clinical manifestations along with regional/generalised EEG changes or emergence of myogenic artefact) time-window (and correlated with the spectrum of semiology for all patients in the series), were obtained: Three matrices comprising the activations, deactivations and net engagement in 10 ICN ROIs derived from resting state fMRI (Smith et al., 2009) were compiled. In addition, two matrices comprising the fMRI BOLD activations and deactivations in 246 cortical and subcortical ROIs of the human Brainnetome Atlas (BNA) (brain areas) (Fan et al., 2016) for each of the 18 patients, were obtained.

Statistical analyses

Principal component analysis

Principal component analysis (PCA) as described in Chapter 5 was conducted. In each dataset the significance of variance represented by the first components was assessed by means of the reference value provided by standardised PCA – specifically, the 0.95 quantile percentage of variance seen in simulated data: It tested the null hypothesis (which is a statement about observations that are accepted/rejected based on any specified mathematical probability) that the percentage of variance explained by the first component and the first plane (which refers to the spatial dimension created by the 1st and 2nd principal components) respectively was not greater than that seen for PCA of independent data composed of the same number of subjects (*I)* and the same number of normally distributed independent variables (*K)* (Husson, Lê, et al., 2010).

Where the first component accounted for significant variance, Wilks Lambda was employed on patient coordinates on the first plane to ascertain whether either seizure type and

epilepsy defined by seizure onset aetiology contributed most to the variance and whether these classifications distinguished significantly between patients.

Cluster analyses

To identify homogenous groups of patients that could distinguish significant clinical and brain features, the result of PCA was employed in agglomerative clustering (see Bonini et al., 2014) as described in Chapter 5 – Common methods. The optimal number of principal components used in the cluster analyses, was determined by Pearson correlational analysis of patient coordinates and clinical signs. The number of principal components (PCs) that showed significant correlation with clinical signs were included in the cluster analysis. In other words, the distances used in clustering were taken from the new variables (principal components) that showed significant correlations with clinical signs.

Hierarchical clustering using Euclidean distance and Ward's criterion was employed. As described in Chapter 5, Ward's criterion minimizes the total within-cluster variance and tends to produce clusters of equal size (Allen & Goldstein, 2013), which is suitable for conducting clustering on principal components (Husson, Julie, et al., 2010). Hierarchical clustering produces an indexed hierarchy (dendogram), that allows the levels at which the features are grouped together to be interpreted. The hierarchical trees were cut at the level of the greatest change in the index which constitutes a practical definition of a good partition (Lebart et al., 1998) and provided for greater homogenous clusters. Thus the evolution of the between-variance from one clustering to another was considered and the number of clusters for which the between-cluster variance was the greatest were retained as nodes in the cluster: Accordingly, the number of clusters (Q) to determine classification based on semiology and/or brain ROIs was determined by a division into Q clusters when the increase of between-inertia between $Q - 1$ and Q clusters was much greater than the one between Q and $Q + 1$ clusters (Husson, Julie, et al., 2010). Specifically, the sum of the within-cluster

variance was calculated for each cluster and the cluster division that showed the highest relative loss of variance (i(clusters n+1)/i(cluster n)) was retained. This division of the clustering tree, generally corresponds to the solution based on mere visual inspection (i.e., when merely looking at it) (Husson, Julie, et al., 2010). Fisher's test was used to examine the significance of the association of clusters with 1) seizure type and with 2) epilepsy defined by seizure onset aetiology (see Table 11.1).

Characterisation of clusters and cluster elements

For each variable in the clusters, test values (v.test) were employed. These are measurements of the distance between the within-cluster value and the overall value (Morineau, 1984), were derived from a normal approximation of the hypergeometric distribution, which is the probability distribution for sampling without replacement under the hypothesis of independence: That is, for each feature (i), such as clinical signs or ROIs, belonging to grouping (j), a test-value t(i, j) that measures the deviation between the relative frequency of the feature within group j relative to its global frequency calculated on the entire set of values, was established. This deviation was normalised, to be considered as a standardized normal variable under the hypothesis of random distribution: Thus the v.test corresponds to the quantile of the normal distribution associated with the hypergeometric probability value (Lebart et al., 2006): The test value represented approximate transformation of the test statistics to standard units and the sign of the test value served to indicate an over (high value) - or underrepresentation (low value) of any one feature or element in the cluster under consideration (Lebart et al., 2006). Stated differently, the test-value is the analogue of the value of a standardized normal variable, which is significant (at the 0.05 level) if it lies between the values <1.96 and >1.96 (Lebart et al., 1998) with the associated probability value corresponding to the hypothesis that the mean of the cluster is equal to the overall mean. It was used as the criterion to compare and rank in order of

importance the features most characteristics of a group/cluster. It provided a test of null hypotheses that related to the representation of features such as ROIs, clinical signs or seizure type in any one cluster.

Multiple comparisons

Correction for multiple comparisons (see Chapter 5 - Common methods) was performed by recording new statistics for each variable from 10 000 relabelled samples taken without replacement from the original dataset, followed by a two-sided test that computed the 95^{th} quantile which represented the values of the 0.05 alpha level. For Analysis two, simulation of 10 000 correlation matrices in R (R Core Development Team, 2017) were computationally prohibitive, so that Bonferroni correction was applied.

Analysis one. Clinical signs and patient classification by seizure type and aetiology

To assess the relationship between clinical signs and patient classification by seizure type and aetiology, the data was standardised (the data was centred, and values were divided by the standard deviation) and principal component analysis (PCA) was performed.
The significance of variance accounted for by the first components was assessed by the 0.95-quantile of a normal distribution obtained by simulating 2949 data tables of equivalent size (Husson, Lê, et al., 2010).

Wilks' test was performed to assess whether the bulk of variance as reflected by the first plane was significantly associated with patient classification based on seizure type and aetiology. It was elaborated with hierarchical clustering performed on the new patient coordinates provided by PCs that showed significant correlation with clinical signs. Fisher's exact test was employed to assess the association between groups of clinical signs and classification of patients respectively by seizure type and seizure onset aetiology.

To identify clinical signs that significantly distinguished between patients, v.tests were conducted to establish differences between the mean for signs belonging to one cluster

of patients, and the mean for signs belonging to all patients. The alpha level was adjusted for multiple comparisons by permutation testing.

Analysis two. Individual ICN ROI correlates of ictal semiology

Kendal correlations were performed to establish the association between a) clinical signs and b) haemodynamic (i) activations, (ii) deactivations in; and (iii) net engagement of ICN defined ROIs. The data in the correlation matrices (ictal signs by patients and ICN ROIs by patients) was scaled and dissimilarity matrices, using correlation as the distance, were computed, which in turn were used to perform automatic agglomerative hierarchical cluster analysis (R software version 2.13.1; R Core Development Team, 2013). The resultant hierarchical trees were cut at the level of the greatest change in the index as previously described. The two dendograms respectively showed patterns of clinical signs and brain areas (ICN ROIs), that is, clinical features and brain areas that commonly appear together during ictal discharge during the ictal established phase.

In a final step, Kendall correlation, Bonferroni corrected for multiple comparisons, was performed to assess the relationship between ictal symptoms and activations, deactivations in and net engagement of individual ICN ROIs, respectively. It allowed for the identification of any significant relationship between clinical signs and individual ICN ROIs.

Analysis three. The association of all ICN ROIs with clinical signs

To assess the association of all ICN ROIs with clinical signs and its relationship with patient classification, principal component analysis (PCA) was performed on clinical signs and ICN ROI engagement. Accordingly, a sign by ICN ROI matrix was constructed. Given different metrics, namely categorical data (0-1-2) for signs and continuous data for ICN ROIs, each variable (column data) in the data matrix was ranked, scaled and normalised (mean 0 and standard deviation 1). Thus, as described in Chapter 5, principal component analysis (PCA) was performed in order to convert all possibly correlated variables (signs and

ICN ROIs) into a smaller number of linearly uncorrelated variables (principal components). One-way MANOVA Wilks Lambda Wilks tests were employed on patient coordinates derived from the plane that accounted for most variance (i.e., the first 2 principal components) to ascertain whether the variance was significantly associated with patient classification based on seizure type and seizure onset aetiology.

It was elaborated with hierarchical clustering as described in the section on statistical analyses: the distances to be used in the clustering was taken from the components of the PCA that showed significant correlation with clinical signs. Thus, using the PCA derived patient coordinates a) a dissimilarity matrix (ictal signs by ICN ROIs), was computed which was used to b) perform automatic agglomerative hierarchical cluster analysis (R software version 2.13.1; R Core Development Team, 2013), using Euclidean distance and Ward's criterion, as described in Chapter 5. Fisher's exact test was used to examine the significance of the association of signs by seizure type and seizure onset aetiology.

As previously described, the clusters and its elements were characterised by considering the differences between the mean of variables belonging to patients in one cluster, and the mean for all patients belonging, expressed in units of standard deviation from the mean (v.test). The separate analyses of activation, deactivation and net engagement allowed for the evaluation of significant brain areas and clinical signs using intensities that were significantly greater or lesser than the respective mean activation, deactivation and net engagement. To accommodate and control for multiple comparison, permutation testing, was performed to adjust the alpha level (α=0.05) for each analysis. It identified the most typically involved ICN ROIs and the most characteristic clinical features, namely patient classification and clinical signs.

Analysis four. The relationship between ICN and anatomically defined ROIs during the ictal established phase

To assess the involvement of ICN ROIs with clinical signs relative to anatomically defined ROIs and any relationship with seizure type and seizure onset aetiology, data matrices as described in the section on statistical analyses were constructed: two data matrices – respectively comprising activations and deactivations - for sign by anatomical and ICN ROIs were constructed. The data was ranked, scaled and normalised (mean 0 and standard deviation 1). A two-dimensional PCA-model was used to impute values for missing data points (Josse & Husson, 2016). PCA as described in the methods were conducted. One-way MANOVA Wilks Lambda test was employed on patient coordinates derived from the first plane to ascertain whether the bulk of variance was significantly associated with either seizure type or epilepsy defined by seizure onset.

As previously described, PCA derived patient coordinates taken from the new variables (principal components) that showed significant correlations with clinical signs were used to compute a) dissimilarity matrices (ictal signs by anatomical ROIs and ictal signs by ICN ROIs) and used to b) perform automatic hierarchical cluster analysis based on Euclidean distance and Ward's criterion, with optimal clustering determined by between cluster variance (Husson et al., 2017).

Fisher's exact test was used to examine the significance of clusters in relation to classification by seizure type and epilepsy defined by seizure onset aetiology. V. tests, controlled for multiple comparison by permutation testing, were employed to characterise cluster elements. The separate analyses of activation, deactivation allowed for the evaluation of significant brain areas and clinical signs using intensities that were significantly greater or lesser than the respective mean activation and deactivation. It identified the involvement of

ICN ROIs relative to anatomical ROIs, features of connectivity and the characteristic clinical features.

Analysis five. The association of ictal engagement of brain areas with impairment of awareness

To explore the relationship between brain areas and impairment of awareness multiple factor analysis (MFA), a multi-table adaptation of PCA was employed: MFA prevents a single table from dominating the overall decomposition and variance and equalizes the contributions from the multiple tables by performing a preliminary PCA separately on each table and then dividing them by their own first singular value which amounts to scaling each table so that it can be compared against the others (Gonzenbach, 2019). MFA proceeds in two steps: First it computes a PCA of each data table and 'normalizes' each data table by dividing all its elements by the first singular value obtained from its PCA. Second, all the normalized data tables are aggregated into a grand data table that is analysed via a PCA that gives a set of new orthogonal variables (i.e., the principal components) so that the usual PCA indices can be computed to identify the important components, observations and variables (Abdi et al., 2013). The RV coefficient, a multivariate generalisation of the squared Pearson correlation coefficient (Robert & Escoufier, 1976), was used to evaluate the association between impairment of awareness and activations and deactivations in groups of ROIs.

ROIs were assigned to groups representing anatomic and functionally defined regions (ICN ROIs). The groups comprised subregions, namely ICNs (10), superior frontal gyrus (14), middle frontal gyrus (14), inferior frontal gyrus (12), orbital gyrus (12), precentral gyrus (12), paracentral lobule (4), superior temporal gyrus (12), middle temporal gyrus (8), inferior temporal gyrus (14), fusiform gyrus (6), para hippocampal gyrus (12), posterior superior temporal sulcus (4), superior parietal lobule (10), inferior parietal lobule (10), precuneus (10), postcentral gyrus (8), insular gyrus (12), cingulate gyrus (14), medioventral

occipital cortex (10), lateral occipital cortex (12), amygdala (4), hippocampus (4), basal ganglia (12), and the thalamus (16).

Results

General characteristics

Focal seizures with no impairment of awareness were characteristic in four patients, and focal seizures with impairment of awareness in 13 patients. One patient's seizures were characterised as focal to bilateral tonic clonic. For the whole group, impairment in consciousness was seen in 78% of cases, proximal distal contralateral tonic posture and elementary motor signs occurred in 44%, contralateral versive signs in 39%, staring behavioural arrest in 33%, asymmetric tonic posture and distal stereotypies in 28%, ipsilateral versive signs, non-localised aura, rictus asymmetric facial contraction, somesthetic localised aura, symmetric proximal axial tonic posture and vocalisation in 17%, manipulation utilisation and autonomic signs in 11%, gelastic seizure, generalised tonic clonic seizure, loss of tone, negative emotional affective expression, positive emotional affective expression and speech arrest in 6% of cases.

Selection of metric: Factor analysis

The results were reported in Chapter 6. While factor analysis identified two latent dimensions, these could not clearly be characterised in terms of spatial, intensity or density features (see Chapter 6). It showed that the normalised mean ICN activation density metric (I_i^M) metric captured most variance correspondent to neural activation across all ictal phases for activations, deactivations and net engagement in the ictal BOLD maps.

ICN ROIs and electroclinical correlations

Analysis one. Patient classification based on clinical signs

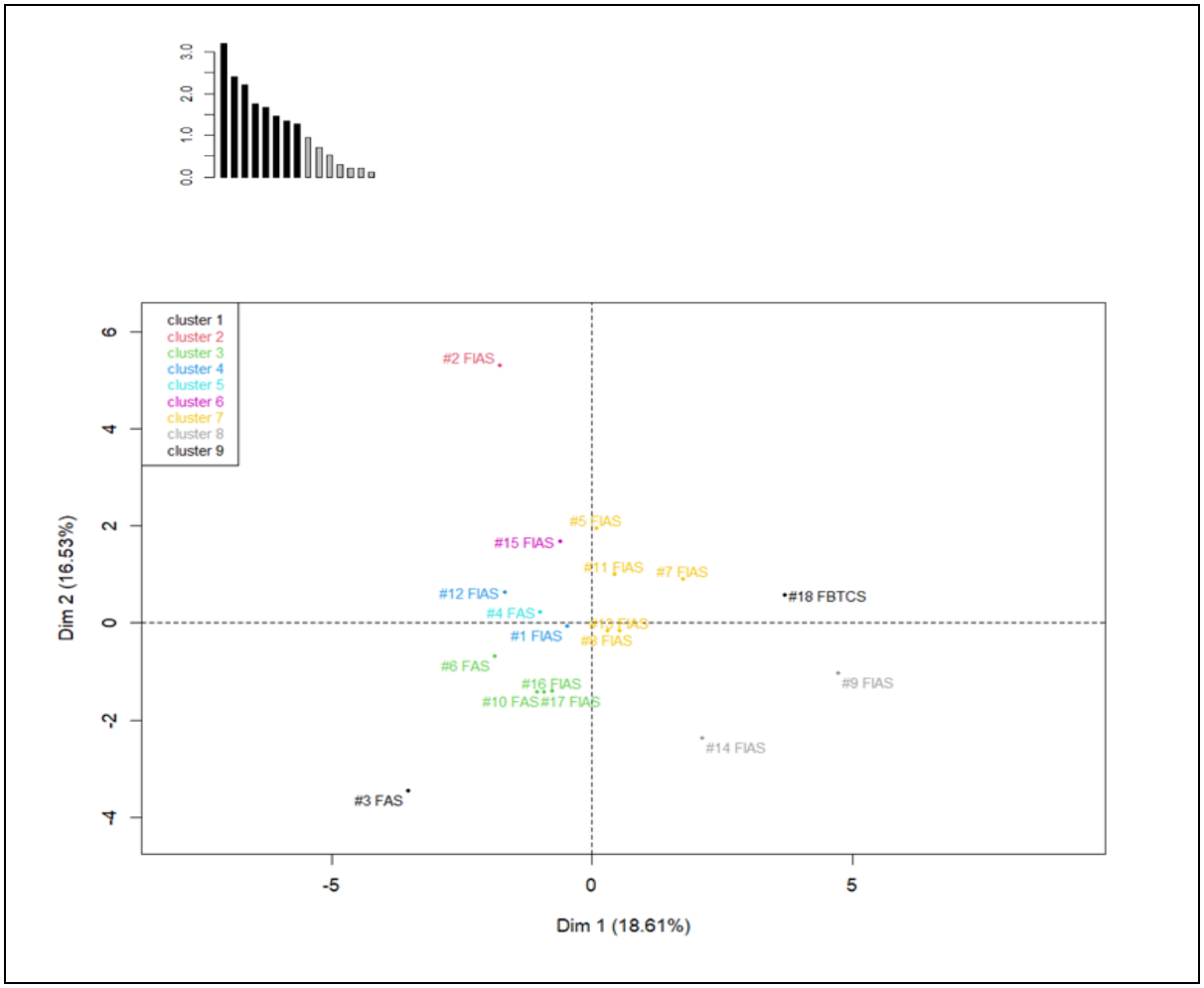
Variability expressed by the first plane of projection associated with PCA of clinical signs was not significant: The variance 35.14% observed on the first plane was smaller than

the reference value of 35.29%, and the variance projected on the first component was smaller than the reference value of 20.16%.

The first nine components of PCA (variance = 87.7%) accounted for significant correlation with all 21 clinical signs included in the study. Optimal clustering of signs as determined by the highest relative decrease in between-cluster variance yielded nine clusters. The factor map on the first two principal components and relative gain in variance associated with the nine-cluster solution are shown in Figure 11.1.

Figure 11.1.

Factor Map on the First Two Principal Components



Note. The gain in between-cluster variance (top left) and the factor map showing cluster membership of patients classified by seizure type relative to the first two principal components.

Patients' clinical signs were better characterised by classification based on seizure type compared to classification by aetiology (P = 0.086, Fisher's exact test) as implemented by Chaudhary and colleagues (Chaudhary et al., 2012). A significant association was seen between the range and frequency of clinical signs and classification by seizure type (P = 0.042, Fisher's exact test).

V. test results corrected for multiple comparison with permutation testing showed that significant classification of patients by seizure type was based on a significantly high presence/frequency of five clinical signs namely, speech arrest, loss of tone, gelastic seizure, negative emotional affective expression and generalised tonic clonic seizure and a significantly lower frequency of three signs, namely elementary motor signs, impairment of consciousness and proximal distal contralateral tonic posture.

Nine clusters of patients were distinguished: Cluster 1 comprised one FAS patient. In this patient speech arrest (v.tes t= 4.123) was significantly present compared to other patients and there was a relatively higher frequency of autonomic signs and non-localised aura relative to other signs. Cluster 2 comprised one FIAS patient, characterised by the significant presence of loss of tone (v.test = 4.123) and relatively higher frequency of manipulation utilization, ipsilateral versive signs and distal stereotypies compared to its presence in other patients.

Cluster 3 was made of two FAS and two FIAS patient that shared a high frequency of staring behavioural arrest, and significantly lower frequencies of elementary motor signs (v.test = -2.338,) and proximal distal contralateral tonic posture (v.test = -1.918). Cluster 4 comprised two FIAS patients, distinguished by a relatively predominance of distal stereotypies and non-localized aura compared to its presence in other patients.

Cluster 5 comprised one FAS patient distinguished by significantly greater presence of gelastic seizure (v.test = 4.123). Cluster 6 was comprised of one FIAS patient with

significantly greater frequency of negative emotional affective expression (v.test = 4.123) and relatively higher frequency of ipsilateral versive signs. Cluster 7 comprised a group of five FIAS patients, characterised by the combination of relatively higher frequency of elementary motor signs and symmetric proximal axial tonic posture and a significantly lower presence of impairment of consciousness (v.test = -1.982).

Cluster 8 comprised two FIAS patients distinguished by the greater presence of vocalisation, asymmetric tonic posture, positive emotional affective expression and contralateral versive signs. Cluster 9 comprised the FBTCS patient distinguished by the significantly greater presence of generalised tonic clonic seizure (v.test = 4.123) and a relatively greater frequency of somesthetic localized aura, than seen in other clusters.

Analysis two. Individual ICN ROI correlates of ictal semiology

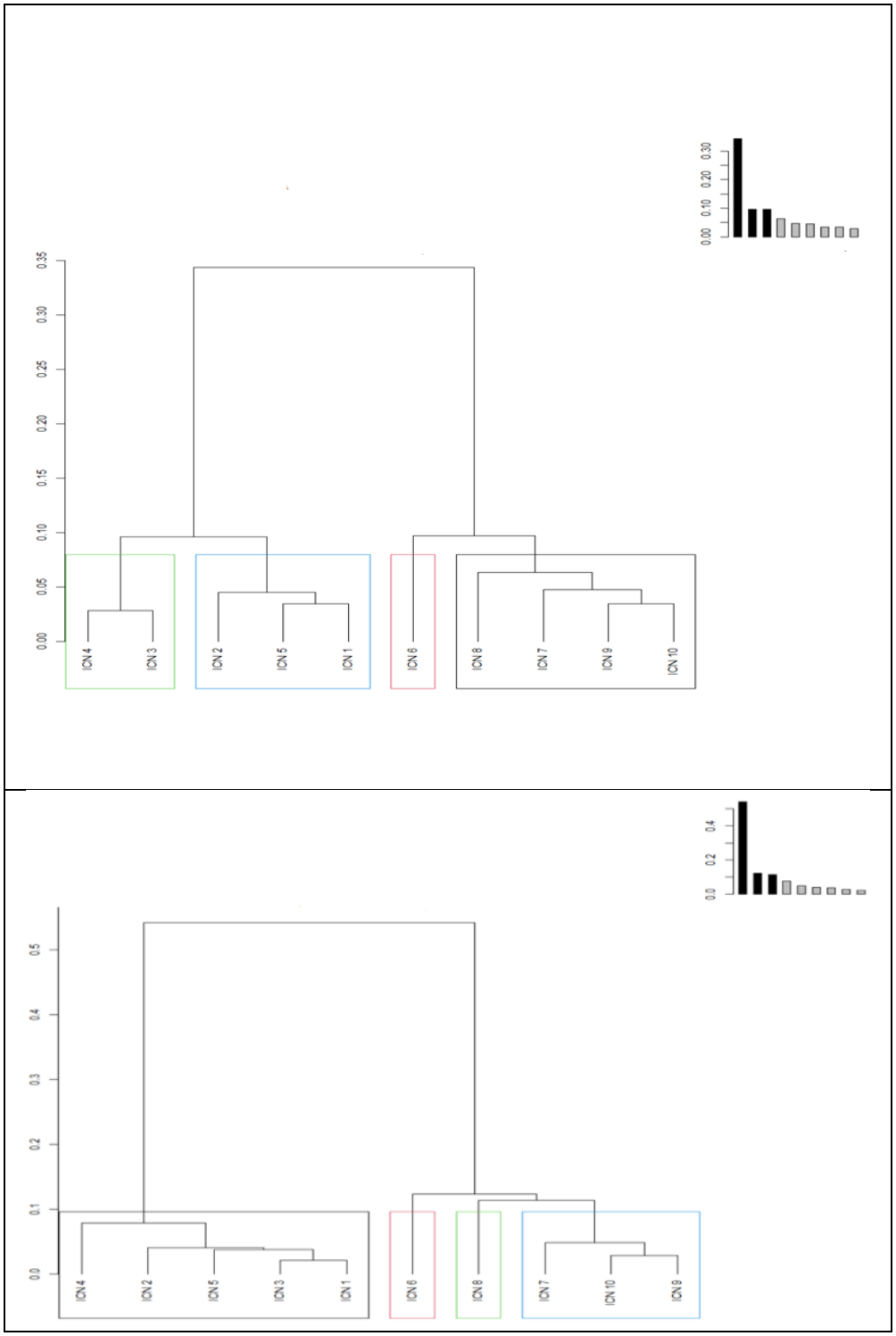
Associated activation and associated deactivation was seen four groups of ICN ROIs, respectively. Association of net engagement was seen in five groups of ICN ROIs (see Figure 11.2).

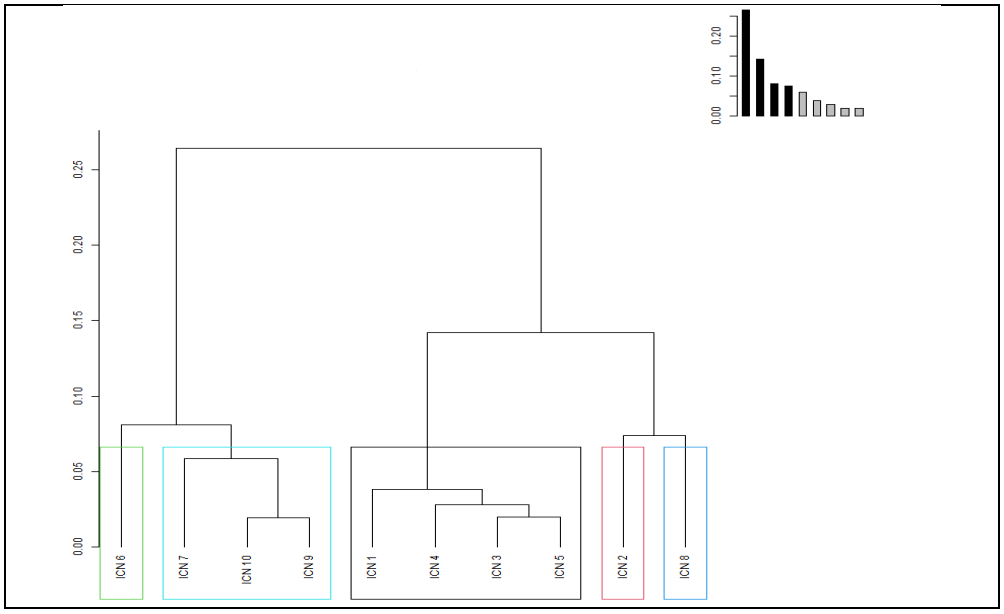
The cluster pattern for activations, deactivations and net engagement respectively showed an arrangement of correlated ICN ROI recruitment along a rostral – caudal axis during the ictal established phase. Frontal and temporal ICN ROIs (7, 9 & 10) were associated; the DMN (ICN ROI 4) was clustered with posterior ICN ROIs, while ICN ROI 6 (sensory motor area) showed distinct involvement. ICN ROI 8 (executive area) showed distinct involvement for deactivation and net engagement, while ICN ROI 2 (visual area) showed distinct involvement for net engagement.

Across all patients, 69% of all ICN ROIs showed net deactivation. The greatest net deactivation was seen for ICN ROI 4 (DMN) and the lowest net deactivation for ICN ROI 6 (sensory motor area).

Figure 11.2.

Correlation of Ictal Clinical Signs





Note. Top: Activations, Middle: Deactivation, Bottom: Net engagement

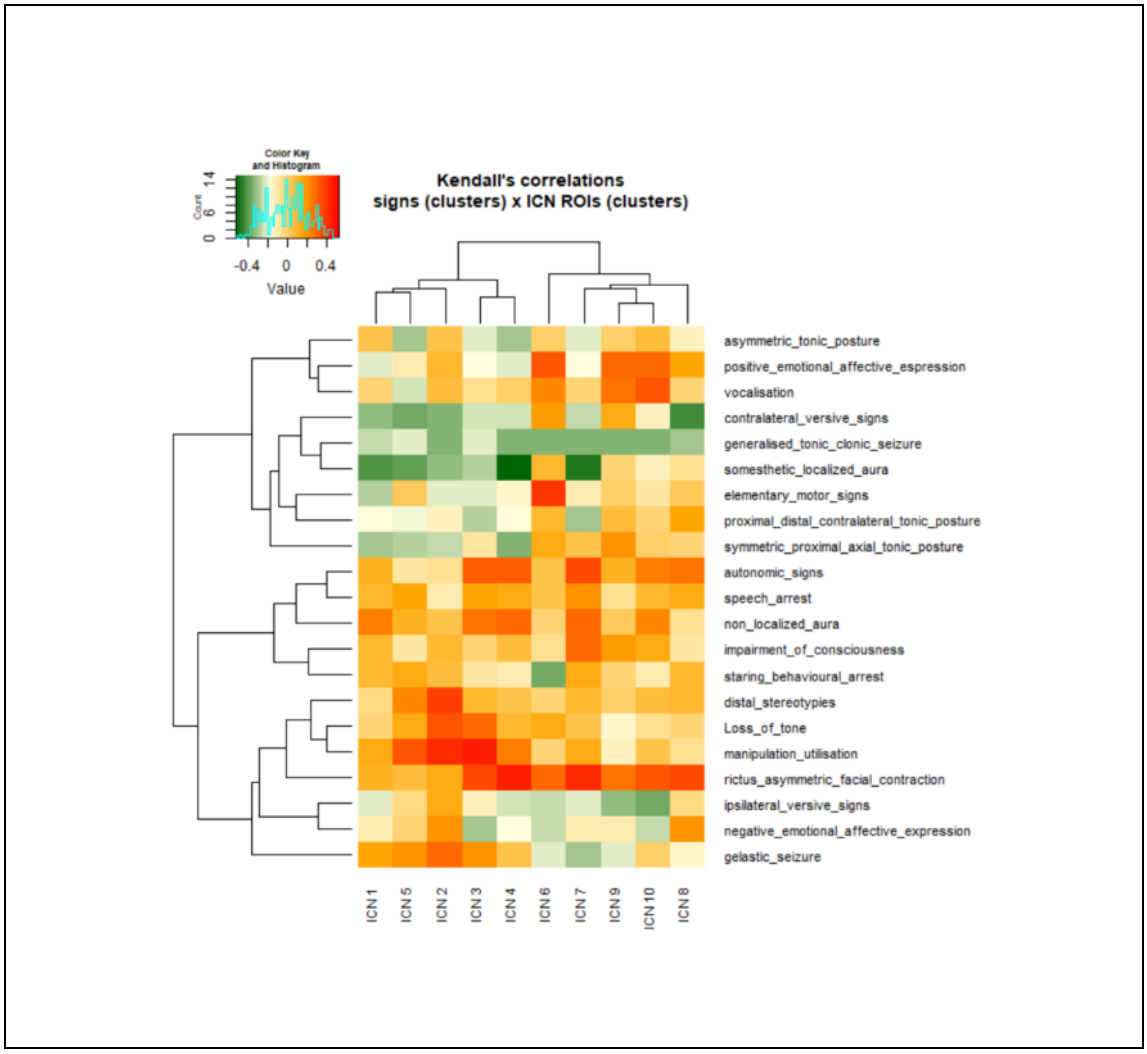
A descending view showing increased evolution of variance and number of clusters. The relative gain in variance associated with the cluster solutions are shown at the top right. The grouping obtained at each step of the hierarchical clustering algorithm represent elements that are the closest to one another. They constitute a node of the hierarchy, and their distance is the index attached to the left of the diagram. From bottom to the top of the tree, the greater the number of already agglomerated elements is, and the greater the minimal distance between the clusters that remain to be agglomerated. The more points are agglomerated, in other words, the closer one gets to the top of the tree, the greater is the distance between the two closest clusters. In the dendograms ICN ROIs that were correlated during ictal discharge, appear close to each other.

Correlation of ictal clinical signs**.** Signs that occurred together were seen in three large clusters (see Figure 11.3). Smaller clusters showed signs that typically and most frequently occur together. Impairment of consciousness was most frequently associated with staring behavioural arrest, and frequently with non-localised aura, speech arrest and autonomic signs. Loss of tone was most frequently associated with distal stereotypies and manipulation utilisation. Negative emotional affective expression was most frequently associated with ipsilateral versive signs; generalised tonic clonic seizure was most frequently associated with somethetic localised aura and contralateral versive signs; and proximal distal contralateral tonic posture was most frequently associated with elementary motor signs. Gelastic seizure was an outlier and not closely associated with the occurrence of other signs.

There were no significant correlations ($p < 0.05$; Bonferroni corrected for multiple comparisons) between activations or deactivations, or net engagement of individual ICNs and clinical signs. The greatest effect sizes were seen for net engagement. (The correlation matrices are shown in Table 1-3, Appendix C). A heatmap of the strength of correlation between signs and activations in ICN ROIs is depicted in Figure 11.3.

Figure 11.3

Heatmap of Correlation between Signs and Activations in ICN ROIs



Note. Correlation matrix between ictal signs and activations within ICNs during the ictal established phase for all patients, ordered as a function of their correlation distance with clustering. Signs that were correlated during seizures, and ROIs that were correlated during ictal discharge, appear close to each other in the dendograms. Yellow-orange-red squares show positive correlation which indicate that both the clinical sign and the extent of activation are increasing/decreasing, and green squares indicate a negative correlation which indicate that as the rank of the sign is increased, the rank of the activation is decreased; or vice versa.

Analysis three. The association of multiple ICN ROIs with clinical signs

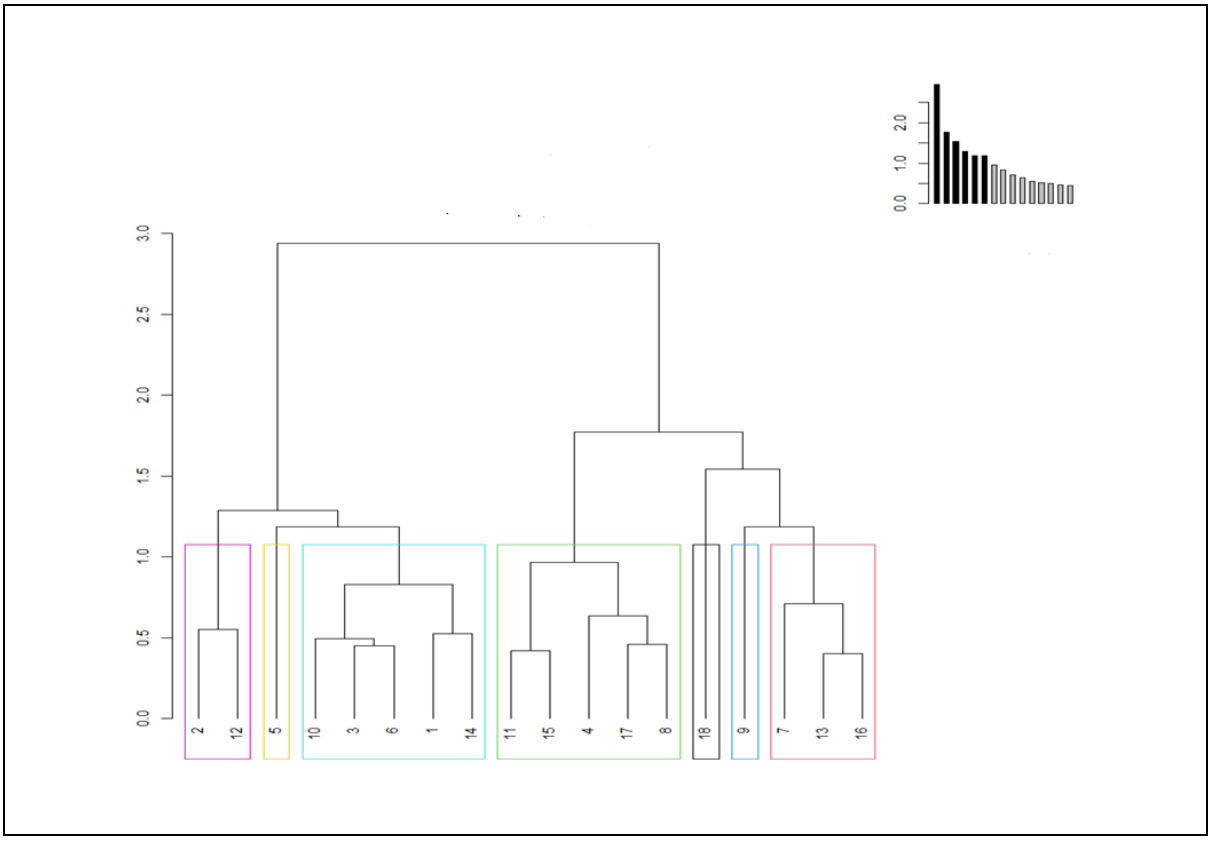
Principal component analyses performed separately for activations, deactivations and net engagement correlated with a total of 20 clinical signs. Clustering showed that 17 clinical signs contributed significantly to distinguishing between patients.

For activations variance expressed by the first plane of projection was significant. The first two components accounted for 43.26% compared to the normal distribution reference value of 32.13% obtained from 2849 simulated datasets of equivalent size. Aetiology (Wilks' $\lambda = 0.486$, $p = 0.497$) better accounted for variance between patients compared to seizure type (Wilks' $\lambda = 0.966$, $p = 0.788$) but was not significant.

The first thirteen components of PCA (variance = 96.50%) showed significant correlation accounting for 18 clinical signs. Optimal clustering yielded seven clusters. The relative gain in variance and the dendogram is shown in Figure 11.4. Patients' classification based on clinical signs and activation in ICN ROIs were better characterised by aetiology ($P = 0.0702$, Fisher's exact test) compared to seizure type ($P = 0.5943$, Fisher's exact test).

Figure 11.4.

Clustering based on Clinical Signs and Activation in ICN ROIs



Note. Patients clustering and ordered as a function of the reciprocal distance in their clinical signs and activations in ICN ROIs. The relative gain in variance associated with the seven-cluster solution is shown at the top right. The clusters are numbered and described in the text from left to right as they appear on the dendogram.

Cluster 1. Patients #2 and #12 were characterised by the significantly greater presence of manipulation utilisation (v.test = 4.123), than other patients and significantly higher values of loss of tone (v.test = 2.828) and distal stereotypies (v.test = 2.811) with significant higher activation in ICN ROI 3 (v.test = 2.490) and relatively low activation in ICN ROI 2, relative to other patients.

Cluster 2. Patient # 5 was distinguished by the significantly greater presence of rictus asymmetric facial contraction (v.test = 2.916) and relatively high values for ICN ROIs 10, 9, 8, 7 and 4, compared to other patients.

Cluster 3. Patients #6, #3, #10, #1 and #14. These patients were characterised by significantly greater presence of non-localized aura (v.test = 2.601) and relatively higher frequency of autonomic signs compared to other patients.

Cluster 4. Patients #11, 15, 4, #8 and #17. Compared to other patients, this group was characterised by significantly lower activations in ICN ROIs 9 (v.test = -2.310) and 10 (v.test = -2.084).

Cluster 5. Patient #18 was distinguished by significant presence generalised tonic clonic seizure (v.test=4.123) and the significant presence of somesthetic localized aura (v.test=2.916) and significantly lower activations compared to other patients in ICN ROIs 2, 4, 6,7, 9 and 10 (v.test = -1.983).

Cluster 6. Patient # 9 showed significantly greater presence of positive emotional expression (v.test = 4.123) and significantly higher values for vocalisation (v.test = 2.482) as well as relatively greater presence of asymmetric tonic posture with relatively higher activations in ICN ROI 6, compared to other patients.

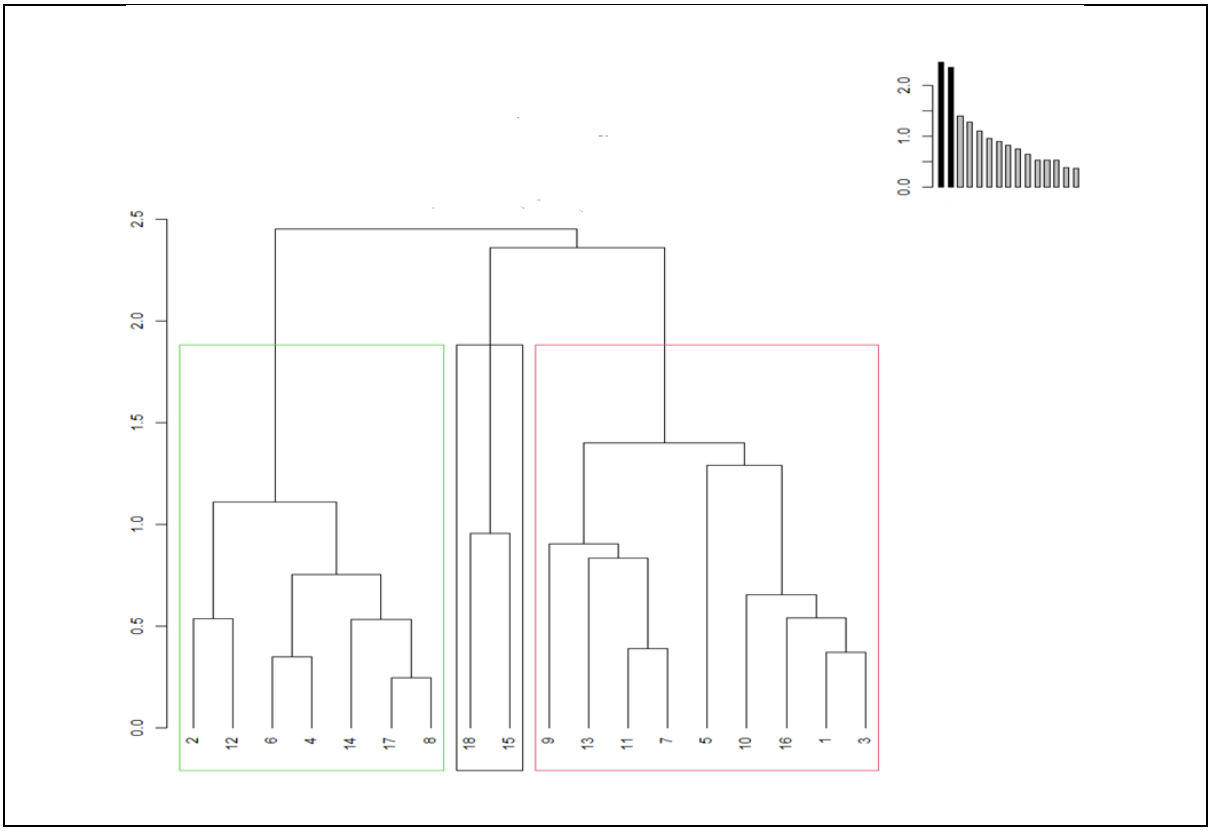
Cluster 7. Patient # 7, #13 and #16. This group was characterised by significant high values for the variable symmetric proximal axial tonic posture (v.test = 2.780) and significantly lower activations in ICN ROI 1 (v.test = -2.529) and ICN ROI 2 (v.test = -2.120) and relatively lower activations in ICN ROI 5.

For deactivations variance expressed by the first plane was significant: The first two component accounted for 39.97% of the total variance compared to the normal distribution reference value of 32.12% - the 0.95-quantile of random distributions obtained from 10000 simulated datasets of equivalent size. Aetiology (Wilks' $\lambda = 0.407$, $p = 0.307$) better accounted for variance between patients in this plane compared to seizure type (Wilks' $\lambda = 0.972$, $p = 0.820$) but was not significant.

The first eleven components of PCA (variance = 90.90) showed significant correlation accounting for 17 clinical signs. An optimum cut for clustering yielded three groups of patients. Patients' classification based on clinical signs and deactivation in ICN ROIs were better characterised by epilepsy defined by seizure type (P = 0.067, Fisher's exact test) compared to aetiology (P = 0.851, Fisher's exact test) but did not reach significance.

Figure 11.5.

Clustering based on Clinical Signs and Deactivation in ICN ROIs



Note. Patients clustering and ordered as a function of the reciprocal distance in their clinical signs and deactivations in ICN ROIs. The relative gain in variance associated with the three-cluster solution is shown at the top right. The clusters are numbered and described in the text from left to right as they appear on the dendogram.

Cluster 1. Patients #2, #12, # 6, #4, # 14, #1 and #8 were distinguished from other patients by significantly reduced deactivation in ICN ROIs 5 (v.test = 3.021), 3 (v.test = 2.795), 1 (v.test = 2.635) and 2 (v.test = 2.300).

Cluster 2. Patient #15 and #18, were distinguished from other patients by the significantly greater presence/frequency of ipsilateral versive signs (v.test = 3.018), negative emotional affective expression (v.test = 2.828) and generalised tonic clonic seizure (v.test = 2.828). It was accompanied by significantly lower deactivations in ICN ROIs 10 (v.test = -2.491), 9 (v.test = -2.491), 6 (v.test = -2.491), 7 (v.test = -2.267) and 5 (v.test = -2.266).

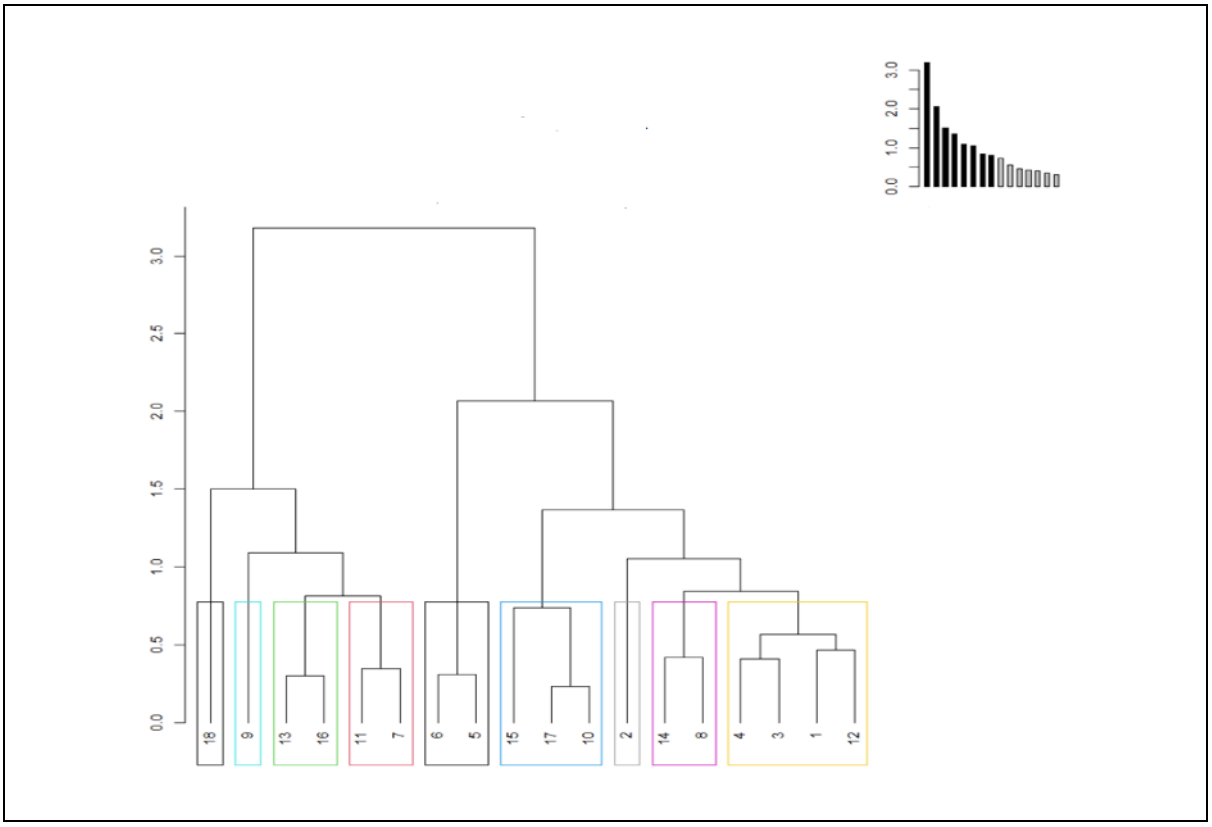
Cluster 3. Patients #5, #9, #13, #16, #1, #3, #7, #10 were characterised by significantly reduced deactivation in ICN ROIs 9 (v.test = 2.642), 8 (v.test = 2.181), 7 (v.test = 2.007) and significantly greater deactivation in ICN ROIs 1 (v.test = -2.260), 2 (v.test = -2.048) and 3 (v.test = -1.968).

Net engagement variance expressed by the first plane was significant: The first two component accounted for 46.33% of the total variance compared to the normal distribution reference value of 31.97%, specifically the 0.95-quantile of random distributions obtained from 10000 simulated datasets of equivalent size. Aetiology (Wilks' $\lambda = 0.394$, $p = 0.278$) better accounted for variance between patients in this plane compared to seizure type (Wilks' $\lambda = 0.890$, $p = 0.441$) but was not significant.

The first eleven components of PCA (variance = 92.89) showed significant correlation ($p<0.05$) accounting for 18 clinical signs. An optimum cut for clustering yielded nine clusters of patients. Patients' classification based on clinical signs and net engagement of ICN ROIs were better characterised by seizure type (P = 0.5162, Fisher's exact test) compared to aetiology (P = 0.946, Fisher's exact test) but was not significant.

Figure 11.6.

Clustering based on Clinical Signs and Net Engagement of ICN ROIs



Note. Patients clustering and ordered as a function of the reciprocal distance in their clinical signs and net engagement of ICN ROIs. The relative gain in variance associated with the nine-cluster solution is shown at the top right. The clusters are numbered and described in the text from left to right as they appear on the dendogram.

Cluster 1. Patient #18 was distinguished from other patients by significantly high values for generalised tonic clonic seizure (v.test = 4.123) and somesthetic localized aura (v.test = 2.916) and significant net deactivation of ICN ROIs 4, 5, 7, 9, 8 and 6 (v.test = -1.985).

Cluster 2. Patient #9 was characterised by significantly high values for positive emotional affective expression (v.test = 4.123, $p<0.05$, vocalisation (v.test = 2.482, $p<0.05$) and relatively higher values for asymmetric tonic posture and net activation of ICN ROI 6.

Cluster 3. Patient #13 and #16, were distinguished from other patients by relatively high values for contralateral versive signs and significant net deactivation of ICN ROIs 2 (v.test = -2.490) and 1 (v.test = -2.490).

Cluster 4: Patients #7 and #11 were characterised by significant absence of impairment of consciousness (v.test = -2.436).

Cluster 5: Patients #5 and #6 had significantly high values for rictus asymmetric facial contraction (v.test = 3.452) with significant net activation of ICN ROIs 7 (v.test = 2.492), 4 (v.test = 2.492), 8 (v.test = 2.491) and 10 (v.test = 2.490) and relatively higher activation of ICN ROI 9.

Cluster 6. Patients #15 and #17 and #10, were distinguished by significantly presence of staring behavioural arrest (v.test = 2.528) and relatively higher presence of negative emotional affective expression.

Cluster 7. Patients #14 and #8 showed relatively higher net activation of ICN ROI 1 and relatively greater presence of contralateral versive signs.

Cluster 8. Patients #4, #3, #1 and #12 were distinguished by significantly high frequency of non-localized aura (v.test = 2.649) and relatively greater net activation of ICN ROI 5.

Cluster 9. Patient #2 distinguished by significant presence of loss of tone (v.test = 4.123), manipulation utilisation (v.test = 2.828), and ipsilateral versive signs (v.test = 2.482). The cluster is characterised by relatively high activation of ICN ROI 3 and 2.

Analysis four. The relationship between ICN and anatomically defined ROIs during the ictal established phase

A total of 18 signs were significantly correlated with the principal components provided by PCA of activations and PCA of deactivations. Several ICN ROIs were engaged in the seizure related series of activations and deactivations. ICN ROIs were less prominent

compared to anatomical ROIs in clusters associated with signs. The clusters of brain areas associated with signs reflected a hierarchy of intensities as well as series of areas with stronger statistical dependencies (defined as areas that showed the same intensity of activation or deactivation): The full list of significantly involved ROIs and clinical signs associated with clusters of patients are shown in Appendix C.

For activations the first two dimensions expressed 31.45% of the total dataset variance, greater than the reference value of 17.63%, obtained from simulating 3057 data tables of equivalent size on the basis of a normal distribution). Aetiology (Wilks' $\lambda = 0.339$, $p = 0.171$) better accounted for variance between patients in this plane compared to seizure type (Wilks' $\lambda = 0.986$, $p = 0.911$) but was not significant.

The first seventeen components of PCA (variance = 100) showed significant correlation accounting for 17 clinical signs. Hierarchical clustering was conducted on all components – therefore the original distances. An optimum cut for clustering yielded nine clusters. Patients' classification based on clinical signs and activation in anatomical and ICN ROIs were better characterised by aetiology ($P = 0.118$, Fisher's exact test) than seizure type ($P = 0.911$, Fisher's exact test).

For deactivations the variance captured by the first plane was significant: The first two principal component dimensions accounted for 32.88% of the total variance, greater than the normal distribution 0.95-quantile of 17.67% variance seen in 10000 simulated data tables of equivalent size.

Aetiology (Wilks' $\lambda = 0.552$, $p = 0.655$) better accounted for variance between patients in this plane compared to seizure type (Wilks' $\lambda = 0.967$, $p = 0.859$) but was not significant.

Seventeen components of PCA (i.e., variance = 100%) showed significant correlation accounting for 16 clinical signs. Clustering was conducted on all components and the original distances. An optimum cut for clustering yielded nine clusters of patients.

Patients' classification based on clinical signs and deactivation in anatomical and ICN ROIs was significant and better characterised by seizure type (P = 0.010, Fisher's exact test) compared to aetiology (P = 0.335, Fisher's exact test).

Subcortical areas were associated with clinical signs. A range of clinical signs involved not only cortical but also engagement of subcortical structures: Generalised tonic clonic seizure and somesthetic localized aura were significantly present and associated with significant activations in the thalamus and hippocampus and with significant deactivations in thalamus and basal ganglia. Manipulation utilisation, loss of tone, gelastic seizure and distal stereotypies were significantly present and associated with significant activations in the hippocampus. Rictus asymmetric facial contraction was significantly present and associated with significant activations in the basal ganglia, thalamus, hippocampus. Positive emotional affective expression and somesthetic localised aura were significantly present and associated with significant deactivations in the hippocampus, amygdala, thalamus. Staring behavioural arrest was significantly present and associated with significant deactivations in the hippocampus.

Clinical signs were associated with unique configuration of activation and deactivation across all ROIs. Eight signs were uniquely and significantly present in clusters of ROI activations and two signs were uniquely and significantly present in clusters of deactivations. Six signs were associated, both with clusters of significantly greater activations and greater deactivations. Significantly lower activations were associated with 14 signs and significantly less deactivations were associated with seven signs. The signs and associated activation/deactivation (in ICN and anatomical ROIs) are shown in Table 11.2.

Table 11.2.

Signs Significantly Correlated with ROIs

Signs associated with significantly greater activations	**Signs associated with significantly lower activations**	**Signs associated with significantly greater deactivations**	**Signs associated with significantly less deactivations**	**Signs associated with both significantly greater activation and greater deactivations**
Asymmetric tonic posture	Generalised tonic clonic seizure	Ipsilateral versive signs	Negative emotional affective expression	Gelastic seizure
Distal stereotypies	Somesthetic localized aura	Staring behavioural arrest	Ipsilateral versive signs	Generalised tonic clonic seizure
Loss of tone	Symmetric proximal axial tonic posture		Symmetric proximal axial tonic posture	Negative emotional affective expression
Manipulation utilisation	Manipulation utilisation		Positive emotional affective expression	Positive emotional affective expression
Non localised aura	Loss of tone		Somesthetic localised aura	Somesthetic localised aura
Speech arrest	Gelastic seizure		Staring behavioural arrest	Symmetric proximal axial tonic posture
Vocalisation	Distal stereotypies		Asymmetric facial Rictus contraction	

Rictus asymmetric facial contraction	Vocalisation			
	Asymmetric tonic posture			
	Speech arrest			
	Non localised aura			
	Negative emotional affective expression			
	Positive emotional affective expression			
	Rictus asymmetric facial contraction			

Note. Signs significantly present and associated with significantly greater and lower activations and significantly greater and lesser deactivations than the mean.

Significant engagement (activations and deactivations) of ICN ROIs were associated with nine signs. ICN ROIs were less prominent than anatomical ROIs in the seizure networks associated with clinical signs (see Tables C1&C2, Appendix C for table with clusters of signs and areas of activation and deactivation):

Significantly greater activations than the mean was seen in ICN ROIs 2, 3 and 5, clustered with activations in occipital, subcortical and temporal anatomical areas and associated with manipulation utilisation, loss of tone, gelastic seizure, and distal stereotypies.

Significantly greater activations were seen in ICN ROI 4 and fronto-temporal ICN ROIs 7, 8, 9, and 10, clustered with subcortical, temporal and frontal anatomical areas

associated with rictus asymmetric facial contraction. ICN 4 and 7, and ICN ROI 8 and 10 showed a higher degree of statistical association compared to other ROIs in the network.

There were significantly greater deactivations than the mean in ICN ROIs 9 and 7, clustered with a series of occipital, subcortical and temporal, frontal and parietal anatomical areas associated with generalised tonic clonic seizure and somesthetic localized aura. ICN ROI 9 showed a higher degree of statistical association with a series of areas comprising the right thalamus, left basal ganglia, right lateral occipital cortex, left parahippocampal gyrus, left superior temporal gyrus and left middle frontal gyrus than with other areas in the series. ICN RO1 7 showed a higher degree of statistical association with the right inferior temporal gyrus, left superior temporal gyrus and right superior temporal gyrus compared to other ROIs in the network.

There were significantly greater deactivations in ICN ROI 10 that was clustered with insular, frontal, lateral occipital, parietal and temporal areas and associated with negative emotional affective expression and ipsilateral versive signs. Within the series, ICN ROI 10 showed a higher degree of statistical association with the right lateral occipital cortex, right superior parietal lobule, left superior parietal lobule than with other areas.

Positive emotional affective expression and somesthetic localized aura were associated with significantly lower deactivation in ICN ROI 6 that was clustered with frontal areas, pre and post central gyri and the precuneus.

There were significantly less deactivations in ICN ROIs 7, 8 and 10 along with thalamic, frontal, temporal, basal ganglia, insular, parietal and lateral occipital areas that were associated with rictus asymmetric facial contraction. ICN ROI 7 showed a higher degree of statistical association strong with the right thalamus and right posterior superior temporal sulcus than with other areas in the series. ICN ROI 10 showed a higher degree of statistical association, specifically the left and right thalamus, left basal ganglia, left insular gyrus, right

parahippocampal gyrus and right orbital gyrus, than with other areas in the series of areas. ICN ROI 8 showed greater association with the left thalamus, left parahippocampal gyrus and right inferior frontal gyrus than with other ROIs.

Analysis five. The association of ICN and anatomically defined ROIs with impairment of awareness

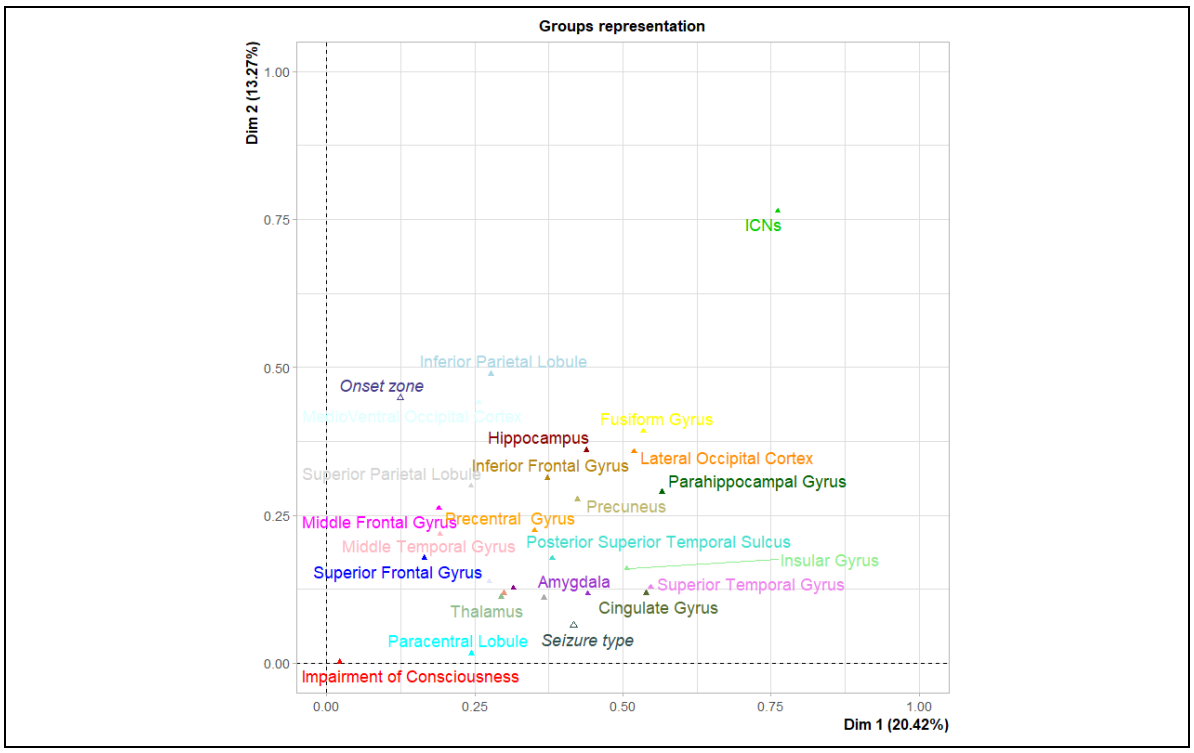
As a group, ICN ROIs showed the largest contribution to the first plane of variance for both activations and deactivations. The variance across groups is illustrated in Figure 11.5. There were no significant correlations between the groups of ROIs and impairment of awareness. Impairment of awareness showed a closer association with anatomical structures, compared to ICNs.

For activations the first two principal components expressed 30.46 % of the total variance. ICN ROIs showed low correlation with impairment of awareness (RV = 0.036). The greatest effect sizes were seen for the superior temporal gyrus (RV =0.158), basal ganglia (RV = 0.148), precuneus (RV = 0.113) and the inferior temporal gyrus (RV = 0.106).

For deactivations the first two principal component accounted for 33.69 % of the total variance. ICN ROIs showed low correlation with impairment of awareness (RV = 0.038). Greater effect sizes were seen for the insular gyrus (RV = 0.192), the amygdala (RV = 0.184), superior temporal gyrus (RV = 0.176) and the parahippocampal gyrus (RV = 0.164).

Figure 11.7.

PCA of Groups of ROIs



Note. ICN ROIs showed the highest variance on the first dimensions of PCA but showed a weaker association with impairment of consciousness compared to anatomical ROIs.

Discussion

Electroclinical characteristics of 18 patients with heterogeneous seizures were studied to explore the role and association of ICN ROIs with clinical signs in the context of patient classification by seizure type and seizure onset aetiology. It was achieved by considering the significance of patient classification in relation to the broader spectrum of clinical signs and neural correlates. Correlational and cluster analyses were employed to establish patterns of ICN ROI engagement as well as the relationship between clinical signs and ICN ROIs, relative to the involvement of anatomical defined ROIs.

Classification of patients

Although the ILAE classification system (see Chapter 1) has benefited from several revisions, questions in relation to semiology and seizure classification have not been settled (Lüders et al., 2019; Rosenow et al., 2020). According to the ILAE seizure classification according to onset has an anatomic basis, whereas classification by level of awareness has a behavioural basis, justified by the practical importance of impaired awareness (Fisher et al., 2017). The current results provided support for the clinical utility of the current classification of seizure type both in terms of clinical expression (clinical signs) and associated neural correlates (i.e., deactivation of brain areas).

Involvement of ICN ROIs in the seizure network

ICN ROIs showed abnormal connectivity. Changes and disruption/changes in normal ICN connectivity during the ictal established phase were reflected in abnormal connectivity involving multiple ICNs, that showed net deactivation across ICN ROIs. It is contrary to cortical-reduced activation observed during specific tasks (Moraschi et al., 2012) which is typically accompanied by positive BOLD activity of similar magnitude in other cortical networks (Berkovich-Ohana et al., 2015) that is in line with the theory that the cortex regulates and balances increased excitation by proportional increased inhibition (Shu, Hasenstaub, & McCormick, 2003). The greatest net deactivation across patients was seen for ICN ROI 4 (DMN) and the accompanied deactivation in other ICN ROIs reflected a marked alteration in the normal balance of activation – deactivation (Gusnard et al., 2001) between functional areas.

These findings are in line with abnormal changes in brain connectivity associated with abnormal phenomenology – that is, the production of seizure semiology (Bartolomei 2017) and elaborates, previous simultaneous fMRI and EEG studies that have reported varying changes in seizure related BOLD changes in areas of intrinsic connectivity networks during different ictal phases (Kozak et al., 2017) and consistent with dynamic network connectivity changes associated with epileptic activity (Laufs et al., 2014; Lopes et al., 2014; Omidvarnia et al., 2017).

The results are consistent with factor analytic validation findings (reported in Chapter 6) that indicated that normal connectivity patterns that underlie ICNs either integrate or disintegrate during seizures - akin to "abnormal binding and disruption in large scale networks" (Bartolomei et al., 2013). Accordingly, large scale functional connectivity is dramatically altered during seizures and changes in neural synchrony provoked by epileptic rhythms are responsible for the production of ictal symptoms (Bartolomei et al., 2013).

Besides the above observations made in the context of seizures, large-scale network connectivity during the interictal state has also been investigated to better understand the cognitive impairments (Bartolomei et al., 2013). In this regard previous resting state fMRI results demonstrating abnormal connectivity – commonly, reduced connectivity within the DMN and associated epileptogenic regions (Haneef et al., 2012; Liao et al., 2010; Mankinen et al., 2012; Widjaja et al., 2013; Zhang & Raichle, 2010; Zhang et al., 2010) in focal (Pittau et al., 2012; Ridley et al., 2015) and generalised epilepsies (Masterton, 2012; McGill, 2012; Song, 2011; Wang, 2011; Yang, 2012, 2013).

ICN ROIs form part of a cascade of cortical and subcortical anatomical engagements**.** Although clustering of correlated ICN ROIs showed that there were unique contributions for ICN ROI 6 (normally associated with sensorimotor function) and ICN ROI 8 (normally associated with executive function), the engagement of these functionally specialised areas was not individually and significantly associated with clinical signs. Rather multivariate analysis showed that signs were associated with a spectrum of activations, namely significantly greater and lower levels of activations and deactivations comprised of an elaborate series of brain areas that also included ICN ROIs. There were different contributions to the seizure network comprised of a series of brain areas involving a hierarchy of intensities, with some areas showing stronger positive statistical and greater functional connectivity compared to others.

There was greater prominence and involvement of anatomical defined areas compared to ICN ROIs, and the seizure networks involved a range of cortical and subcortical areas consistent with the view that epilepsy is not as a disorder that affects one discrete brain region but involves spatially distributed brain areas. It elaborated previous studies that have shown the role not only of cortical structures (Rosenow & Luders, 2001) such as the insula (Peltola et al., 2020; Singh et al., 2020) and its subregion connectivity (Wang et al., 2020) but the importance of subcortical structures (Norden & Blumenfeld, 2002; Pizzo et al., 2020). It has long been known that subcortical structures are involved (Vaudano et al., 2012) and contribute significantly to clinical expression in focal seizures (He et al., 2020; Vuong & Devergnas, 2017). Thalamic involvement specifically has not only been implicated as common in different seizure types but postulated to be a possible marker of the epileptogenic network extension and of post-surgical prognosis (Pizzo et al., 2020).

Organisation of ICNs during the ictal established phase**.** During the ictal established phase ICN ROIs were organised along an anatomical axis: Anterior-temporal ICN ROIs were engaged together at one end of the spectrum and the posterior ROIs - visual ICNs and the cerebellum - at the other end. While a rostro-caudal axis associated with the production of signs has previously been shown for FLE patients (Bonini et al., 2014) the results were consistent with previous observation that clinical signs reflect organisation and cerebral evolution of the seizure discharge (Chauvel et al., 2019). It suggests that the evolution of the seizure discharge is associated with a unique series of brain areas (anatomical and ICN ROIs) from which ictal symptoms arise rather than from abnormal deployment of function associated with any normal functional connectivity network.

ICN ROIs 4 and 7, and ICN ROIs 8 and10 were connected and clustered with close and remote anatomical areas, including sub cortical areas in a network associated with rictus asymmetric facial contraction. ICN ROI 9 was connected with closer and remote anatomical, including subcortical areas and associated with clinical signs generalised tonic clonic seizure and somesthetic localized aura. Thus, the results showed that signs are associated with a network comprised of hierarchy of activations/deactivations in a series of brain areas that can include multiple subnetworks reflected by greater connectivity consistent with observations that partial seizures involve several cortical and subcortical structures during their time course (Bartolomei et al., 2013) and concomitant ictal hyper and hypoperfusion in different brain areas (Blumenfeld et al., 2004; Van Paesschen et al., 2003; Varghese et al., 2009).

Inhibition of brain function play a role in seizure semiology. Activation reflects increased neuronal activity and energy demand (Kobayashi et al., 2006), while deactivation, which has recently been correlated with autonomic nervous system (ANS) function and interindividual differences (Iacovella et al., 2018) is more difficult to explain: EEG–fMRI results have showed that discharges followed by a slow wave are likely to result in-deactivation, with neuronal inhibition as the likely underlying phenomenon (Kobayashi et al., 2006) so that focal deactivations in the context of IED serves as a likely electrographic correlate of prolonged inhibition (Pittau et al., 2013). It is in line with neurophysiological recordings of patients implanted with multi-electrode arrays that, unlike the view that associates seizures with hyperexcitability and hypersynchrony (Steriade et al., 1994), have shown association with low levels of firing activity and greatly reduced firing for the majority of neurons (Truccolo et al., 2011). Thus, negative BOLD response has been associated with neuronal activity suppression or a decrease in neuronal activity under its basal level rather than "blood steal (Devor et al., 2005; Kannurpatti & Biswal, 2004; Liu et al., 2011).

EEG-fMRI studies have shown that deactivations are frequent for focal and generalised discharges (Kobayashi et al., 2006) and have been attributed to the downstream effects of IEDs on brain activity (Salek-Haddadi et al., 2006). While clinical signs have been attributed to excessive neural discharge (Rosenow & Luders, 2001), deactivations, have in patients with generalised epilepsy been associated with clinical phenomena, specifically changes in conscious resting state activity (Hamandi et al., 2008) such as transitory cognitive impairment (Moeller, Muhle, et al., 2010).

The results here showed that a range of clinical signs and the classification of seizure type were significantly and also uniquely associated with deactivation in brain areas. It indicates that the suspension or inhibition of normal activity across brain areas contribute significantly to clinical expression. An association of slow wave activity with the semiology network is consistent with previous observation of slow-wave activity arising from the same area as epileptiform activity in the EEG of paediatric patients with focal epilepsy (Vanrumste, 2005), and that seizures involve both inhibition and activation of neural structures (Norden & Blumenfeld, 2002) with different contributions to processing and integration of information in clinical expression (Morano et al., 2016).

Clinical signs and ICN ROIs. Signs shared series' of activated and deactivated brain areas, which is consistent with observation that seizures with similar semiology could involve neuronal activity in the same brain networks (O'Muircheartaigh & Richardson, 2012). Each sign was associated with a unique configuration of brain areas involving different levels of intensity (that is, intensities that were significantly greater or lesser than the mean activation and deactivation). Although individual experience and behaviour have been associated with engagement of ICN ROIs (S. M. Smith et al., 2009) and normal connectivity networks have been implicated in ictal signs (Chaudhary et al., 2012) correlational analysis showed that activation, and deactivation in, or net engagement of individual ICN ROIs were not significantly associated with specific clinical signs but contributed to more elaborate seizure networks that were significantly associated with clinical signs. These findings contradict the approach and the results in a recent EEG–fMRI study that utilised ICN_atlas to evaluate the patient's specific epileptic network using IEDs and its association with clinical signs (Mirandola et al., 2021): Cases with an ICN involvement (i.e., motor network) and the presence of corresponding ictal/postictal semeiology (i.e., tonic clonic seizures) were defined as true positive (TP), whereas true negative (TN) were the cases without ICNs engagement

and absence of corresponding ictal/postictal semeiology. The authors found that four main ICNs were preferentially involved, namely, motor, visual, auditory/motor speech, and the default mode network. Their results showed high specificity in detecting engagement of an ICN and the corresponding ictal/postictal symptom, and good positive predictive value at the single-subject level, in all networks except the visual one (Mirandola et al., 2021). Rather, than significant association with individual ICN ROIs the findings here showed that ICN ROIs contributed to more elaborate seizure networks that were significantly associated with clinical signs.

In the Common Methods (Chapter 5) reference was made to the fact that the DMN has been the focus of many studies in attempts to describe and elucidate fMRI maps, and that the presence of multiple networks raised the question of bias in the context of it historical eminence (Raichle et al., 2001; Shulman et al., 1997) or its relative ease of study. Given the evidence of dynamic change in the integration and segregation of networks (Cohen & D'Esposito, 2016; Lord et al., 2017; Shine et al., 2016) the approach taken in this work yielded quantification of the relationship between many networks simultaneously and provided a view into the role of multiple networks and effects of disease, and the effect of seizures, on specialised functioning (Bassett et al., 2015; Sadaghiani et al., 2015).

Deactivation of the DMN is one of the most reliable observations in neuroimaging (Gu et al., 2019) and previous observation of pathologic BOLD decreases in the DMN network during GSWDs and IED have been associated with changes in consciousness (Gotman et al., 2005; Laufs, Lengler, et al., 2006). While the current results showed that clinical signs involved deactivation in the DMN, there was greater involvement of other brain areas. Specifically, greater effect sizes were seen for the relationship between impairment of awareness and activations in the superior temporal gyrus, basal ganglia, precuneus and the inferior temporal gyrus and for deactivations in the insula, amygdala, superior temporal gyrus

and the parahippocampal gyrus. A lack of association with any identified seizure network and brain area implicates mechanisms other than direct effects of seizure discharge. It supports observations that impairment of awareness result not only from the epileptic discharge but also from its effect on normal brain function (Gotman et al., 2005), specifically indirectly through effects on subcortical arousal systems (Englot et al., 2010).

Conclusions

The range and frequency of clinical signs across epilepsies clustered patients into groups that were significantly concordant with seizure type and deactivation in brain areas were significantly related to classification by seizure type. Beyond its practical importance, impairment of awareness serves as a significant classifying feature of clinical expression with a neural basis associated with the inhibition of normal brain functions. Each seizure network and its associated clinical expression was characterised by varying levels of activation, inhibition and connectivity across cortical and subcortical areas. ICN ROIs showed changes in normal connectivity and were engaged with idiosyncratic seizure spread in an anatomically configuration along a rostro-caudal axis. Canonical ICNs including the DMN are not a meaningful framework for the study of seizure spread and ictal semiology. Anatomical characterisation of seizure networks and semiology with EEG-fMRI is possible.

Clinical utility

While the results do not demonstrate clinical utility for ICNs in mapping semiology the results suggest a potential role for EEG-fMRI and atlasing in standardising the study of semiology networks across cortical and subcortical structures. Delineation of the seizure network may provide an additional and non-invasive tool which could help implantation planning and focus imaging studies toward identification of lesions in the presurgical workup (Bonini et al., 2014). The results support previous reports (Chauvel & McGonigal, 2014; Pizzo et al., 2020) of the involvement of cortical, including the insula and its subregions

(Isnard et al., 2004; Ostrowsky et al., 2000; Singh et al., 2020; Wang et al., 2019) and different thalamic and basal ganglia subregions.

The result provides a methodology and additional information that may help interpret complex EEG-fMRI BOLD maps aimed at localisation of epileptic zones in the presurgical workout (Chaudhary et al., 2012; Thornton et al., 2010). Specifically, it provides perspective on clinical and biological significance of BOLD clusters of interictal spikes - and seizures remote from the presumed seizure onset zone and epileptogenic zone and may be particularly valuable in addressing questions in line with previous observations (Aupy et al., 2019; Brodovskaya et al., 2021; Guedj et al., 2012) in relation to the role of subcortical structures.

Limitations

Group studies requires a careful consideration of similarity between the subjects investigated and the population to which the findings are generalised (Shadish, 2002). The study was conducted in a small group of patients with heterogeneous pathologies that limits the reliability and the clinical relevance of findings. In addition, the sensitivity and specificity of the BOLD signal to reveal the underlying neural activity associated with the seizure networks and semiology were potentially impacted by a range of factors:

As previously discussed, (see Mathematical modelling of hemodynamic responses in EEG-fMRI studies in Chapter 4) the accuracy of results is founded upon a range of uncertainties, including a presumption of the extent of haemodynamic delay which could be different on account of pathological processes.

A further limitation relates to limited spatial coverage. Specifically, there is little or no EEG recording of epileptiform activity in deep structures or small regions of epileptogenic cortex as the signal reflects summarised activity of pyramidal neurons near the surface of the brain (see EEG fMRI Data acquisition and processing in Chapter 4).

In five cases, the haemodynamic signature derived from the ictal activity in the established phase associated with clinical signs, represent a combination of early, established and late phases (Chaudhary et al., 2012), therewith potentially confounding ictal phase modelling intended to aid the identified specificity of association between ICNs and signs. Similarly, multiple seizures were grouped as a single effect for the purpose of modelling and may in fact not represent the same dynamics.

The value of the ictal phase modelling approach employed by Chaudhary and colleagues' rests on its potential capacity to identify haemodynamic change specific to the semiological meaningful part of the seizures: While the role of early spread was not considered, it is uncertain whether the early ictal and the preictal state correspond to distinct states that fundamentally differ from the ictal established phase.

The data reflects the investigator defined ictal established phase - that is, the identification of the ictal established phase was based on the objective emergence of clinical semiology (Chaudhary et al., 2012) and subjective signs can readily be missed, such as in cases of gelastic seizures associated with hypothalamic hamartoma (Cross & Spoudeas, 2017). Indeed, the results of clustering showed that gelastic seizure was an outlier and not closely associated with the occurrence of other signs (see section on Correlation of ictal clinical signs and Figure 11.3). It may reflect the missed or incomplete observation of clinical signs.

To model BOLD changes, epileptic events were based on the timing information retrieved from the EEG and depicted as boxcar signals, analogous to those used in cognitive fMRI studies (Chaudhary et al., 2012). However, the haemodynamic changes that take place during a seizure of identified duration does not necessarily correspond to a neuronal event with fixed intensity over the same duration and therefore may not be faithfully represented by event blocks (Leite et al., 2013). Moreover, representation of BOLD changes in the design

matrix as variable duration blocks is insensitive to the evolutionary recruitment of these areas on a temporal scale within a single ictal phase.

The data did not account for the effect of different types of focal seizure patterns (Wendling et al., 1996), that potentially involve different brain regions (Li et al., 2019; Salami et al., 2015, 2020): typical patterns have been identified for frontal lobe epilepsy (Smith, 2005), and different patterns have been distinguished for neocortical epilepsy and mesial temporal epilepsy (Smith, 2005) as well as lateral versus mesial temporal seizures (Smith, 2005; Yan et al., 2020).

The effects of different AED on networks were not considered. BOLD changes in DMN related areas during performance of a cognitive task are different under the influence of Topiramate as compared to other AEDs (see section on AED in Chapter 9). In epilepsy, AEDs may influence on functional connectivity within or between different brain networks.

Sensitivity and specificity are further affected by unquantified limitations in the signal to noise ratio: Motion during seizures can deteriorate data quality and increase false positive results, particularly in the context of low temporal resolution of fMRI (~3 seconds). One of the potential limitations of the original dataset is that all seizures irrespective of motion were included which may corrupt fMRI signal. However, the original study results reportedly accounted for motion and physiological confounds by inclusion of as complete and thorough a model of the effects of motion and physiological confounds such as pulse on the fMRI signal and seizure activations were reported not to be significantly associated with the amount of head motion (Chaudhary et al., 2012).

Appendix C

ICN ROI Correlations with Clinical Signs

Table C.1.

Activations

ICN	ICN 1	ICN 2	ICN 3	ICN 4	ICN 5	ICN 6	ICN 7	ICN 8	ICN 9	ICN 10
asymmetric tonic posture	0.048	0.048	-0.2	-0.3	-0.3	0.0096	-0.22	-0.12	0.0096	0.067
autonomic signs	0.11	-0.057	0.31	0.31	-0.086	0.057	0.37	0.29	0.11	0.26
contralateral versive signs	-0.33	-0.35	-0.22	-0.24	-0.36	0.19	-0.26	-0.43	0.13	-0.12
distal stereotypies	-0.029	0.39	0.11	0.048	0.24	-0.01	0.11	0.11	0.0096	0.086
elementary motor signs	-0.28	-0.21	-0.21	-0.15	0.033	0.41	-0.099	0.033	0.017	-0.083
gelastic seizure	0.18	0.29	0.22	0.059	0.22	-0.22	-0.29	-0.14	-0.22	0.02
generalised tonic clonic seizure	-0.25	-0.33	-0.22	-0.33	-0.22	-0.33	-0.33	-0.29	-0.33	-0.33
impairment of consciousness	0.09	0.09	0	0.072	-0.072	-0.054	0.31	-0.072	0.18	0.14
ipsilateral versive signs	-0.2	0.15	-0.13	-0.22	-0.035	-0.25	-0.2	-0.035	-0.32	-0.37
Loss of tone	-0.02	0.33	0.29	0.098	0.14	0.14	0.059	-0.02	-0.14	-0.059
manipulation utilisation	0.14	0.43	0.46	0.26	0.34	0	0.14	-0.057	-0.11	0.057
negative emotional affective expression	-0.098	0.22	-0.29	-0.18	-0.02	-0.25	-0.098	0.22	-0.098	-0.25
non localized aura	0.26	0.053	0.28	0.31	0.12	-0.011	0.31	-0.053	0.032	0.24
positive emotional affective expression	-0.22	0.098	-0.18	-0.22	-0.098	0.33	-0.18	0.18	0.29	0.29
proximal distal contralateral tonic posture	-0.16	-0.11	-0.27	-0.16	-0.18	0.095	-0.3	0.16	0.078	-0.009
rictus asymmetric facial contraction	0.13	0.15	0.37	0.46	0.083	0.29	0.44	0.37	0.27	0.34
somesthetic localized aura	-0.41	-0.32	-0.27	-0.53	-0.39	0.11	-0.48	-0.059	-0.012	-0.13
speech arrest	0.098	-0.098	0.18	0.14	0.18	0.059	0.22	0.14	-0.059	0.098
staring behavioural arrest	0.09	0.072	-0.072	-0.09	0.14	-0.36	0.14	0.09	0	-0.09
symmetric proximal axial tonic posture	-0.29	-0.25	-0.083	-0.34	-0.27	0.15	0.059	-0.012	0.2	0.012
vocalisation	-0.012	0.083	-0.059	0.012	-0.22	0.22	-0.012	-0.012	0.27	0.34

Table C.2.

Deactivations

ICN	ICN 1	ICN 2	ICN 3	ICN 4	ICN 5	ICN 6	ICN 7	ICN 8	ICN 9	ICN 10
asymmetric tonic posture	0.14	-0.067	-0.14	-0.34	-0.13	0.048	-0.11	-0.067	-0.067	-0.16
autonomic signs	-0.014	0.072	-0.072	0.19	0.24	-0.014	0.1	-0.043	0.16	0.1
contralateral versive signs	-0.24	-0.56	-0.26	-0.31	-0.31	0.15	-0.15	-0.33	0.08	0.027
distal stereotypies	-0.019	0.39	0.15	0.096	0.019	-0.039	0.12	0.039	-0.039	-0.039
elementary motor signs	-0.22	-0.24	-0.12	-0.058	-0.24	0.37	0.0083	0.041	0.025	-0.075
gelastic seizure	0.02	0.22	0.22	0.14	0.33	-0.14	-0.3	-0.22	-0.02	0.26
generalised tonic clonic seizure	-0.22	-0.26	-0.26	-0.3	-0.26	-0.33	-0.33	-0.33	-0.33	-0.3
impairment of consciousness	0.13	0.073	-0.13	-0.15	0	-0.073	0.27	-0.054	0	0.073
ipsilateral versive signs	-0.083	0.18	-0.012	-0.2	-0.3	-0.3	-0.32	-0.11	-0.39	-0.46
Loss of tone	-0.02	0.33	0.33	-0.02	0.098	0.098	0.02	-0.14	-0.059	-0.14
manipulation utilisation	0.11	0.46	0.46	0.23	0.23	-0.057	0.14	-0.14	-0.14	-0.057
negative emotional affective expression	0.059	0.18	-0.14	-0.059	-0.33	-0.3	-0.26	0.26	-0.3	-0.33
non localized aura	0.095	0.053	0.074	0.33	0.12	-0.074	0.35	-0.074	0.14	0.26
positive emotional affective expression	-0.18	-0.098	-0.22	-0.22	-0.098	0.33	-0.059	0.098	0.26	0.098
proximal distal contralateral tonic posture	-0.026	-0.27	-0.17	0.11	-0.39	0.043	-0.27	0.23	-0.078	-0.25
rictus asymmetric facial contraction	0.2	0.2	0.27	0.32	0.32	0.27	0.18	0.083	0.2	0.11
somesthetic localized aura	-0.3	-0.34	-0.2	-0.39	-0.34	0.13	-0.34	-0.083	0.059	-0.25
speech arrest	-0.12	0	-0.079	0.039	0.039	-0.039	0.24	0.039	0.16	0.2
staring behavioural arrest	0.082	0.21	-0.009	-0.21	-0.045	-0.34	0.23	0.34	0.0091	0.0091
symmetric proximal axial tonic posture	-0.15	-0.18	-0.083	-0.39	-0.34	0.13	0.15	0.059	0.13	-0.035
vocalisation	-0.024	-0.17	-0.14	0.047	-0.071	0.24	0.071	-0.024	0.26	0.17

Table C.3.

Net engagement

ICN	ICN 1	ICN 2	ICN 3	ICN 4	ICN 5	ICN 6	ICN 7	ICN 8	ICN 9	ICN 10
asymmetric tonic posture	0.027	-0.003	-0.31	-0.4	-0.24	0.075	-0.31	-0.19	-0.061	-0.011
autonomic signs	0.25	0.061	0.42	0.43	0.23	0.067	0.44	0.29	0.14	0.33
contralateral versive signs	-0.45	-0.53	-0.49	-0.39	-0.42	0.12	-0.4	-0.59	-0.0076	-0.043
distal stereotypies	0.04	0.63	0.29	0.18	0.26	-0.033	0.0054	-0.036	-0.026	-0.0013
elementary motor signs	-0.24	-0.13	-0.27	-0.11	-0.19	0.5	-0.18	-0.047	0.12	0.045
gelastic seizure	0.15	-0.07	0.2	0.19	0.22	0.031	0.14	0.055	-0.11	-0.0032
generalised tonic clonic seizure	-0.24	-0.28	-0.3	-0.45	-0.38	-0.43	-0.43	-0.53	-0.46	-0.32
impairment of consciousness	0.01	0.19	-0.031	-0.14	0.0078	-0.18	0.018	-0.24	-0.048	-0.02
ipsilateral versive signs	-0.066	0.48	0.012	-0.15	-0.23	-0.25	-0.3	-0.13	-0.34	-0.48
Loss of tone	0.053	0.58	0.4	0.11	0.22	0.17	0.06	-0.041	-0.042	-0.0058
manipulation utilisation	0.2	0.69	0.58	0.31	0.46	-0.047	0.094	-0.1	-0.085	0.017
negative emotional affective expression	-0.028	0.24	-0.23	-0.1	-0.36	-0.31	-0.27	0.13	-0.21	-0.51
non localized aura	0.23	0.048	0.22	0.32	0.23	-0.083	0.14	-0.096	-0.097	0.06
positive emotional affective expression	-0.2	0.027	-0.28	-0.21	-0.1	0.45	-0.18	0.065	0.28	0.27
proximal distal contralateral tonic posture	-0.11	-0.12	-0.38	-0.096	-0.41	0.012	-0.42	0.064	-0.01	-0.17
rictus asymmetric facial contraction	0.3	0.34	0.46	0.52	0.42	0.45	0.67	0.64	0.61	0.63
somesthetic localized aura	-0.32	-0.33	-0.38	-0.54	-0.48	-0.091	-0.54	-0.42	-0.24	-0.21
speech arrest	0.15	-0.07	0.2	0.19	0.22	0.031	0.14	0.055	-0.11	-0.0032
staring behavioural arrest	-0.03	0.076	-0.045	-0.26	0.071	-0.44	-0.0019	0.092	-0.067	-0.22
symmetric proximal axial tonic posture	-0.28	-0.39	-0.18	-0.39	-0.39	0.19	0.00072	-0.18	0.12	-0.028
vocalisation	-0.028	0.0053	-0.21	-0.023	-0.12	0.3	-0.13	-0.064	0.18	0.22

Rank Ordered Signs and Associated ROIs

Table C.4a.

Prominence of Activation

Cluster	Pat #Id & Seizure type	Signs associated with cluster	V.test	Significantly greater activations - top to bottom in descending levels of activation	V.test	Significantly lower activations - top to bottom in descending levels of activation	V.test
$`1`	#18 Reflex /FBTCS	Generalised tonic clonic seizure	4.123106	Thalamus Otha L	1.99954	Middle Frontal Gyrus A8vl R	-1.983871
		Somesthetic localized aura	2.91577	Parahippocampal Gyrus TL L	1.998357	Middle Frontal Gyrus IFJ R	-1.983871
				Thalamus Otha R	1.992988	Middle Frontal Gyrus IFJ L	-1.983871
				Hippocampus cHipp L	1.987181	Postcentral Gyrus A1/2/3ulhf L	-1.983953
						Inferior Temporal Gyrus A37vl L	-1.983953
						Orbital Gyrus A12/47o R	-1.983953
						Precuneus dmPOS L	-1.984419
						Superior Frontal Gyrus A8dl R	-1.984446
						Middle Temporal	-1.984454

						Gyrus aSTS R	
						Superior Frontal Gyrus A9l L	-1.984454
						Middle Frontal Gyrus A9/46d L	-1.984838
						Thalamus mPMtha R	-1.985012
						Superior Parietal Lobule A7ip L	-1.985206
						Basal Ganglia dCa R	-1.985373
						Thalamus Stha R	-1.986319
						Inferior Parietal Lobule A39rv R	-1.987591
						Superior Temporal Gyrus A38m L	-1.988211
						Precentral Gyrus A4tl L	-1.990727
						Inferior Frontal Gyrus A45c L	-2.007774
$`2`	#13 Multifocal /FIAS	Symmetric proximal axial tonic posture	2.482263	Inferior Temporal Gyrus A37elv R	1.98753	lateral Occipital Cortex OPC L	-1.983953
				Inferior	1.987198	MedioVentral	-1.983953

				Temporal Gyrus A20cl R		Occipital Cortex rLinG R	
				Inferior Temporal Gyrus A20cv R	1.984529	Fusiform Gyrus A37mv R	-1.983953
				Inferior Temporal Gyrus A20cv L	1.984528	Fusiform Gyrus A37mv L	-1.98406
				Postcentral Gyrus A1/2/3tonIa L	1.984161	Inferior Frontal Gyrus A44d R	-1.98406
				Fusiform Gyrus A37lv R	1.983953	lateral Occipital Cortex OPC R	-1.984161
						Superior Frontal Gyrus A9m L	-1.984511
						Cingulate Gyrus A24rv R	-1.984529
						MedioVentral Occipital Cortex vmPOS R	-1.984629
						Middle Frontal Gyrus A8vl L	-1.984635
						Superior Frontal Gyrus A9l R	-1.984698
						MedioVentral Occipital Cortex	-1.984749

						vmPOS L	
						Middle Frontal Gyrus A46 L	-1.985042
						Middle Frontal Gyrus A9/46v R	-1.985131
						MedioVentral Occipital Cortex cCunG R	-1.986234
						Thalamus mPFtha R	-1.986342
						Hippocampus cHipp L	-1.986345
						Middle Frontal Gyrus A6vl R	-1.986345
						Basal Ganglia NAC R	-1.987639
						Basal Ganglia dlPu R	-1.989292
						Inferior Frontal Gyrus A44op R	-1.990523
						Amygdala mAmyg L	-1.991063
						Basal Ganglia vmPu R	-1.998366
						Basal Ganglia NAC L	-1.998366
						Insular Gyrus vIa R	-2.005791
$`3`	#7 PLE/ FIAS					Inferior Temporal Gyrus A20r R	-1.997214

	#8 FLE/ FIAS					Inferior Parietal Lobule A40rd L	-2.021679
	#17 FLE /FIAS					Parahippocampal Gyrus A35/36r R	-2.036764
	# 16 FLE /FIAS					Basal Ganglia dlPu L	-2.045401
						Superior Temporal Gyrus A22r R	-2.045446
						Orbital Gyrus A11l L	-2.122993
						Parahippocampal Gyrus A28/34 R	-2.137425
						Fusiform Gyrus A37lv R	-2.260208
						Orbital Gyrus A14m R	-2.26084
						Inferior Temporal Gyrus A37elv R	-2.261949
						Precuneus A31 R	-2.31223
						Basal Ganglia vmPu L	-2.378839
						Superior Temporal Gyrus A38l L	-2.39223
						Amygdala lAmyg L	-2.395121
						Inferior Temporal	-2.416914

						Gyrus A20iv R	
						Middle Frontal Gyrus A10l R	-2.418125
						Insular Gyrus dId R	-2.49542
						Thalamus mPMtha L	-2.625761
						Thalamus lPFtha L	-2.708297
						Middle Temporal Gyrus A37dl L	-2.714836
						Orbital Gyrus A14m L	-2.762733
$`4`	#2 Reflex /FIAS	Manipulation utilisation	3.259601	Lateral Occipital Cortex V5/MT+ L	2.791597	Middle Frontal Gyrus A9/46d R	-2.123351
	#4 HH/ FAS	Loss of tone	2.236068	Lateral Occipital Cortex iOccG R	2.791302		
	#12 TLE /FIAS	Gelastic seizure	2.236068	lateral Occipital Cortex iOccG L	2.791261		
		Distal stereotypies	1.999812	ICN 2	2.790494		
				Inferior Temporal Gyrus A37elv L	2.648839		

				ICN 3	2.648072		
				Fusiform Gyrus A20rv L	2.529755		
				Lateral Occipital Cortex V5/MT+ R	2.459836		
				Inferior Parietal Lobule A39rv L	2.340175		
				Fusiform Gyrus A37lv L	2.340175		
				lateral Occipital Cortex mOccG L	2.340098		
				Hippocampus rHipp L	2.340028		
				MedioVentral Occipital Cortex cLinG R	2.205545		
				MedioVentral Occipital Cortex cLinG L	2.202293		
				lateral Occipital Cortex OPC L	2.197563		
				Fusiform Gyrus A37mv L	2.12175		
				Inferior	2.120703		

				Temporal Gyrus A37vl L			
				ICN 5	2.091285		
				Inferior Temporal Gyrus A20r R	2.045499		
				Fusiform Gyrus A37mv R	2.04447		
				Precuneus A31 L	2.015463		
$`5`	#14 Multifocal /FIAS	Vocalisation	2.482263	Precuneus A7m L	2.001853	Cingulate Gyrus A24rv L	-1.983871
		Asymmetric tonic posture	2.178186	Precuneus A31 L	1.997781	Middle Temporal Gyrus A37dl R	-1.983871
		Non localised aura	2.046818	lateral Occipital Cortex msOccG R	1.986769	Orbital Gyrus A13 L	-1.983871
				Superior Parietal Lobule A5l L	1.986133	Superior Frontal Gyrus A8dl L	-1.98406
				Inferior Parietal Lobule A39rd L	1.985092	Paracentral Lobule A4ll R	-1.984419
				Inferior Parietal Lobule A40rd L	1.984799	Superior Frontal Gyrus A6dl L	-1.984446

				Precuneus A40rv R	1.984529	Superior Temporal Gyrus A38l R	-1.984454
				Fusiform Gyrus A37mv L	1.984529	Superior Frontal Gyrus A9m R	-1.984509
				Precuneus dmPOS L	1.984511	Thalamus rTtha L	-1.985042
				lateral Occipital Cortex lsOccG R	1.983871	Orbital Gyrus A11m R	-1.985962
				Inferior Parietal Lobule A40rd R	1.983832	Cingulate Gyrus A32sg R	-1.986113
						Middle Frontal Gyrus A9/46d R	-1.986466
						Thalamus PPtha R	-1.986715
						Basal Ganglia GP R	-1.987358
						Superior Temporal Gyrus A22c L	-1.987975
						Middle Frontal Gyrus A6vl L	-1.992209
						Parahippocampal Gyrus TL L	-1.996247
						Inferior Frontal Gyrus A44v L	-2.000028
						Thalamus cTtha L	-2.013343

$`6`	#1 Reflex /FIAS	Speech arrest	2.236068	Middle Temporal Gyrus A21r L	2.45667	Middle Frontal Gyrus A6vl L	-1.993911
	#3 PLE/ FAS	Non localised aura	2.192037	Middle Temporal Gyrus A21c L	2.198499	posterior Superior Temporal Sulcus cpSTS L	-2.024796
	#11 Reflex /FIAS			Orbital Gyrus A11m R	2.117657	Cingulate Gyrus A23d L	-2.027333
				Middle Frontal Gyrus A10l R	1.993233	Amygdala mAmyg R	-2.113343
						Superior Parietal Lobule A7r R	-2.116779
						Inferior Parietal Lobule A39rd L	-2.195826
						MedioVentral Occipital Cortex cCunG L	-2.462923
						MedioVentral Occipital Cortex rCunG R	-2.794521
$`7`	#15 TLE /FIAS	Negative emotional affective expression	2.828427	Superior Frontal Gyrus A10m R	2.49445	Middle Temporal Gyrus A21r L	-2.09865
	#10 FLE /FAS			Cingulate Gyrus A32p	2.266448	Superior Frontal Gyrus	-2.099594

				L		A6m R	
				Superior Frontal Gyrus A10m L	2.265671	Postcentral Gyrus A1/2/3tonIa R	-2.100716
				lateral Occipital Cortex OPC R	2.265657	Superior Temporal Gyrus A22c R	-2.100716
				Insular Gyrus vIa R	2.122705	Precuneus A5m L	-2.265671
				Orbital Gyrus A14m L	2.100582	Superior Parietal Lobule A7pc L	-2.265823
						Precentral Gyrus A4ul L	-2.265823
						Superior Parietal Lobule A5l R	-2.266081
						Postcentral Gyrus A2 L	-2.266528
						Cingulate Gyrus A23d R	-2.266724
						Precentral Gyrus A4hf L	-2.490645
						Postcentral Gyrus A1/2/3tru L	-2.49092
						Paracentral Lobule A1/2/3ll L	-2.491218
						Paracentral Lobule A4ll L	-2.493708

$`8`	#9 Multifocal /FIAS	Positive emotional affective expression	4.123106	Parahippocampal Gyrus A28/34 L	1.990506	Inferior Parietal Lobule A39c L	-1.983871
		Vocalisation	2.482263	Precuneus A7m R	1.990403	Basal Ganglia dCa L	-1.98406
		Asymmetric tonic posture	2.178186	Middle Frontal Gyrus A6vl L	1.989555	Inferior Temporal Gyrus A37vl R	-1.986676
				Superior Parietal Lobule A7r L	1.988211	MedioVentral Occipital Cortex rCunG L	-1.987744
				Superior Frontal Gyrus A6m R	1.9873	Insular Gyrus vId/vIg R	-1.995663
				Paracentral Lobule A4ll L	1.98721		
				Middle Frontal Gyrus A9/46d R	1.98721		
				Middle Frontal Gyrus A6vl R	1.987181		
				Parahippocampal Gyrus A28/34 R	1.986873		
				Superior Frontal Gyrus A6m L	1.98684		
				Superior Parietal Lobule A7r R	1.985373		
				Fusiform Gyrus A20rv R	1.985226		

				Middle Frontal Gyrus A8vl L	1.985104		
				Superior Parietal Lobule A7pc R	1.984838		
				Middle Frontal Gyrus A9/46d L	1.984838		
				Paracentral Lobule A4ll R	1.984511		
				Postcentral Gyrus A1/2/3tru R	1.984509		
				Precentral Gyrus A6cvl L	1.984161		
				Middle Frontal Gyrus IFJ R	1.984161		
				Middle Frontal Gyrus IFJ L	1.984161		
				Postcentral Gyrus A2 L	1.98406		
				Postcentral Gyrus A1/2/3tru L	1.983871		
				Precuneus A5m R	1.983871		
				Superior Parietal Lobule A5l R	1.983871		
				Paracentral Lobule	1.983832		

				A1/2/3ll R			
				Precentral Gyrus A4hf R	1.983832		
				Postcentral Gyrus A1/2/3ulhf L	1.983781		
				Superior Parietal Lobule A7pc L	1.983781		
				Precentral Gyrus A4ul R	1.983781		
				Precentral Gyrus A4ul L	1.983781		
				Precentral Gyrus A4hf L	1.983781		
				Postcentral Gyrus A2 R	1.983769		
				Precentral Gyrus A6cdl L	1.983769		
$`9`	#5 FLE /FIAS	Rictus asymmetric facial contraction	3.452424	Parahippocampal Gyrus TH L	2.544876	Inferior Temporal Gyrus A20cl L	
	#6 HH/ FAS			Parahippocampal Gyrus TL R	2.52662	Inferior Temporal Gyrus A20iv L	
				Insular Gyrus dId L	2.521355	Inferior Temporal Gyrus A20r L	
				Basal Ganglia vmPu R	2.508557		
				Basal Ganglia NAC L	2.508557		

				Insular Gyrus vIa L	2.508391		
				Basal Ganglia vCa R	2.504878		
				Basal Ganglia GP L	2.504004		
				Thalamus mPFtha L	2.503209		
				Precentral Gyrus A4tl L	2.503209		
				Basal Ganglia vCa L	2.502228		
				Parahippocampal Gyrus TH R	2.502228		
				Cingulate Gyrus A24cd L	2.498949		
				posterior Superior Temporal Sulcus cpSTS R	2.497684		
				Basal Ganglia dlPu R	2.496677		
				Basal Ganglia vmPu L	2.496244		
				Cingulate Gyrus A24cd R	2.495817		
				Thalamus PPtha R	2.495359		
				Thalamus mPFtha R	2.49494		
				Thalamus lPFtha L	2.494765		
				Thalamus	2.49445		

				Stha R			
				Basal Ganglia dCa R	2.494305		
				Thalamus mPMtha L	2.494035		
				Basal Ganglia NAC R	2.493996		
				Thalamus PPtha L	2.493739		
				Thalamus rTtha R	2.493276		
				Thalamus rTtha L	2.493276		
				Basal Ganglia GP R	2.493241		
				Thalamus mPMtha R	2.493115		
				Middle Temporal Gyrus aSTS R	2.492305		
				Hippocampus cHipp R	2.492208		
				Insular Gyrus dId R	2.492208		
				Insular Gyrus dIg L	2.491729		
				Orbital Gyrus A12/47o L	2.491729		
				Inferior Frontal Gyrus A44d L	2.491729		
				Superior Frontal Gyrus A6dl R	2.491642		
				Superior Frontal Gyrus	2.491642		

				A8dl R			
				Superior Frontal Gyrus A8m R	2.49164		
				Insular Gyrus dIg R	2.491179		
				Orbital Gyrus A11l R	2.491179		
				Orbital Gyrus A13 L	2.49092		
				Orbital Gyrus A13 R	2.490485		
				Orbital Gyrus A11l L	2.490485		
				ICN 7	2.489677		
				ICN 4	2.489677		
				posterior Superior Temporal Sulcus cpSTS L	2.319826		
				Basal Ganglia dlPu L	2.311368		
				Insular Gyrus vId/vIg L	2.286723		
				Insular Gyrus vId/vIg R	2.2823		
				Inferior Frontal Gyrus A45r R	2.277439		
				Inferior Frontal Gyrus A45r L	2.276515		
				Inferior Frontal Gyrus A44op R	2.274977		
				Inferior	2.271267		

				Frontal Gyrus A45c R			
				Inferior Frontal Gyrus A44v R	2.271102		
				Cingulate Gyrus A32sg L	2.270311		
				Precentral Gyrus A4tl R	2.269633		
				Posterior Superior Temporal Sulcus rpSTS L	2.267846		
				Basal Ganglia dCa L	2.266528		
				Orbital Gyrus A12/47l L	2.266528		
				Insular Gyrus G R	2.266448		
				Precuneus A40rv L	2.265823		
				Superior Frontal Gyrus A8m L	2.265671		
				Superior Temporal Gyrus A41/42 L	2.265657		
				Inferior Parietal Lobule A40c L	2.265574		
				Orbital Gyrus A12/47o R	2.265574		
				ICN 10	2.264931		

				ICN 8	2.264931		
				Insular Gyrus dIa R	2.157671		
				Inferior Frontal Gyrus A44v L	2.121037		
				Thalamus lPFtha R	2.108333		
				Thalamus cTtha R	2.106358		
				Superior Temporal Gyrus A38l L	2.106358		
				Superior Temporal Gyrus A22r R	2.105267		
				Inferior Frontal Gyrus IFS R	2.101766		
				Cingulate Gyrus A32sg R	2.099649		
				Orbital Gyrus A14m R	2.09781		
				Orbital Gyrus A12/47l R	2.097694		
				Superior Frontal Gyrus A9m R	2.097694		
				Superior Frontal Gyrus A8dl L	2.097543		
				Middle Temporal Gyrus A21c R	2.096875		
				lateral	2.096647		

				Occipital Cortex mOccG R			
				ICN 9	2.09604		

Note. All activations ($p<0.05$) are ordered greater to lesser

Table C.4b.

Prominence of Deactivation

Cluster	Pat #Id & Seizure type	Signs associated with cluster/* low frequency of sign	V.test	Significantly less deactivations - top to bottom in ascending levels of deactivation	V.test	Significantly greater deactivations - top to bottom in ascending levels of deactivation	V.test
$`1`	#18 Reflex/FBTCS	Generalised tonic clonic seizure	4.123106			Thalamus mPMtha R	-1.98406
		Somesthetic localized aura	2.91577			Basal Ganglia vmPu L	-1.98406
						lateral Occipital Cortex V5/MT+ R	-1.98406
						Parahippocampal Gyrus A28/34 L	-1.98406
						Parahippocampal Gyrus A35/36r L	-1.98406
						Superior Temporal Gyrus A38m L	-1.98406
						Middle Frontal Gyrus A8vl L	-1.98406
						ICN 9	-1.98406
						Basal Ganglia NAC L	-1.984161
						posterior Superior Temporal Sulcus cpSTS L	-1.984161
						Orbital Gyrus A12/47o R	-1.984161
						Insular Gyrus	-1.984454

						vId/vIg R	
						Insular Gyrus dIa L	-1.984454
						Postcentral Gyrus A1/2/3tonIa L	-1.984454
						Middle Frontal Gyrus A9/46v L	-1.984454
						Inferior Frontal Gyrus A45r R	-1.984511
						Cingulate Gyrus A23c L	-1.984529
						Cingulate Gyrus A23d L	-1.984529
						Inferior Temporal Gyrus A37vl R	-1.984529
						Inferior Temporal Gyrus A20il R	-1.984529
						Orbital Gyrus A11l L	-1.984529
						Middle Frontal Gyrus A10l L	-1.984529
						Insular Gyrus vIa L	-1.984819
						Middle Temporal Gyrus A37dl R	-1.985092
						Parahippocampal Gyrus TI R	-1.985104
						Inferior Frontal Gyrus A44v R	-1.985226
						Inferior Temporal Gyrus A37elv R	-1.985373

						Inferior Temporal Gyrus A20iv R	-1.985373
						Superior Temporal Gyrus A22r L	-1.985373
						Superior Temporal Gyrus A22c L	-1.985373
						Superior Temporal Gyrus A41/42 R	-1.985373
						ICN 7	-1.985373
						Thalamus lPFtha L	-1.985395
						Basal Ganglia GP R	-1.985865
						Cingulate Gyrus A32p R	-1.985865
						Cingulate Gyrus A32p L	-1.985865
						Insular Gyrus vIa R	-1.986478
						Cingulate Gyrus A24cd L	-1.98656
						Cingulate Gyrus A24rv L	-1.986769
						Basal Ganglia dlPu R	-1.987409
						Cingulate Gyrus A24cd R	-1.987646
						Middle Temporal Gyrus aSTS R	-1.988211
						Superior Temporal Gyrus	-1.988211

						A38l L	
						Inferior Frontal Gyrus A44v L	-1.988211
						Superior Temporal Gyrus A22r R	-2.007063
$`2`	#15 TLE/FIAS	Negative emotional affective expression	4.123106	Insular Gyrus dIa R	1.984511	Insular Gyrus dId L	-1.98406
		Ipsilateral versive signs	2.482263	Cingulate Gyrus A32sg L	1.984356	Inferior Frontal Gyrus IFS L	-1.98406
				Inferior Temporal Gyrus A20cl L	1.98406	Inferior Frontal Gyrus A44d L	-1.98406
				Amygdala lAmyg R	1.983953	Middle Frontal Gyrus IFJ L	-1.98406
						Superior Parietal Lobule A7ip R	-1.984161
						ICN 10	-1.984454
						lateral Occipital Cortex lsOccG R	-1.984529
						Superior Parietal Lobule A5l R	-1.984529
						Superior Parietal Lobule A5l L	-1.984529
						Superior Parietal Lobule A7c L	-1.984529
						Postcentral Gyrus A2 L	-1.985226
						Superior Parietal Lobule A7ip L	-1.985226
						Superior Parietal Lobule A7r R	-1.986769

						Inferior Temporal Gyrus A20r L	-1.991334
$`3`	#13 Multifocal/ FIAS	Symmetric proximal axial tonic posture		Superior Temporal Gyrus A38l L	1.991334	Orbital Gyrus A11m R	-1.98406
				Precentral Gyrus A4t R	1.987409	Superior Frontal Gyrus A9l L	-1.98406
				Inferior Temporal Gyrus A37elv R	1.986769	Basal Ganglia vCa R	-1.984454
				Middle Temporal Gyrus aSTS L	1.986769	Cingulate Gyrus A32sg L	-1.984528
				Superior Temporal Gyrus A22r L	1.986769	MedioVentral Occipital Cortex rCunG L	-1.984529
				Superior Temporal Gyrus A22c L	1.986769	Superior Frontal Gyrus A9m L	-1.985116
				Precentral Gyrus A4tl L	1.984529	MedioVentral Occipital Cortex rCunG R	-1.985226
				Postcentral Gyrus A2 L	1.984454	Parahippocampal Gyrus A35/36c L	-1.985373
				Superior Parietal Lobule A5l R	1.98406	MedioVentral Occipital Cortex cLinG L	-1.986769
				Postcentral Gyrus A2 R	1.983953		
				Inferior Parietal Lobule A40c R	1.983953		
				Superior Parietal	1.983953		

				Lobule A7pc R			
				Inferior Temporal Gyrus A20cv R	1.983953		
				Middle Temporal Gyrus A21c R	1.983953		
				Superior Parietal Lobule A7ip R	1.983871		
				Precuneus A40rv L	1.983832		
				Inferior Parietal Lobule A40rd R	1.983832		
				Inferior Temporal Gyrus A20cl R	1.983832		
$`4`	#4 HH/FAS	Gelastic seizure	2.828427			Postcentral Gyrus A1/2/3tru R	-2.09665
	#11 Reflex/ FIAS	*Impairment of consciousness	-2.436358			Postcentral Gyrus A1/2/3ulhf R	-2.09665
						Postcentral Gyrus A2 R	-2.26557
						Insular Gyrus G R	-2.26559
						Precentral Gyrus A4tl L	-2.26585
						Insular Gyrus dId R	-2.49072
						Insular Gyrus vId/vIg L	-2.49118
						Precuneus A40rv R	-2.49227

						Insular Gyrus dIg R	-2.49431
$`5`	#7 PLE/ FIAS	Positive emotional affective expression	2.828427	Superior Frontal Gyrus A9m L	2.491685	Parahippocampal Gyrus TL L	-2.096613
	#9 Multifocal/ FIAS	Somesthetic localised aura	2.654419	Postcentral Gyrus A1/2/3tru L	2.49092	Hippocampus rHipp L	-2.096647
				Precuneus A5m R	2.490716	Amygdala mAmyg R	-2.096696
				Precentral Gyrus A6cvl R	2.490485	Fusiform Gyrus A37lv L	-2.096729
				Superior Frontal Gyrus A8m R	2.490485	Thalamus PPtha L	-2.096861
				Superior Frontal Gyrus A8m L	2.490485	Fusiform Gyrus A20rv L	-2.09712
				Middle Frontal Gyrus A6vl R	2.265574	Middle Temporal Gyrus aSTS L	-2.098061
				ICN 6	2.265555	Hippocampus cHipp L	-2.265574
				Middle Frontal Gyrus A8vl L	2.097543	Thalamus rTtha L	-2.265587
				Precuneus A5m L	2.096729	Thalamus Stha R	-2.265657
						lateral Occipital Cortex lsOccG L	-2.265671
						posterior Superior Temporal Sulcus rpSTS L	-2.265671
						Amygdala mAmyg L	-2.265845
						Inferior Frontal	-2.270167

						Gyrus A45r L	
						Thalamus PPtha R	-2.490396
						Thalamus rTtha R	-2.490485
						Thalamus Otha L	-2.490496
						Inferior Parietal Lobule A39c L	-2.490496
						Thalamus mPFtha R	-2.490645
						Thalamus Otha R	-2.490716
						Thalamus lPFtha R	-2.491179
						Thalamus cTtha R	-2.492269
						Thalamus cTtha L	-2.495658
$`6`	# 16 FLE /FIAS	Staring behavioural arrest	2.436358	Insular Gyrus dIa L	2.492305	Parahippocampal Gyrus TH R	-2.096861
	#10 FLE/ FAS			Inferior Frontal Gyrus A44op L	2.492305	Superior Frontal Gyrus A6dl L	-2.097216
				Insular Gyrus vIa L	2.492119	Superior Parietal Lobule A7pc L	-2.265574
				Basal Ganglia GP R	2.491872	Precentral Gyrus A4ul R	-2.265574
				Superior Frontal Gyrus A9l R	2.490485	Cingulate Gyrus A23v L	-2.265657
				Insular Gyrus vIa R	2.269083	Paracentral Lobule A1/2/3ll L	-2.267197
				Basal Ganglia	2.267824	Paracentral	-2.270311

				dlPu R		Lobule A4ll L	
				Orbital Gyrus A12/47l L	2.265574	Precuneus A5m L	-2.490369
				Insular Gyrus dId L	2.097543	Precentral Gyrus A4ul L	-2.490369
				Middle Frontal Gyrus A9/46v R	2.096613	Hippocampus cHipp R	-2.490396
						Cingulate Gyrus A23v R	-2.490396
						Precuneus A7m R	-2.490396
						Precuneus A7m L	-2.490396
						Parahippocampal Gyrus A35/36c R	-2.490396
						Parahippocampal Gyrus TL R	-2.490645
						Precentral Gyrus A4t L	-2.490645
						Precuneus dmPOS R	-2.491398
						Precuneus A5m R	-2.491398
						Precentral Gyrus A4t R	-2.492964
$`7`	#8 FLE/ FIAS	*proximal distal contralateral tonic posture	-2.237835	Parahippocampal Gyrus A35/36c L	3.135508	Parahippocampal Gyrus A35/36r	-2.078212
	#17 FLE/ FIAS			Paracentral Lobule A1/2/3ll L	3.135508		
	#2 Reflex/			Parahippocampal	2.79023		

	FIAS			Gyrus TI L			
	#1 Reflex/ FIAS			Superior Parietal Lobule A7pc L	2.404233		
	#3 PLE/ FAS			Thalamus lPFtha L	2.327773		
				Thalamus Otha R	2.252479		
				Thalamus Stha R	2.221718		
				Thalamus PPtha R	2.063995		
				Thalamus lPFtha R	2.059595		
				Thalamus Otha L	2.003985		
$`8`	#6 HH/ FAS			lateral Occipital Cortex msOccG L	2.792472		
	#14 Multifocal /FIAS			Cingulate Gyrus A23v L	2.791917		
	#12 TLE/ FIAS			Cingulate Gyrus A23d L	2.791609		
				Fusiform Gyrus A20rv L	2.791381		
				Fusiform Gyrus A37lv L	2.791261		
				Cingulate Gyrus A23d R	2.648812		
				Parahippocampal Gyrus A35/36r R	2.555665		
				Precuneus dmPOS L	2.459836		
				Inferior Temporal Gyrus	2.459836		

				A20r R			
				ICN 4	2.459364		
				Inferior Temporal Gyrus A20iv L	2.341502		
				Precuneus A31 R	2.340262		
				Parahippocampal Gyrus A28/34 R	2.327902		
				lateral Occipital Cortex iOccG L	2.326447		
				Cingulate Gyrus A23v R	2.234621		
				Fusiform Gyrus A37mv L	2.234621		
				Precuneus A31 L	2.234264		
				Fusiform Gyrus A37mv R	2.144914		
				Superior Parietal Lobule A7r L	2.120757		
				lateral Occipital Cortex OPC L	2.056231		
				MedioVentral Occipital Cortex cCunG R	1.994547		
$`9`	#5 FLE/ FIAS	asymmetric facial Rictus contraction	2.91577	Thalamus cTtha L	1.991334		
				Inferior Frontal Gyrus A44v L	1.991334		
				Orbital Gyrus A11l R	1.988211		
				Thalamus cTtha R	1.986769		

				posterior Superior Temporal Sulcus cpSTS R	1.986769		
				ICN 7	1.986769		
				Cingulate Gyrus A24cd L	1.986443		
				Cingulate Gyrus A24rv L	1.986234		
				Basal Ganglia vCa R	1.985373		
				Insular Gyrus vId/vIg L	1.985226		
				Superior Temporal Gyrus #ÉRTÉK! R	1.985226		
				ICN 10	1.985226		
				Thalamus PPtha L	1.984529		
				Thalamus mPMtha R	1.984529		
				Basal Ganglia dCa L	1.984529		
				Basal Ganglia vmPu L	1.984529		
				Insular Gyrus dIg L	1.984529		
				Parahippocampal Gyrus TH R	1.984529		
				Orbital Gyrus A11m R	1.984529		
				Superior Parietal Lobule A7ip L	1.984454		
				Thalamus Otha L	1.984161		

				Thalamus Stha R	1.984161		
				lateral Occipital Cortex lsOccG R	1.98406		
				Cingulate Gyrus A23c L	1.98406		
				Superior Parietal Lobule A7c L	1.98406		
				Orbital Gyrus A11l L	1.98406		
				Thalamus PPtha R	1.983953		
				Basal Ganglia vCa L	1.983953		
				Precuneus A7m L	1.983953		
				Precentral Gyrus A4hf R	1.983953		
				Orbital Gyrus A11m L	1.983953		
				Inferior Frontal Gyrus IFS R	1.983953		
				Basal Ganglia NAC L	1.983871		
				Thalamus Stha L	1.983832		
				Parahippocampal Gyrus TL L	1.983832		
				Inferior Frontal Gyrus A44op R	1.983832		
				ICN 8	1.983832		

Note. All deactivations ($p<0.05$) are ordered greater to lesser

Chapter 12

Overall Discussion

Summary of Main Findings

ICN_atlas

Consistent with previous studies (Kozak et al., 2017) ICN_atlas was validated for spatial extent and activation levels. The ICN construct was upheld in the language maps of TLE patients but was not evident for ictal phases or in simulated ICN_atlas data. A review of the metrics to align more uniformly with spatial and intensity dimensions of ICNs was recommended.

Language

1. Significantly higher IQ and semantic fluency were seen for controls relative to patients.
2. In controls, we found that ICN recruitment was stable between sessions. Amodal linguistic processing was evident in ICN ROIs. A predominantly left lateralised language network was seen for most right-handed subjects and the relevance of temporal regions for word retrieval in the context of naming requirements and the relevance of frontal areas for word retrieval in the context of fluency were demonstrated.
3. ICNs derived from resting state and task fMRI and previously identified as having strongly similarity (Smith et al., 2009), showed significant different activation to language tasks across subjects.
4. ICN activation was significantly associated with VF performance outside the scanner.
5. There was a significant association between a greater number of AED and poorer VF across patient groups.

6. Across both patient groups a lower monthly seizure frequency was significantly correlated with greater AN deactivation in the DMN (task ICN 13) and a higher number of AEDs was significantly correlated with reduced VF activation in temporal and frontal ICNs. An earlier age of onset was significantly correlated with greater atypically lateralised deactivating VF in task ICN 5.

7. Across subjects there were no significant differences in LI achieved by different paradigms in the ATL. However, across paradigms the ATL showed significantly greater activation compared to ICN ROIs and a significantly greater proportion of controls was atypically lateralised for FF in the ATL compared to LTLE.

8. The ATL showed significant IFG&MFG connectivity for naming paradigms and significant PTL connectivity for auditory naming, FF and SF.

9. Activation in temporal lobe networks serve as a predictor for naming and fluency decline. Left lateralised PN in the PTL and task ICN 12 showed 80% PPV for significant naming decline after ATLR. Left lateralisation in both the PTL and the ATL and both task ICN 1 and the PTL showed 24 % PPV for significant decline in semantic fluency. Left lateralised VF in task ICN 16 provided a PPV of 14% for significant phonetic fluency decline. We observed an increasing likelihood of significant decline with greater magnitude of left LI for VF, SF and naming.

Intrinsic connectivity networks and seizure semiology

1. Canonical ICNs including the DMN are not a meaningful framework for the study of seizure spread and ictal semiology. Clinical signs were associated with seizure networks that showed varying levels of haemodynamic activation and deactivation involving multiple ICN ROIs that showed abnormal connectivity and that were recruited along an

anterior-posterior axis along with other cortical and subcortical areas that showed varying degrees of connectivity.

2. Beyond its practical importance, impairment of awareness serves as a significant classifying feature of clinical expression with its neural basis associated with the inhibition of normal brain functions.

Neurobiological and clinical implications

Experimental work presented in this thesis established the following:

Recruitment of ICNs is reliable across sessions in healthy controls

1. The result establishes the study of ICNs in healthy controls as normative reference. However, test-retest reliability of ICNs in patients were not investigated and represents a crucial question that need to be addressed in future work.

Language networks as observed in the recruitment of ICNs are affected by disease

1. We found a significant impact of disease features on intensities of ICN activation and deactivation, and lateralisation. We observed cross dominance between language tasks in individual patients, across paradigms.
2. Acquired lesions can cause intra-and inter-hemispheric reorganisation (Staudt, 2010; Staudt et al., 2008) and language reorganisation in LTLE includes intra and inter-hemispheric changes (Mbwana et al., 2009). The network abnormalities that have previously been reported for age of onset (Duke et al., 2012; Miro et al., 2014; Trimmel et al., 2018; Wellmer et al., 2009a; Yuan et al., 2006), number of AEDs (Helmstaedter & Witt, 2008; Szaflarski & Allendorfer, 2012; Wandschneider et al., 2014; Xiao et al., 2018; Yasuda et al., 2013) and seizure frequency (Jayakar et al., 2002) were seen in three ICNs that encompass left frontal-parietal regions, the DMN and task ICN 5, that encompasses cortical and subcortical structures - the inferior

temporal gyrus, fusiform gyrus, para-hippocampal gyrus, cingulate gyrus, medioventral occipital cortex, hippocampus, and thalamus – anatomical areas previously shown to have language involvement. The effects on fMRI BOLD maps compound prediction of language decline in the clinical context and TLE patients have showed more widespread activations compared to controls, particularly in the posterior language areas (Federico, 2011; Rosenberger et al., 2009). Furthermore, in patients with epilepsy has shown language areas over wide and atypical areas of the left lateral cortex (Schäffler et al., 1996). Thus, vigilance as to the potential impact of disease features as it relates to peak activation and lateralisation is required and reiterates importance of a panel of tasks and consideration of metrics in addition to activation peaks.

Features of disease can have significant impact on performance

1. We found a significant association between greater number of AEDs and poorer VF performance, consistent with report of an adverse effect of a higher drug load and network abnormalities on cognitive function (Feldman et al., 2018; Holmes, 2015; Witt et al., 2015).

fMRI activations of intrinsic connectivity networks and anatomical ROIs can predict clinically significant language dysfunction following ATLR

1. We saw that a standardised atlasing methodology (ICN_atlas) and investigation of ICNs can provide meaningful contribution to the presurgical workup. ICN activation contributed to predictive sensitivity and specificity of naming and fluency decline, indicating a role for support networks in retaining language competence following ATLR.

a. We found that temporal lobe networks predict postoperative naming and fluency deficits after ATLR. The role of temporal lobe networks in prediction has now been reiterated in a range of studies (Gonzálvez et al., 2016; Sabsevitz et al., 2003; Trimmel et al., 2018, 2019) that have also shown a more posterior localisation for picture naming compared to auditory naming (Hamberger et al., 2007; Trimmel et al., 2019). We have shown the importance of the PTL and task ICN 12 in prediction of naming decline after ATLR. The relevance of these ROIs are consistent with cortico-cortical evoked potential results that have shown involvement of posterior temporal language regions in object naming, and indicated that reorganisation can involve shifts away from the densely connected termination area of the anterior—posterior language fibre pathways to cortex beyond the typical language areas (Trimmel et al., 2013). The greatest structural overlap between these posterior networks were seen in the left fusiform gyrus. It implicates a crucial role for the left medioventral fusiform gyrus in prediction in line with recent findings (Trimmel et al., 2019) and voxel based morphometry results that implicate left posterior temporal cortices in semantic and lexical naming mechanisms (Migliaccio et al., 2016).

b. Our results showed an increasing likelihood of significant decline with greater magnitude of left LI for VF, SF and naming, consistent with Trimmel and colleagues who showed that a PN LI of higher than 0.34 gave 100% sensitivity and 92% specificity (Trimmel et al., 2019).

2. Descriptive data suggest that language is reorganised following surgery.

a. Pre to post-operative connectivity shifts were seen for PN from atypical to left dominance for the decline group and left to atypical lateralisation for the no decline group. Post operatively the remnant of the ATL showed greater connectivity with the PTL for both groups; the decline group with the left lateralised PTL and the no decline group with the atypically lateralised PTL. Postoperative language reorganisation has been observed in a number of diffusion tensor imaging (Pustina et al., 2014; Yogarajah et al., 2010) and fMRI studies (Backes et al., 2005; Bonelli et al., 2012; Helmstaedter et al., 2006; Wong et al., 2009), and after stroke (Saur et al., 2006). Our results are partly in line with an association between better clinical naming and functional connectivity of left posterior temporal lobe networks in TLE (Trimmel et al., 2018).

3. Language performance is related to reorganisation.

a. For LTLE patients, regardless of pathology, pre-operative reorganisation to the left or right PTL determined naming outcome after ATLR. Descriptive data suggest that groups with and without decline showed stronger connectivity between the remnant of the ATL and the PTL post operatively with greater activation but ineffective recruitment of the ipsilateral PTL in decline patients and greater activation and effective recruitment of the contralateral PTL in those that did not decline.

b. Our results suggest that prediction of naming decline at four months is determined by preoperative interhemispheric reorganisation and post-operative intra-hemispheric reorganisation to posterior temporal networks. The results are partly in line with preservation of naming in patients with hippocampal

sclerosis after ATLR which has been attributed to intra-hemispheric reorganisation, in particular to the posterior and inferior temporal regions (Hamberger, Seidel, et al., 2007).

c. fMRI activations of intrinsic connectivity networks and anatomical ROIs can predict clinically significant language dysfunction following ATLR.

EEG-fMRI and anatomical atlasing can delineate semiology networks

1. Rather than indicating clinical utility for ICNs in mapping semiology, our results suggest a potential role for EEG-fMRI in standardising (e.g., use of atlasing) the study of semiology networks across anatomically defined cortical and subcortical structures. The methodology may provide information that help with the interpretation of EEG-fMRI BOLD maps in the presurgical workout, specifically the question of BOLD clusters of interictal spikes and seizures remote from the presumed seizure onset zone and epileptogenic zone. Furthermore, it may be particularly valuable in addressing questions in relation to the role of subcortical structures.
2. Clinical signs are associated with transient networks that comprise varying degrees of activation, deactivation and connectivity across cortical and subcortical areas. The findings highlight idiosyncratic connectivity features across different structures and suggests the importance of considering inhibition in seizure semiology that may help to inform presurgical implantation strategy and the interpretation of its results.
3. In conclusion, simultaneous EEG-fMRI can reveal haemodynamic changes and associated clinical signs related to the seizure network, across anatomical and ICN ROIs. However, the quality of EEG data obtained within the MRI environment is strongly affected by subject motion (two patients were excluded from the study on

account of large movement artifact - see Chapter 11), as well as artefacts caused by the scanning gradients and the heartbeat. It has limited its application in populations such as paediatric patients or to study epileptic seizure onset (Maziero et al., 2016). It highlights the need for technical developments to optimise data quality to realise the potential of EEG-fMRI in clinical epilepsy practise.

Limitations

Limitations of experimental work were reported and discussed in the relevant sections at the conclusion of each experimental study. However, throughout, and particularly in the investigation of semiology, studies were limited by heterogenous pathologies, and small subject numbers. While the multivariate methods rely on group analyses the heterogenous pathologies, and small subject numbers, particularly in the investigation of ictal semiology calls for single subject case designs**.** Hypotheses and analysis were confined to a priori defined regions of interest analysis so that possible mechanisms in other brain areas were not assessed. While the results showed potential utility for EEG-fMRI in mapping seizure networks and associated clinical signs, any conclusions are likely to be compounded by circadian timescales reportedly linked to variation in seizure pathways in individual patients with focal epilepsy (Schroeder et al., 2020). The findings in language studies were based on patients who predominantly suffered from unilateral TLE with hippocampal sclerosis and the findings here will need to be established in larger groups of patients with different pathologies.

The fMRI results presented in this work are based on group findings. Individual difference is not represented in group observations and the post-operative naming deficits seen in righthanded patients with right TLE indicate a focus in neuroimaging analysis for

patient specific profiles to predict both seizure and language outcomes following surgical interventions.

Individual case data presented in Chapter 9 showed marked within-group differences which are of immediate clinical relevance. Subgroups that represented homogenous fMRI patterns across patients and controls did not show significant differences in relation to age, handedness, IQ, clinical scores, or disease characteristics. It suggests that there are multiple patterns of resting and task driven fMRI activation in patients with similar mesial TLE, and that the impact of these features is not readily detected in group level haemodynamic patterns or that our methods still lack the sophistication to distinguish the impact of these features in haemodynamic patterns.

Language performance, relevant in a number of fMRI studies were based on single assessments that are subject to measurement error, and quantification of decline using a visual confrontation task is not necessarily synonymous with a clinically significant decline. Although Auditory naming may be a more accurate measure of everyday and subjective naming difficulties, the AN task did not have a direct out of scanner analogue. AN activation was different from that seen for PN and given the relevance to language performance in everyday function, it would be important to develop and employ out of scanner analogues for AN in future work.

Finally, the language studies did not consider the parameters of resection in individual patients and significant differences in extent of tissue removal may contribute to cognitive impairment (Alpherts et al., 2008; Helmstaedter et al., 2011).

Future perspectives

In conclusion, we have shown that fMRI can elucidate biological properties that reflect patient clinical history and status and the ability to predict psychological dimensions, as it relates to surgical outcome.

The observed change in connectivity involving structural and functional networks in the context of pre-operative differences and post-operative changes in performance is consistent with observations of reduced functional connectivity in cognitive impairment (Voets et al., 2009) and is an area that should be elaborated in further studies. That is, investigation of neural activation across the whole brain using connectivity parameters as predictive indices.

This work suggested that greater disease burden and right lateralised activation in posterior temporal networks constitute lesser vulnerability to decline after left ATLR in LTLE whereas greater disease burden and left activation confer a greater risk of decline in RTLE. It should be investigated in further studies.

While significant impairment in language function at a relatively early post operative period is likely to significant impact on social and occupation function and provide insights as to plasticity, language reorganisation and recovery of function may continue well beyond a four-month period at which our patients were assessed postoperatively. That is, four months might be too early for compensatory responses to become fully functional. Thus, studies of language organisation and functional ability after surgery in both patients and healthy controls at longer post operative intervals will provide further insights into recovery and plasticity.

While functional connectivity promises a better understanding of seizure propagation and the spread of signs, the results indicated both fragmentation and binding of canonical

ICNs - reflecting alteration in normal connectivity. The results here have shown that seizures involve both inhibition and activation of neural structures (Norden & Blumenfeld, 2002) in line with electrophysiological features of epileptic seizures which have shown that ahead of an ictal wavefront, there is an extreme discrepancy between the very high level of synaptic and the low level of local neuronal firing at any given moment during an ongoing ictal event: There is a focus of recruited, and a penumbra of restrained territories (Trevelyan & Schevon, 2013).

The findings that suspension or inhibition of normal activity across brain areas is significantly associated with clinical expression, are in line with observations in generalised epilepsy (Hamandi et al., 2008) and with methods such as direct electro-cortical stimulation and the intracarotid amytal test that demonstrate behavioural effects when function is temporarily interrupted (Golby & McConnell, 2005), including changes in consciousness that are accompanied by widespread changes in brain physiology (Quraishi et al., 2018). The results in this thesis showed that two signs were uniquely and significantly present in clusters of deactivations. It calls for a greater focus on the nature of the relationship between seizure semiology /functional correlates of haemodynamic deactivation and will likely benefit from further insights of seizure mechanisms at the microscale, encompassing cellular signalling and communication (Farrell et al., 2019).

Although cognitive fMRI can help to inform the viability of surgery as it relates to outcome, research into its therapeutic viability (FMRI neurofeedback) has to date not yielded significant results (Thibault et al., 2018). Recent work employing simultaneous bimodal neurofeedback that exploit the fast response (milliseconds) characteristic of EEG and a high spatial resolution of fMRI have shown promise (Savelov et al., 2019). EEG has seen development from diagnostic method to therapeutic implementation in the context of EEG

neurofeedback and effectiveness across a range of disorders and diagnoses, including seizure control in epilepsy (Hetkamp et al., 2019; Tan et al., 2009; Van Doren et al., 2019) have been reported. In this context targeting and alteration of abnormal large-scale network connectivity during the interictal state may have utility in relation to seizure frequency and semiology.

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