UNIVERSITÉ TOULOUSE III – PAUL SABATIER
FACULTÉ DE SANTÉ

ANNÉE 2023 2023 TOU3 1577

THÈSE

POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

MÉDECINE SPÉCIALISÉE CLINIQUE

Présentée et soutenue publiquement

par

Pauline CALVAT

le 13 septembre 2023

L'analyse des crises épileptiques à des échelles multiples grâce à des électrodes hybrides intracrâniennes – les tétrodes – chez des patients épileptiques pharmacorésistants

Directeur de thèse : Dr Jonathan CUROT

JURY

Monsieur le Professeur Jérémie PARIENTE	Président
Monsieur le Docteur Luc VALTON	Assesseur
Monsieur le Docteur Jonathan CUROT	Assesseur
Madame le Docteur Rachel DEBS	Assesseur
Monsieur le Docteur Emmanuel BARBEAU	Suppléant
Monsieur le Professeur Sylvain RHEIMS	Membre invité

UNIVERSITÉ TOULOUSE III PAUL SABATIER

FACULTE DE SANTE
Département Médecine Maieutique et Paramédicaux
Tableau des personnels HU de médecine
Mars 2022

Professeurs Honoraires

Doyen Honoraire	M. CHAP Hugues
Doyen Honoraire	M. GUIRAUD-CHAUMEIL Bernard
Doyen Honoraire	M. LAZORTHES Yves
Doyen Honoraire	M. PUEL Pierre
Doyen Honoraire	M. ROUGE Daniel
Doyen Honoraire	M. VINEL Jean-Pierre
Professeur Honoraire	M. ABBAL Michel
Professeur Honoraire	M. ADER Jean-Louis
Professeur Honoraire	M. ADOUE Daniel
Professeur Honoraire	M. ARBUS Louis
Professeur Honoraire	M. ARLET Philippe
Professeur Honoraire	M. ARLET-SUAU Elisabeth
Professeur Honoraire	M. ARNE Jean-Louis
Professeur Honoraire	M. BARRET André
Professeur Honoraire	M. BARTHE Philippe
Professeur Honoraire	M. BAYARD Francis
Professeur Honoraire	M. BLANCHER Antoine
Professeur Honoraire	M. BOCCALON Henri
Professeur Honoraire	M. BONAFE Jean-Louis
Professeur Honoraire	M. BONEU Bernard
Professeur Honoraire	M. BONNEVIALLE Paul
Professeur Honoraire	M. BOUNHOURE Jean-Paul
Professeur Honoraire	M. BOUTAULT Franck
Professeur Honoraire Associé	M. BROS Bernard
Professeur Honoraire	M. BUGAT Roland
Professeur Honoraire	M. CAHUZAC Jean-Philippe
Professeur Honoraire	M. CARATERO Claude
Professeur Honoraire	M. CARLES Pierre
Professeur Honoraire	M. CARON Philippe
Professeur Honoraire	M. CARRIERE Jean-Paul
Professeur Honoraire	M. CARTON Michel
Professeur Honoraire	M. CATHALA Bernard
Professeur Honoraire	M. CHABANON Gérard
Professeur Honoraire	M. CHAMONTIN Bernard
Professeur Honoraire	M. CHAP Hugues
Professeur Honoraire	M. CHAVOIN Jean-Pierre
Professeur Honoraire	M. CLANET Michel
Professeur Honoraire	M. CONTE Jean
Professeur Honoraire	M. COSTAGLIOLA Michel
Professeur Honoraire	M. COTONAT Jean
Professeur Honoraire	M. DABERNAT Henri
Professeur Honoraire	M. DAHAN Marcel
Professeur Honoraire	M. DALOUS Antoine
Professeur Honoraire	M. DALY-SCHVEITZER Nicolas
Professeur Honoraire	M. DAVID Jean-Frédéric
Professeur Honoraire	M. DELSOL Georges
Professeur Honoraire	Mme DELISLE Marie-Bernadette
Professeur Honoraire	Mme DIDIER Jacqueline
Professeur Honoraire	M. DUCOS Jean
Professeur Honoraire	M. DUFFAUT Michel
Professeur Honoraire	M. DUPRE M.
Professeur Honoraire	M. DURAND Dominique
Professeur Honoraire associé	M. DUTAU Guy
Professeur Honoraire	M. ESCHAPASSE Henri
Professeur Honoraire	M. ESCOURROU Jean
Professeur Honoraire	M. ESQUERRE J.P.
Professeur Honoraire	M. FABIE Michel
Professeur Honoraire	M. FABRE Jean
Professeur Honoraire	M. FOURNIAL Gérard
Professeur Honoraire	M. FOURNIE Bernard
Professeur Honoraire	M. FOURTANIER Gilles
Professeur Honoraire	M. FRAYSSE Bernard
Professeur Honoraire	M. FREXINOS Jacques
Professeur Honoraire	Mme GENESTAL Michèle
Professeur Honoraire	M. GERAUD Gilles
Professeur Honoraire	M. GHISOLFI Jacques
Professeur Honoraire	M. GLOCK Yves
Professeur Honoraire	M. GOUZI Jean-Louis
Professeur Honoraire	M. GRAND Alain
Professeur Honoraire	M. GUIRAUD CHAUMEIL Bernard
Professeur Honoraire	M. HOFF Jean
Professeur Honoraire	M. JOFFRE Francis
Professeur Honoraire	M. LAGARRIGUE Jacques
Professeur Honoraire	M. LANG Thierry
Professeur Honoraire	Mme LARENG Marie-Blanche
Professeur Honoraire	M. LAURENT Guy
Professeur Honoraire	M. LAZORTHES Franck
Professeur Honoraire	M. LAZORTHES Yves
Professeur Honoraire	M. LEOPHONTE Paul
Professeur Honoraire	M. MAGNAVAL Jean-François
Professeur Honoraire	M. MALECAZE François
Professeur Honoraire	M. MANELFE Claude
Professeur Honoraire	M. MANSAT Michel
Professeur Honoraire	M. MARCHOU Bruno
Professeur Honoraire	M. MASSIP Patrice
Professeur Honoraire	Mme MARTY Nicole
Professeur Honoraire	M. MAZIERES Bernard
Professeur Honoraire	M. MONROZIES Xavier
Professeur Honoraire	M. MOSCOVICI Jacques
Professeur Honoraire	M. MURAT
Professeur Honoraire associé	M. NICODEME Robert
Professeur Honoraire	M. OLIVES Jean-Pierre
Professeur Honoraire	M. PARINAUD Jean
Professeur Honoraire	M. PASCAL Jean-Pierre
Professeur Honoraire	M. PERRET Bertrand
Professeur Honoraire	M. PESSEY Jean-Jacques
Professeur Honoraire	M. PLANTE Pierre
Professeur Honoraire	M. PONTONNIER Georges
Professeur Honoraire	M. POURRAT Jacques
Professeur Honoraire	M. PRADERE Bernard
Professeur Honoraire	M. PRIS Jacques
Professeur Honoraire	Mme PUEL Jacqueline
Professeur Honoraire	M. PUEL Pierre
Professeur Honoraire	M. PUJOL Michel
Professeur Honoraire	M. QUERLEU Denis
Professeur Honoraire	M. RAILHAC Jean-Jacques
Professeur Honoraire	M. REGIS Henri
Professeur Honoraire	M. REGNIER Claude
Professeur Honoraire	M. REME Jean-Michel
Professeur Honoraire	M. RISCHMANN Pascal
Professeur Honoraire	M. RIVIERE Daniel
Professeur Honoraire	M. ROCHE Henri
Professeur Honoraire	M. ROCHICCIOLI Pierre
Professeur Honoraire	M. ROLLAND Michel
Professeur Honoraire	M. ROQUES-LATRILLE Christian
Professeur Honoraire	M. RUMEAU Jean-Louis
Professeur Honoraire	M. SALVADOR Michel
Professeur Honoraire	M. SALVAYRE Robert
Professeur Honoraire	M. SARRAMON Jean-Pierre
Professeur Honoraire	M. SERRE Guy
Professeur Honoraire	M. SIMON Jacques
Professeur Honoraire	M. SUC Jean-Michel
Professeur Honoraire	M. THOUVENOT Jean-Paul
Professeur Honoraire	M. TREMOULET Michel
Professeur Honoraire	M. VALDIGUIE Pierre
Professeur Honoraire	M. VAYSSE Philippe
Professeur Honoraire	M. VINEL Jean-Pierre
Professeur Honoraire	M. VIRENQUE Christian
Professeur Honoraire	M. VOIGT Jean-Jacques

Professeurs Emérites

Professeur ARLET Philippe
Professeur BOUTAULT Franck
Professeur CARON Philippe
Professeur CHAMONTIN Bernard
Professeur CHAP Hugues
Professeur GRAND Alain
Professeur LAGARRIGUE Jacques
Professeur LAURENT Guy
Professeur LAZORTHES Yves
Professeur MAGNAVAL Jean-François
Professeur MARCHOU Bruno
Professeur PERRET Bertrand
Professeur RISCHMANN Pascal
Professeur RIVIERE Daniel
Professeur ROUGE Daniel

FACULTE DE SANTE
Département Médecine Maieutique et Paramédicaux

P.U. - P.H.
Classe Exceptionnelle et 1ère classe

M. ACAR Philippe	Pédiatrie
M. ACCADBLED Franck (C.E)	Chirurgie Infantile
M. ALRIC Laurent (C.E)	Médecine Interne
M. AMAR Jacques	Thérapeutique
Mme ANDRIEU Sandrine	Epidémiologie, Santé publique
M. ARBUS Christophe	Psychiatrie
M. ARNAL Jean-François (C.E)	Physiologie
M. ATTAL Michel (C.E)	Hématologie
M. AVET-LOISEAU Hervé	Hématologie, transfusion
M. BERRY Antoine	Parasitologie
Mme BERRY Isabelle (C.E)	Biophysique
M. BIRMES Philippe	Psychiatrie
M. BONNEVILLE Fabrice	Radiologie
M. BOSSAVY Jean-Pierre (C.E)	Chirurgie Vasculaire
M. BRASSAT David	Neurologie
M. BROUCHET Laurent	Chirurgie thoracique et cardio-vascul
M. BROUSSET Pierre (C.E)	Anatomie pathologique
M. BUJAN Louis (C. E)	Urologie-Andrologie
Mme BURA-RIVIERE Alessandra (C.E)	Médecine Vasculaire
M. BUREAU Christophe	Hépato-Gastro-Entérologie
M. BUSCAIL Louis (C.E)	Hépato-Gastro-Entérologie
M. CALVAS Patrick (C.E)	Génétique
M. CANTAGREL Alain (C.E)	Rhumatologie
M. CARRERE Nicolas	Chirurgie Générale
M. CARRIE Didier (C.E)	Cardiologie
M. CHAIX Yves	Pédiatrie
Mme CHARPENTIER Sandrine	Médecine d'urgence
M. CHAUFOUR Xavier	Chirurgie Vasculaire
M. CHAUVEAU Dominique	Néphrologie
M. CHAYNES Patrick	Anatomie
M. CHIRON Philippe (C.E)	Chir. Orthopédique et Traumatologie
M. CHOLLET François (C.E)	Neurologie
M. CONSTANTIN Arnaud	Rhumatologie
M. COURBON Frédéric	Biophysique
Mme COURTADE SAIDI Monique (C.E)	Histologie Embryologie
M. DAMBRIN Camille	Chir. Thoracique et Cardiovasculaire
M. DE BOISSEZON Xavier	Médecine Physique et Réadapt Fonct.
M. DEGUINE Olivier (C.E)	Oto-rhino-laryngologie
M. DELABESSE Eric	Hématologie
M. DELOBEL Pierre	Maladies Infectieuses
M. DELORD Jean-Pierre (C.E)	Cancérologie
M. DIDIER Alain (C.E)	Pneumologie
M. DUCOMMUN Bernard	Cancérologie
Mme DULY-BOUHANICK Béatrice (C.E)	Thérapeutique
M. ELBAZ Meyer	Cardiologie
M. FERRIERES Jean (C.E)	Epidémiologie, Santé Publique
M. FOURCADE Olivier	Anesthésiologie
M. FOURNIÉ Pierre	Ophtalmologie
M. GALINIER Michel (C.E)	Cardiologie
M. GAME Xavier	Urologie
Mme GARDETTE Virginie	Epidémiologie, Santé publique
M. GEERAERTS Thomas	Anesthésiologie et réanimation
Mme GOMEZ-BROUCHET Anne-Muriel	Anatomie Pathologique
M. GOURDY Pierre (C.E)	Endocrinologie
M. GROLLEAU RAOUX Jean-Louis (C.E)	Chirurgie plastique
Mme GUIMBAUD Rosine	Cancérologie
Mme HANAIRE Hélène (C.E)	Endocrinologie
M. HUYGHE Eric	Urologie
M. IZOPET Jacques (C.E)	Bactériologie-Virologie
M. KAMAR Nassim (C.E)	Néphrologie

P.U. Médecine générale

M. OUSTRIC Stéphane (C.E)

Mme LAMANT Laurence (C.E)	Anatomie Pathologique
M. LANGIN Dominique (C.E)	Nutrition
Mme LAPRIE Anne	Radiothérapie
M. LARRUE Vincent	Neurologie
M. LAUQUE Dominique (C.E)	Médecine d'Urgence
M. LAUWERS Frédéric	Chirurgie maxillo-faciale
M. LEOBON Bertrand	Chirurgie Thoracique et Cardio-vasculaire
M. LEVADE Thierry (C.E)	Biochimie
M. LIBLAU Roland (C.E)	Immunologie
M. MALAVAUD Bernard	Urologie
M. MANSAT Pierre	Chirurgie Orthopédique
M. MARQUE Philippe (C.E)	Médecine Physique et Readaptation
M. MAS Emmanuel	Pédiatrie
M. MAURY Jean-Philippe (C.E)	Cardiologie
Mme MAZEREEUW Juliette	Dermatologie
M. MAZIERES Julien (C.E)	Pneumologie
M. MINVILLE Vincent	Anesthésiologie Réanimation
M. MOLINIER Laurent (C.E)	Epidémiologie, Santé Publique
M. MONTASTRUC Jean-Louis (C.E)	Pharmacologie
Mme MOYAL Elisabeth (C.E)	Cancérologie
M. MUSCARI Fabrice	Chirurgie Digestive
Mme NOURHASHEMI Fatemeh (C.E)	Gériatrie
M. OLIVOT Jean-Marc	Neurologie
M. OSWALD Eric (C.E)	Bactériologie-Virologie
M. PARIENTE Jérémie	Neurologie
M. PAUL Carle (C.E)	Dermatologie
M. PAYOUX Pierre (C.E)	Biophysique
M. PAYRASTRE Bernard (C.E)	Hématologie
M. PERON Jean-Marie (C.E)	Hépato-Gastro-Entérologie
M. RASCOL Olivier (C.E)	Pharmacologie
Mme RAUZY Odile	Médecine Interne
M. RAYNAUD Jean-Philippe (C.E)	Psychiatrie Infantile
M. RECHER Christian(C.E)	Hématologie
M. RITZ Patrick (C.E)	Nutrition
M. ROLLAND Yves (C.E)	Gériatrie
M. RONCALLI Jérôme	Cardiologie
M. ROUGE Daniel (C.E)	Médecine Légale
M. ROUSSEAU Hervé (C.E)	Radiologie
M. ROUX Franck-Emmanuel	Neurochirurgie
M. SAILLER Laurent (C.E)	Médecine Interne
M. SALES DE GAUZY Jérôme (C.E)	Chirurgie Infantile
M. SALLES Jean-Pierre (C.E)	Pédiatrie
M. SANS Nicolas	Radiologie
M. SCHMITT Laurent (C.E)	Psychiatrie
Mme SELVES Janick (C.E)	Anatomie et cytologie pathologiques
M. SENARD Jean-Michel (C.E)	Pharmacologie
M. SERRANO Elie (C.E)	Oto-rhino-laryngologie
M. SIZUN Jacques (C.E)	Pédiatrie
M. SOL Jean-Christophe	Neurochirurgie
Mme SOTO-MARTIN Maria-Eugénia	Gériatrie et biologie du vieillissement
M. SOULAT Jean-Marc	Médecine du Travail
M. SOULIE Michel (C.E)	Urologie
M. SUC Bertrand	Chirurgie Digestive
Mme TAUBER Marie-Thérèse (C.E)	Pédiatrie
M. TELMON Norbert (C.E)	Médecine Légale
Mme TREMOLLIERES Florence	Biologie du développement
Mme URO-COSTE Emmanuelle (C.E)	Anatomie Pathologique
M. VAYSSIERE Christophe (C.E)	Gynécologie Obstétrique
M. VELLAS Bruno (C.E)	Gériatrie
M. VERGEZ Sébastien	Oto-rhino-laryngologie

FACULTE DE SANTE
Département Médecine Maieutique et Paramédicaux

P.U. - P.H.
2ème classe

M. ABBO Olivier	Chirurgie infantile
M. AUSSEIL Jérôme	Biochimie et biologie moléculaire
Mme BONGARD Vanina	Epidémiologie, Santé publique
M. BONNEVIALLE Nicolas	Chirurgie orthopédique et traumatologique
M. BOUNES Vincent	Médecine d'urgence
Mme BOURNET Barbara	Gastro-entérologie
Mme CASPER Charlotte	Pédiatrie
M. CAVAIGNAC Etienne	Chirurgie orthopédique et traumatologie
M. CHAPUT Benoit	Chirurgie plastique
M. COGNARD Christophe	Radiologie
Mme CORRE Jill	Hématologie
Mme DALENC Florence	Cancérologie
M. DE BONNECAZE Guillaume	Anatomie
M. DECRAMER Stéphane	Pédiatrie
M. EDOUARD Thomas	Pédiatrie
M. FAGUER Stanislas	Néphrologie
Mme FARUCH BILFELD Marie	Radiologie et imagerie médicale
M. FRANCHITTO Nicolas	Addictologie
M. GARRIDO-STÖWHAS Ignacio	Chirurgie Plastique
M. GUIBERT Nicolas	Pneumologie
M. GUILLEMINAULT Laurent	Pneumologie
M. HERIN Fabrice	Médecine et santé au travail
M. LAIREZ Olivier	Biophysique et médecine nucléaire
M. LAROCHE Michel	Rhumatologie
Mme LAURENT Camille	Anatomie Pathologique
M. LE CAIGNEC Cédric	Génétique
M. LEANDRI Roger	Biologie du dével. et de la reproduction
M. LOPEZ Raphael	Anatomie
M. MARCHEIX Bertrand	Chirurgie thoracique et cardiovasculaire
M. MARTIN-BLONDEL Guillaume	Maladies infectieuses, maladies tropicales
Mme MARTINEZ Alejandra	Gynécologie
M. MARX Mathieu	Oto-rhino-laryngologie
M. MEYER Nicolas	Dermatologie
M. PAGES Jean-Christophe	Biologie cellulaire
Mme PASQUET Marlène	Pédiatrie
M. PORTIER Guillaume	Chirurgie Digestive
M. PUGNET Grégory	Médecine interne
M. REINA Nicolas	Chirurgie orthopédique et traumatologique
M. RENAUDINEAU Yves	Immunologie
Mme RUYSSEN-WITRAND Adeline	Rhumatologie
Mme SAVAGNER Frédérique	Biochimie et biologie moléculaire
M. SAVALL Frédéric	Médecine légale
M. SILVA SIFONTES Stein	Réanimation
M. SOLER Vincent	Ophtalmologie
Mme SOMMET Agnès	Pharmacologie
M. TACK Ivan	Physiologie
Mme VAYSSE Charlotte	Cancérologie
Mme VEZZOSI Delphine	Endocrinologie
M. YRONDI Antoine	Psychiatrie
M. YSEBAERT Loic	Hématologie

P.U. Médecine générale
M. MESTHÉ Pierre
Mme ROUGE-BUGAT Marie-Eve

Professeurs Associés

Professeur Associé de Médecine Générale
M. ABITTEBOUL Yves
Mme BOURGEOIS Odile
M. BOYER Pierre
M. CHICOULAA Bruno
Mme IRI-DELAHAYE Motoko
M. PIPONNIER David
M. POUTRAIN Jean-Christophe
M. STILLMUNKES André

Professeur Associé de Bactériologie-Hygiène
Mme MALAVAUD Sandra

FACULTE DE SANTE
Département Médecine Maieutique et Paramédicaux

MCU - PH

Mme ABRAVANEL Florence	Bactériologie Virologie Hygiène
M. APOIL Pol Andre	Immunologie
Mme ARNAUD Catherine	Epidémiologie
Mme AUSSEIL-TRUDEL Stéphanie	Biochimie
Mme BASSET Céline	Cytologie et histologie
Mme BELLIERES-FABRE Julie	Néphrologie
Mme BERTOLI Sarah	Hématologie, transfusion
M. BIETH Eric	Génétique
Mme BREHIN Camille	Pneumologie
M. BUSCAIL Etienne	Chirurgie viscérale et digestive
Mme CAMARE Caroline	Biochimie et biologie moléculaire
M. CAMBUS Jean-Pierre	Hématologie
Mme CANTERO Anne-Valérie	Biochimie
Mme CARFAGNA Luana	Pédiatrie
Mme CASPAR BAUGUIL Sylvie	Nutrition
Mme CASSAGNE Myriam	Ophtalmologie
Mme CASSAING Sophie	Parasitologie
Mme CASSOL Emmanuelle	Biophysique
Mme CHANTALAT Elodie	Anatomie
M. CHASSAING Nicolas	Génétique
M. CLAVEL Cyril	Biologie Cellulaire
Mme COLOMBAT Magali	Anatomie et cytologie pathologiques
M. CONGY Nicolas	Immunologie
Mme COURBON Christine	Pharmacologie
M. CUROT Jonathan	Neurologie
Mme DAMASE Christine	Pharmacologie
Mme DE GLISEZENSKY Isabelle	Physiologie
M. DEDOUIT Fabrice	Médecine Légale
M. DEGBOE Yannick	Rhumatologie
M. DELMAS Clément	Cardiologie
M. DELPLA Pierre-André	Médecine Légale
M. DESPAS Fabien	Pharmacologie
M. DUBOIS Damien	Bactériologie Virologie Hygiène
Mme ESQUIROL Yolande	Médecine du travail
Mme EVRARD Solène	Histologie, embryologie et cytologie
Mme FILLAUX Judith	Parasitologie
Mme FLOCH Pauline	Bactériologie-Virologie
Mme GALINIER Anne	Nutrition
Mme GALLINI Adeline	Epidémiologie
M. GANTET Pierre	Biophysique
M. GASQ David	Physiologie
M. GATIMEL Nicolas	Médecine de la reproduction
Mme GENNERO Isabelle	Biochimie
Mme GENOUX Annelise	Biochimie et biologie moléculaire
Mme GRARE Marion	Bactériologie Virologie Hygiène
M. GUERBY Paul	Gynécologie-Obstétrique
Mme GUILBEAU-FRUGIER Céline	Anatomie Pathologique
Mme GUYONNET Sophie	Nutrition
M. HAMDI Safouane	Biochimie
Mme HITZEL Anne	Biophysique
Mme INGUENEAU Cécile	Biochimie
M. IRIART Xavier	Parasitologie et mycologie
Mme JONCA Nathalie	Biologie cellulaire
M. KIRZIN Sylvain	Chirurgie générale
Mme LAPEYRE-MESTRE Maryse	Pharmacologie
M. LEPAGE Benoit	Biostatistiques et Informatique médicale
M. LHERMUSIER Thibault	Cardiologie
M. LHOMME Sébastien	Bactériologie-virologie
Mme MASSIP Clémence	Bactériologie-virologie
Mme MAUPAS SCHWALM Françoise	Biochimie
Mme MONTASTIER Emilie	Nutrition
M. MONTASTRUC François	Pharmacologie
Mme MOREAU Jessika	Biologie du dév. Et de la reproduction
Mme MOREAU Marion	Physiologie
M. MOULIS Guillaume	Médecine interne
Mme NASR Nathalie	Neurologie
Mme NOGUEIRA M.L.	Biologie Cellulaire
Mme PERROT Aurore	Hématologie
M. PILLARD Fabien	Physiologie
Mme PLAISANCIE Julie	Génétique
Mme PUISSANT Bénédicte	Immunologie
Mme QUELVEN Isabelle	Biophysique et médecine nucléaire
Mme RAYMOND Stéphanie	Bactériologie Virologie Hygiène
M. REVET Alexis	Pédo-psychiatrie
M. RIMAILHO Jacques	Anatomie et Chirurgie Générale
Mme SABOURDY Frédérique	Biochimie
Mme SAUNE Karine	Bactériologie Virologie
Mme SIEGFRIED Aurore	Anatomie et cytologie pathologiques
M. TAFANI Jean-André	Biophysique
M. TREINER Emmanuel	Immunologie
Mme VALLET Marion	Physiologie
M. VERGEZ François	Hématologie
Mme VIJA Lavinia	Biophysique et médecine nucléaire

M.C.U. Médecine générale

M. BISMUTH Michel
M. BRILLAC Thierry
Mme DUPOUY Julie
M. ESCOURROU Emile

Maîtres de Conférence Associés

M.C.A. Médecine Générale

M. BIREBENT Jordan
Mme BOUSSIER Nathalie
Mme FREYENS Anne
Mme LATROUS Leila
Mme PUECH Marielle

REMERCIEMENTS

Monsieur le Professeur Jérémie PARIENTE
Président du jury,
Professeur des Universités,
Praticien hospitalier en neurologie.

Je suis honorée par votre présence et je vous remercie d'avoir accepté de présider le jury cette thèse.
J'admire vos enseignements remarquables qui ont contribué à me faire choisir et aimer la neurologie.
J'apprécie l'énergie avec laquelle vous transmettez votre passion pour la clinique et le soin des patients ainsi que leur famille.
Que ce travail soit l'occasion de vous témoigner mon profond respect.

Monsieur le Professeur Sylvain RHEIMS
Professeur des universités,
Praticien hospitalier en neurologie.

Je suis très honorée que vous ayez accepté de faire partie de ce jury et je tiens à exprimer toute ma gratitude pour votre contribution à ce travail.
J'admire la qualité de votre pédagogie et de vos enseignements en épileptologie.
Soyez assuré de mon profond respect.

Monsieur le Docteur Luc VALTON
Praticien hospitalier en neurologie.

Je tiens à exprimer ma chaleureuse gratitude pour votre participation en tant que membre de ce jury.
Je vous remercie de m'avoir insufflé la curiosité de l'épileptologie. Votre optimisme et votre bienveillance sont des qualités que j'apprécie particulièrement. Je suis reconnaissante pour la confiance que vous m'avez témoignée au cours de ces deux dernières années.
Soyez assuré de mon respect le plus profond.

Monsieur le Docteur Jonathan CUROT
Maître de conférences des universités,
Praticien hospitalier en neurologie.

Je te remercie sincèrement de m'avoir fait l'honneur de diriger cette thèse. Je tiens à te remercier du fond du cœur pour la confiance que tu m'as accordée et pour ton dynamisme et ton soutien constants tout au long de cette aventure.
Tu as su me transmettre ta curiosité et le goût pour la recherche. J'ai été ravie de mener ce projet de thèse avec toi. J'ai découvert le monde passionnant des microélectrodes, où il reste encore tant à découvrir.
Ta rigueur et ton engagement dans les projets que tu entreprends sont une source d'inspiration.
Que ce travail soit l'occasion de te témoigner tout le respect que je te porte.

Madame le Docteur Rachel DEBS
Praticien hospitalier en neurologie.

Tu me fais l'honneur de siéger dans ce jury et de juger mon travail et je t'en remercie.
Merci de m'avoir accueillie dans l'univers fascinant du sommeil et ses multiples facettes. J'y ai beaucoup appris, tant sur le plan professionnel qu'humain et personnel. Tes enseignements et nos échanges enrichissants ont été très précieux. Je te remercie pour ta bienveillance au quotidien.
C'est un honneur et un plaisir de travailler à tes côtés chaque jour.

Monsieur le Docteur Emmanuel BARBEAU
Directeur de recherche CNRS,
Équipe DYNAMO, Centre de Recherche Cerveau & Cognition.

Je vous remercie d'avoir accepté de siéger dans ce jury et de me faire l'honneur de juger ce travail. Votre vision d'ensemble et vos conseils durant cette période ont été précieux, et je tiens à vous en remercier.
Soyez assuré de ma reconnaissance et de mon profond respect.

SERMENT D'HIPPOCRATE

« Au moment d'être admise à exercer la médecine,
je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé
dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté,
sans aucune discrimination selon leur état ou leurs convictions.
J'interviendrai pour les protéger si elles sont affaiblies, vulnérables
ou menacées dans leur intégrité ou leur dignité.
Même sous la contrainte, je ne ferai pas usage de mes connaissances
contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance
et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera.
Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés.
Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers
et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies.
Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission.
Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai
pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ;
que je sois déshonorée et méprisée si j'y manque. »

Conseil national de l'Ordre des médecins

TABLE DES MATIÈRES

ABRÉVIATIONS

ECoG : électrocorticographie

EEG : électroencéphalographie

EFPR : épilepsie focale pharmaco-résistante

ELT : épilepsie du lobe temporal

FR : *fast ripples* (ondulations rapides)

iEEG : EEG intracrânien

ILAE : *International League Against Epilepsy* (ligue internationale contre l'épilepsie)

IRM : imagerie par résonance magnétique

IRMf : IRM fonctionnelle

LFP *: local field potential* (potentiel de champ local)

MEG : magnétoencéphalographie

SEEG : stéréo-électroencéphalographie

ZE : zone épileptogène

ZNI : zone non impliquée

ZP : zone de propagation

INTRODUCTION

1. Généralités sur l'épilepsie

L'épilepsie est une maladie chronique caractérisée par la survenue imprévisible et répétée de crises épileptiques. Les crises épileptiques, qui semblent liées à une décharge cérébrale d'un groupe de neurones, peuvent atteindre l'ensemble du cortex cérébral lorsqu'elles sont généralisées, ou toucher seulement une partie limitée du cerveau lorsqu'elles sont focales. Si les crises restent l'élément le plus visible de l'épilepsie, les comorbidités d'ordres neurologiques, cognitives, psychologiques et sociales peuvent impacter significativement le quotidien et la qualité de vie.

C'est l'une des maladies les plus anciennement identifiées chez l'homme, dont les premières descriptions écrites ont été retrouvées en Mésopotamie en -4000 avant J.-C. (Laulan 1954). À l'heure actuelle, l'épilepsie reste la maladie neurologique handicapante la plus fréquente en Europe (rapport de l'OMS, 2011). On estime à environ **600 000 le nombre de personnes souffrant d'épilepsie en France**, dont la moitié ont moins de 20 ans (SNIIRAM – Régime Général – année 2014). Environ 60% des patients porteurs d'épilepsie présentent une forme focale (Fiest et al. 2017; Ioannou et al. 2022). L'épilepsie ne connaît pas de frontières géographiques, raciales ou sociales. Dans le monde, la prévalence est estimée à 50 millions de personnes (Beghi et al. 2019), dont plus des trois quarts vivent dans des pays à revenu faible ou intermédiaire.

L'épilepsie peut revêtir des formes différentes et peut provenir d'une diversité étendue d'étiologies. Parmi celles-ci, les **épilepsies généralisées idiopathiques** (comme par exemple dans l'épilepsie myoclonique juvénile ou l'épilepsie-absence) regroupent des présentations typiques intégrant des crises tonico-cloniques généralisées, des absences et des myoclonies, et comprennent souvent une composante génétique, dont la nature n'est pas toujours démontrable en pratique clinique. Les **épilepsies symptomatiques**, en revanche, sont caractérisées par des crises à point de départ focal et résultent d'une anomalie cérébrale congénitale ou acquise, telle qu'une tumeur, un accident vasculaire cérébral, une malformation congénitale ou une anomalie du développement cortical, un traumatisme crânien, une infection du système nerveux central, etc. Enfin, les **épilepsies cryptogéniques** englobent les formes d'épilepsie dont la cause reste inconnue, ou n'a pas pu être identifiée

par les moyens médicaux actuellement disponibles, malgré l'ensemble des explorations réalisées. Le nombre d'épilepsies cryptogéniques est en constante diminution, grâce aux avancées continues des techniques d'exploration. Cette classification repose essentiellement sur l'évaluation des symptômes cliniques et des données de l'électroencéphalographie (EEG). Ainsi, il n'existe pas une forme homogène d'épilepsie, mais une diversité d'expressions cliniques, d'étiologies et de trajectoires évolutives différentes, restant spécifiques à chaque patient. Cette réalité complexe souligne la nécessité d'adopter une approche personnalisée pour le diagnostic et la prise en charge de l'épilepsie, en tenant compte des caractéristiques uniques de chaque patient et de sa maladie.

Les premiers **médicaments anti-épileptiques**, dénommés à juste titre anti-convulsivants par les anglo-saxons puis par une recommandation en 2022 de la Ligue Internationale contre l'Epilepsie (ILAE, *International League Against Epilepsy*) ont été introduits sur le marché au cours des années 1910. Depuis, malgré la découverte et le développement d'une vingtaine de molécules, avec des mécanismes d'action différents, on estime toujours qu'environ **20 à 30% des patients ne répondent pas entièrement au traitement** et continuent à présenter des crises (Mann and Pons 2008). L'**épilepsie pharmacorésistante** (Kwan et al. 2010) a été définie par l'ILAE comme la persistance de crises, de nature épileptique certaine, suffisamment fréquentes ou invalidantes, après l'échec de deux médicaments anti-convulsivants en monothérapie ou en association, correctement prescrits et biens tolérés, chez un patient observant. Le diagnostic est retenu après au moins 2 ans d'un traitement antiépileptique bien conduit. En effet, au-delà de deux traitements différents, la probabilité de rémission avec une troisième molécule est réduite (Kwan and Brodie 2000).

Parmi les facteurs de risques de présenter une épilepsie pharmacorésistante, on retrouve les anomalies à l'examen clinique, anomalies sur l'EEG (Ko and Holmes 1999; Shafer et al. 1988), le nombre élevé de crises avant le début du traitement, l'état de mal épileptique (Callaghan et al. 2007), la présence d'une anomalie sur l'imagerie, notamment la sclérose temporale médiale (Semah et al. 1998) mais également le type de crises, à savoir les crises focales (Gilioli et al. 2012).

2. Contexte actuel concernant les épilepsies focales pharmaco-résistantes

Chez certains de ces patients, porteurs d'une épilepsie focale pharmacorésistante (EFPR), une prise en charge chirurgicale avec résection de la **zone dite épileptogène** (ZE), permet une diminution de la fréquence des crises, voire même permet de les faire disparaître. La chirurgie de l'épilepsie est aujourd'hui reconnue comme le traitement le plus efficace pour parvenir à contrôler les crises chez des patients bien sélectionnés, enfants et adultes, souffrant d'épilepsie focale réfractaire (Cross et al. 2006; Engel et al. 2003, 2012; Wiebe et al. 2001). Dans l'épilepsie du lobe temporal (ELT), le traitement chirurgical a démontré son efficacité en comparaison avec le traitement médical optimal : 73% des patients sont libres de crise à deux ans de la chirurgie, contre aucun patient dans le cas du traitement médical seul (Engel et al. 2012). On retrouve des bénéfices dans les autres domaines concernés tels que la cognition, la vie psychosociale, la qualité de vie, la morbi-mortalité ainsi que l'aspect financier (Scott Perry and Duchowny 2013).

Le pronostic post-opératoire est évalué cliniquement au moyen de deux échelles : la classification d'Engel, développée dans les années 90, (Engel 1993), et la classification de l'ILAE (Wieser et al. 2001) (traduction française en *Annexe 1*).

Cependant, le facteur décisif concernant l'absence de crise après la chirurgie réside dans l'identification précise de la zone cérébrale responsable de la génération des crises et sa résection complète. L'**implantation stéréotaxique d'électrodes intracrâniennes** ou **stéréo-électroencéphalographie** (SEEG) permet de s'affranchir des barrières osseuses et cutanées pour s'approcher du point de départ des crises et recueillir des informations à forte valeur localisatrice. Néanmoins, cette évaluation demeure imparfaite car à long terme, les études indiquent qu'environ 20 à 70 % des patients présenteront une récidive de crises (Cohen-Gadol et al. 2006; Jeha et al. 2007; Rosenow and Lüders 2001; Thorsteinsdottir et al. 2019; Wetjen et al. 2009).

Plusieurs caractéristiques liées à la ZE sont associées à un succès suite à l'intervention chirurgicale. En premier lieu, on retrouve le caractère **focal** de la ZE, plutôt qu'une ZE multifocale ou généralisée. Deuxièmement, la **détermination de la ZE avec une précision et exactitude suffisantes**, est primordiale. Troisièmement, la **ZE ne doit pas impliquer une région corticale susceptible d'engendrer un déficit fonctionnel majeur** après l'ablation

chirurgicale, tels que des troubles du langage, de la mémoire ou de la motricité (Ryvlin, Cross, and Rheims 2014). En effet, la balance bénéfice/risque est jaugée avec prudence, afin que l'intervention chirurgicale ne génère pas de handicap plus sévère que l'épilepsie elle-même. La décision de recourir à une intervention chirurgicale n'est envisagée qu'après une évaluation pré-chirurgicale complète et standardisée, réalisée dans un centre expert, ayant pour but la détermination de la ZE.

En France, la première phase du **bilan pré-chirurgical (phase I)** comprend plusieurs investigations non invasives (HAS conférence de consensus 2004). Après des données d'anamnèse et cliniques, le bilan peut comprendre :

- un **EEG de surface**,
- une **vidéo-EEG** avec données intercritiques et comprenant l'enregistrement de crises spontanées,
- une **IRM encéphalique** avec des coupes sagittales de 5 mm d'épaisseur en écho de spin en T1, des coupes axiales en écho de spin rapide en T2 et en FLAIR et coupes coronales et axiales d'une épaisseur maximale de 4 mm, en séquence pondérée en T1, en T2 et/ou en FLAIR, selon les recommandations de la HAS en 2004,
- un **bilan neuropsychologique**,
- une **tomographie cérébrale d'émission monophotonique ictale** (**SPECT**),
- une **tomographie par émission de positon au fluorodésoxyglucose interictale (TEP au $^{18F-}$FDG**),
- et parfois une **évaluation psychiatrique**.

Les données récoltées sont soumises à une analyse approfondie au sein d'une réunion multidisciplinaire rassemblant des épileptologues, des radiologues, des médecins spécialistes de médecine nucléaire, des neurochirurgiens et des neuropsychologues, avec pour but de définir la meilleure stratégie thérapeutique possible en fonction des informations disponibles.

A l'issue de l'évaluation de la phase I, trois scénarios de réponse peuvent se présenter :

(1) Dans la première situation, **la ZE a pu être déterminée avec certitude par le biais des moyens non invasifs**. Dans ce cas, une **chirurgie de résection** pourrait être envisagée d'emblée ou bien après explorations complémentaires non invasives. Par exemple, dans le cas d'une épilepsie temporale médiale avec sclérose hippocampique, il serait possible de proposer une lobectomie temporale antéro-médiale unilatérale. Dans le cas d'une lésion cérébrale avec une épilepsie périlésionnelle caractéristique, une lésionectomie pourrait être proposée d'emblée.

(2) Dans la deuxième situation, **des hypothèses ont pu être formulées sur la ZE**, **mais il persiste des ambiguïtés dans la définition de la ZE** (par exemple, absence de lésion visible à l'IRM cérébrale ou anomalies intercritiques dans des territoires différents du point de départ des crises), ou ses relations avec le cortex éloquent doivent être définies. Dans ce cas, **l'implantation d'électrodes intracrâniennes** peut être envisagée afin d'avoir une évaluation plus précise de la ZE et d'estimer la faisabilité d'une résection chirurgicale.

(3) Dans la troisième situation, **l'analyse du bilan de phase I marque la fin du processus d'exploration**. Soit aucune neurochirurgie n'est possible (par exemple en cas de crises multifocales ou d'un foyer situé dans une zone fonctionnelle), soit aucune hypothèse précise sur la ZE ne peut être formulée, rendant impossible la poursuite des investigations.

3. Déterminer la zone épileptogène en intracrânien

A. La SEEG : des pionniers Bancaud et Talairach à nos jours

En 1954, suite aux débuts de la chirurgie de l'épilepsie, Penfield et Jasper, ont proposé l'idée novatrice de recueillir les informations EEG directement depuis la surface corticale avec l'électrocorticographie (ECoG) puis en profondeur (**Figure 1**). Néanmoins, à cette époque, les implantations chirurgicales se faisaient peu précises, insérées de manière approximative (Penfield and Jasper 1954). Par la suite, le développement de l'outil stéréotaxique a permis d'atteindre une meilleure précision anatomique. La SEEG a été inventée à la fin des années 50 par deux français, Jean Talairach, neurochirurgien, et Jean Bancaud, neuropsychiatre et électrophysiologiste.

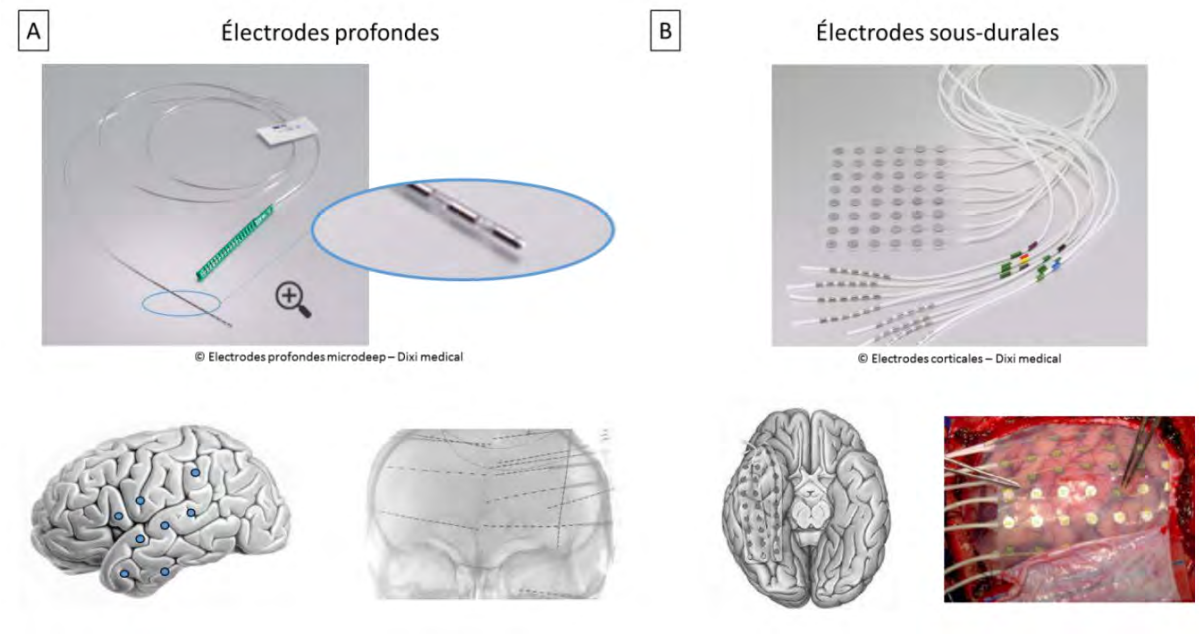


Figure 1. Deux méthodes sont employées pour l'enregistrement de l'EEG intracérébral : la stéréo-électroencéphalographie et l'électrocorticographie (ECoG). *(A) Les électrodes profondes permettent un suivi bilatéral des structures corticales, tant superficielles que profondes. Environ quinze électrodes peuvent être implantées par patient. (B) Les électrodes sous-durales assurent une couverture étendue de la surface du cortex cérébral et sont généralement implantées sur un seul hémisphère. Elles n'explorent que les structures cérébrales superficielles (Despouy 2019).*

A l'heure actuelle, la SEEG est établie en routine clinique comme faisant partie du **bilan pré-chirurgical de phase II**, réalisée dans la plupart des centres experts de la chirurgie de l'épilepsie en France et à travers le monde (Isnard et al. 2018). Le schéma d'implantation des régions cérébrales d'intérêt, en accord avec les hypothèses relatives à la ZE, est préalablement décidé en réunion multidisciplinaire (plan des implantations en *Annexe 2*) à l'aide des données obtenues de manière non invasive dans la première phase du bilan.

L'implantation des 8 à 15 électrodes intracérébrales en stéréotaxie est une intervention réalisée sous anesthésie générale par un neurochirurgien expérimenté. Cette opération est aujourd'hui guidée par assistance d'un robot chirurgical, conjugué à un cadre de stéréotaxie permettant un corréler chaque point du crâne dans un espace stéréotaxique, garantissant une précision de l'ordre du millimètre. Chaque **macroélectrode** (diamètre 0.8mm) comporte 5, 10 à 15 plots ou contacts répartis le long de l'électrode séparés de 1.5mm, permettant l'enregistrement simultané de plusieurs sites, y compris des régions médiales et latérales (**Figure 2**).

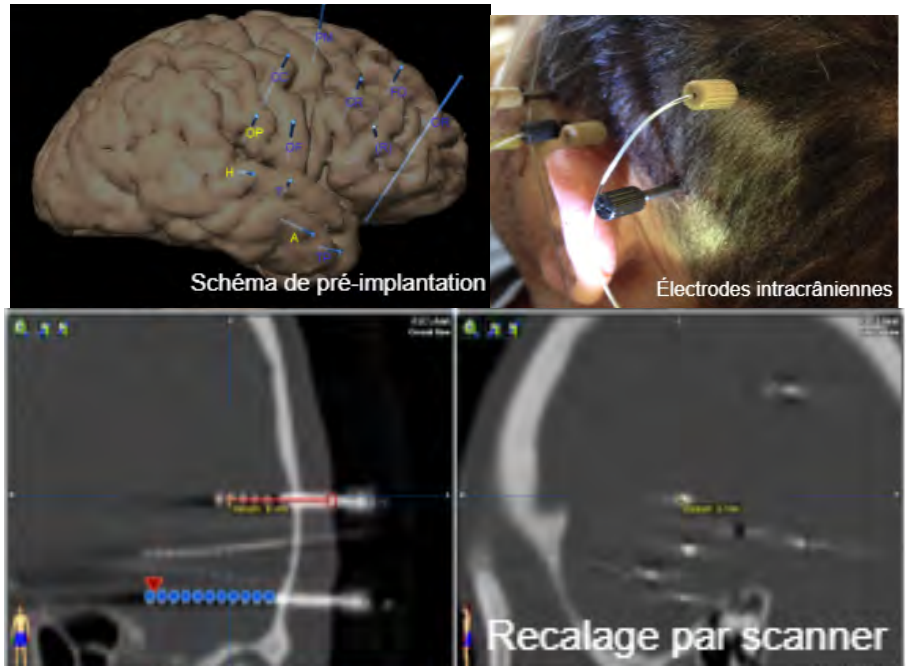


Figure 2. *En haut à gauche, schéma de pré-implantation prévu en amont de la réalisation de la SEEG en fonction des hypothèses concernant la ZE et des contraintes anatomiques. En haut à droite, photo présentant le crâne d'un patient après l'implantation des électrodes. En bas à gauche et à droite, le positionnement anatomique de chaque électrode est vérifié après l'intervention par recalage avec un scanner.*

Le signal des macroélectrodes profondes est enregistré en monitorage continu 24h/24 sous surveillance vidéo, pendant plusieurs jours jusqu'à plusieurs semaines. Pour aboutir à l'identification de la ZE, il est essentiel d'enregistrer des crises d'épilepsie spontanées, parfois favorisées par une diminution ou un sevrage médicamenteux. La réalisation de **stimulations électriques cérébrales de faible intensité** (< 5mA, par chocs 1 à 50 Hz, de manière bipolaire sur des paires de macrocontacts, durant 1 ms à 5 secondes) sert non seulement à affiner la localisation de la ZE par le déclenchement de crises provoquées, mais permet également de réaliser une **cartographie fonctionnelle** via le repérage des aires motrices, sensitives et sensorielles.

La SEEG offre ainsi la possibilité de réaliser une prise en charge thérapeutique personnalisée, avec exérèse chirurgicale sur mesure, adaptée aux spécificités du patient et de son épilepsie. Néanmoins, le nombre restreint d'électrodes et l'échantillonnage spatial demeurent limités pour chaque patient, ce qui peut constituer une contrainte à l'exploration exhaustive du réseau épileptogène par rapport à des évaluations plus globales du réseau cérébral (par exemple IRM fonctionnelle, magnétoencéphalographie ou MEG).

B. Les consensus actuels : réseau épileptogène, réseau de propagation et réseau non impliqué

Le concept de **foyer épileptogène**, remplacé par celui de ZE, a été historiquement défini dans les années 1950 par Bancaud et Talairach grâce à la SEEG. Il représente les régions à partir de laquelle les décharges critiques émergent et ainsi que leurs voies de propagation primaires (Talairach and Bancaud 1966). **La ZE comprendrait en effet le site d'amorce et d'organisation primaire des crises épileptiques**, cette définition s'intégrant dans une approche pré-chirurgicale des épilepsies focales (Munari Claudio and Bancaud Jean 1987). Cette notion de ZE est complétée par la présence d'une **zone irritative**, où se manifestent les anomalies intercritiques, ainsi que par la zone lésionnelle, la **zone symptomatogène** et la **zone de déficit fonctionnel**. Ensemble, ces composantes contribuent à définir la **structure anatomo-fonctionnelle de la ZE**, comme détaillé dans le **Erreur ! Source du renvoi introuvable.** (Penfield and Jasper 1954).

Zone	Définition	Mesure
Zone épileptogène	Zone cérébrale nécessaire et suffisante pour initier les crises et dont la résection ou la déconnexion garantit la disparition des crises	Concept théorique
Zone irritative	Zone corticale qui génère des pointes intercritiques	Techniques d'électrophysiologie (invasives et non invasives)
Zone de départ des crises	Zone corticale d'où proviennent les crises (incluant les zones de propagation précoce sous certaines circonstances)	Techniques d'électrophysiologie (invasives et non invasives)
Lésion épileptogène	Anomalie cérébrale structurelle, en lien avec les crises épileptiques	Imagerie structurelle et analyse des tissus
Zone symptomatogène	Région cérébrale responsable des symptômes cliniques initiaux	Observations cliniques
Zone de déficit fonctionnel	Zone corticale sans dysfonction épileptique	Examen neurologique, tests neuropsychologiques, EEG, PET, SPECT

Tableau 1. Description des différentes régions cérébrales impliquées dans les crises épileptiques. *Adapté de Engel et al. 2013,* Despouy et al. 2019.

Par la suite, le concept de ZE a évolué avec la pratique aboutissant à une redéfinition de la ZE, par les équipes nord-américaines. La **ZE est alors caractérisée comme la zone de cortex minimale à réséquer** (inactivée ou totalement déconnectée) **pour supprimer totalement les crises** (Lüders et al. 2006). Cette description théorique de la ZE implique que la confirmation de sa délimitation ne peut être effectuée qu'après la réalisation de l'intervention chirurgicale.

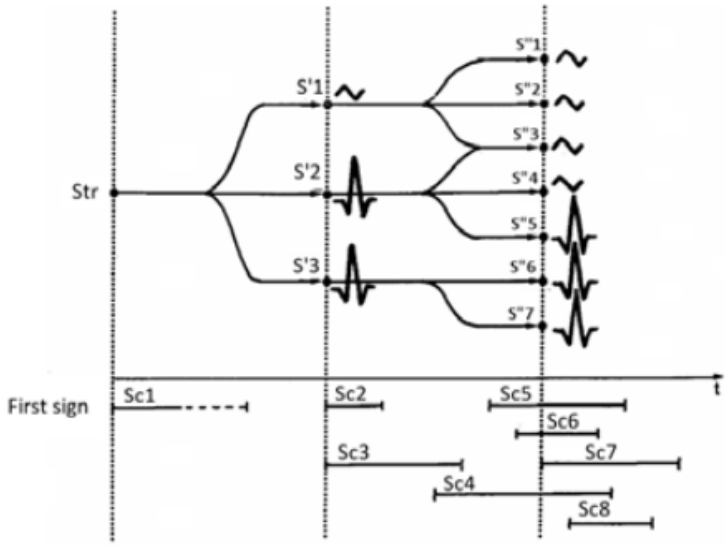


Figure 3. Représentation schématique de la corrélation entre les modifications électriques observées en SEEG et l'apparition de signes cliniques, d'après Bancaud et Talairach*. L'apparition des manifestations cliniques (Sc1, Sc2, etc.) est coordonnée temporellement à l'implication de différentes régions cérébrales (S'1, S'2, etc.), selon une progression "en série" ou en "parallèle"* (Bartolomei et al. 2017).

Récemment, la vision focale traditionnelle (**Figure 3**) a cédé la place au concept de **réseau épileptogène**, qui a émergé progressivement avec l'essor de la SEEG (Bartolomei et al. 2017). Ce modèle a été introduit afin de permettre une description plus réaliste de la **dynamique complexe des crises et leur expression clinique** ainsi que la distribution des anomalies épileptogènes au sein du cerveau. Dès les débuts de la SEEG par Bancaud et Talairach, il a été constaté que les perturbations électriques ne respectaient pas les frontières anatomiques mais que les crises pouvaient impliquer simultanément ou très rapidement plusieurs régions cérébrales parfois spatialement éloignées (**Figure 4**). Par la suite, l'apport de techniques d'imagerie avec une meilleure résolution spatiale répartie sur l'ensemble du cerveau a permis de fournir des arguments supplémentaires au concept de réseau épileptogène. On peut citer des techniques telles que le **couplage EEG-IRM**

simultanés (Chaudhary et al. 2012; Thornton et al. 2011), l'**imagerie fonctionnelle** (IRMf) (Van Diessen et al. 2013; Guye et al. 2010; Stam et al. 2016) ou encore la **MEG** (Englot et al. 2015; Malinowska et al. 2014; Schoffelen and Gross 2009).

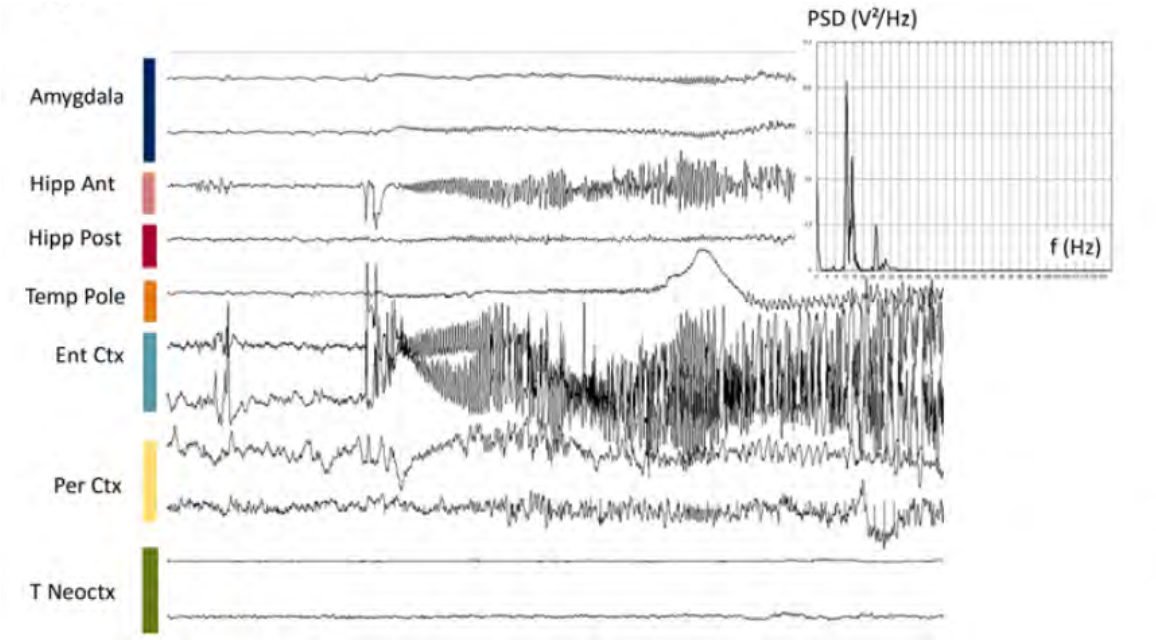


Figure 4. Exemple d'un enregistrement en SEEG d'une crise chez un patient porteur d'une épilepsie du lobe temporal*. La crise commence dans différentes régions du lobe temporal : une décharge rapide de bas voltage affecte les contacts de l'amygdale, de l'hippocampe (électrodes de contacts internes de l'hippocampe antérieur et postérieur et du cortex entorhinal). La densité spectrale de puissance (PSD,* power spectral density*) est mesurée à partir de la décharge rapide du cortex entorhinal et révèle une fréquence fondamentale à 15 Hz.*

Ainsi, le **réseau épileptogène englobe l'ensemble des régions cérébrales capables de déclencher des crises**. Le **réseau de propagation** représente l'ensemble des zones par lesquelles la crise se propage. Enfin, le **réseau non impliqué** représente les zones cérébrales qui demeurent insensibles à l'apparition de la crise (**Figure 5**). Cette conceptualisation est celle qui est aujourd'hui mise en application dans l'analyse des signaux en EEG intracrânien (iEEG).

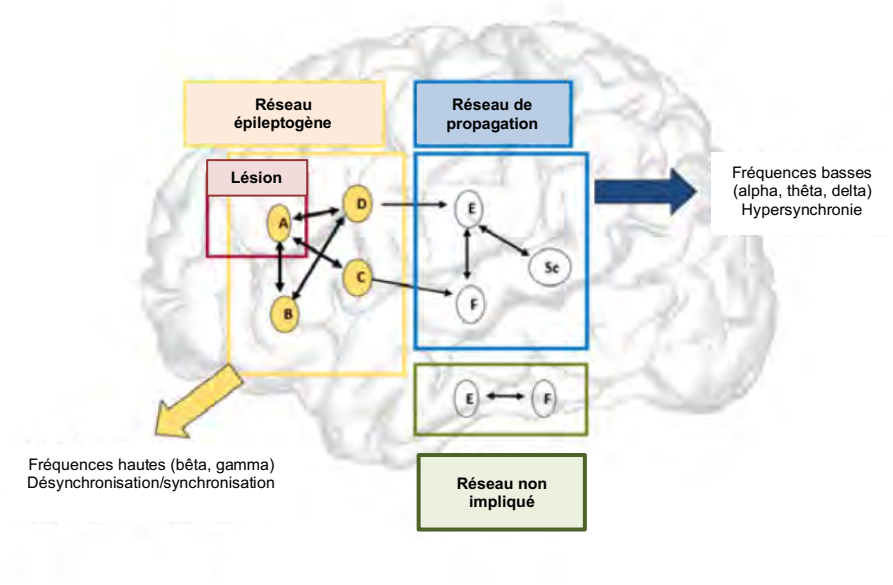


Figure 5. Représentation schématique du concept de réseau épileptogène dans les épilepsies focales. *Les régions cérébrales sont représentées par des lettres (A, B, etc.). La ZE comprend des zones capables de générer des crises, formant le « réseau épileptogène » ou « réseau de la ZE » (A, B, C et D). La structure A désigne une zone avec une lésion putative (visible ou non). Le « réseau de propagation » est activé secondairement par la crise et représente un groupe de zones moins propices à provoquer des crises (E, F et Sc). Sc représente l'implication des zones sous-corticales, comme par exemple le thalamus. Certaines zones ne jouent aucun rôle dans la propagation des crises et constituent le réseau non impliqué (G et H). (Figure adaptée de* Bartolomei et al. 2017).

La SEEG offre ainsi une opportunité unique d'accéder directement aux tissus capables de produire des crises et pouvant aboutir à une cartographie cérébrale détaillée. Certains **biomarqueurs** ont été proposés pour compléter l'analyse des signaux SEEG. L'**index d'épileptogénicité**, développé par l'équipe de F. Bartolomei (Bartolomei, Chauvel, and Wendling 2008), est basé sur les propriétés spectrales des signaux iEEG, avec la présence d'**oscillations rapides** remplaçant l'activité de fond mais également temporales avec le **délai d'apparition** par rapport au début de la crise. Cet index a été mis en relation avec la propension d'une région cérébrale à générer des crises. De la même manière, la détection des oscillations rapides ou ***fast ripples*** **(FR)** a été corrélé avec la ZE (Bragin et al. 2002; Jacobs et al. 2008). La résection des zones cérébrales génératrices des FR est associé à un meilleur pronostic post-opératoire (Nevalainen et al. 2020). Des études ont identifié différents **schémas d'apparition des crises**, dans l'analyse de départ de crises en iEEG avec des électrodes classiques (Lagarde et al. 2019). Ces patterns peuvent correspondre à des processus d'ictogenèse différents, et sont associés à des pronostics variables.

En revanche, malgré la croissance de l'électrophysiologie intracrânienne dans l'évaluation pré-chirurgicale et des avancées continues dans ce domaine, plusieurs études ont démontré que les **taux de rémission après une chirurgie de l'épilepsie restent relativement stables autour de 70%** au cours des deux dernières décennies (Barba et al. 2022; Baud et al. 2018). Il est clairement nécessaire de perfectionner nos stratégies de localisation et d'étude de la ZE mais également d'envisager une meilleure estimation du pronostic postopératoire. À l'heure actuelle, nous manquons de biomarqueurs fiables et spécifiques de cette zone pathologique. Examiner les crises épileptiques à travers les **différentes échelles électrophysiologiques** simultanées pourrait considérablement renforcer notre compréhension des mécanismes physiopathologiques sous-jacents aux crises (Schevon et al. 2019). L'intégration des **microélectrodes** vient enrichir l'électrophysiologie traditionnelle en ajoutant une couche supplémentaire de données à une échelle restreinte. Ainsi, l'adoption plus systématique de cette **approche multimodale**, englobant une combinaison d'informations découlant des crises spontanées, des stimulations cérébrales, des FR, des techniques de traitement de signal et potentiellement d'**analyses multiéchelles**, pourrait ouvrir la voie à une meilleure compréhension du processus d'ictogenèse et à terme, conduire à l'amélioration du pronostic des patients pris en charge.

C. Apport des microélectrodes

1) Naissance et évolution des microélectrodes intracrâniennes

La mise au point d'électrodes extracellulaires en verre avec les micropipettes (Renshaw, Forbes, and Morison 1940) a ouvert la voie à l'enregistrement de cellules uniques dans le cerveau humain vivant, une technique décrite pour la première fois en 1955 (Ward et Thomas, 1955), dans le contexte d'un enregistrement peropératoire (Rayport and Waller 1967). Cette approche a ensuite été perfectionnée avec l'utilisation d'électrodes micro-implantées dans le cadre de l'évaluation pré-chirurgicale dans les années 1970 par Babb et Wyler, initialement chez le singe puis chez l'homme (Wyler, Fetz, and Ward 1973; Wyler, Ojemann, and Ward 1982; Wyler and Ward 1986). En effet, les microélectrodes suscitent un intérêt notable par leur capacité à approcher des

phénomènes à une échelle plus localisée (enregistrement du potentiel de champ local ou LFP à une échelle submillimétrique). Grâce à la taille réduite du **microcontact** (autour de 20 à 50µm), les microélectrodes permettent également l'enregistrement des décharges neuronales dans leur ensemble (**activité multiunitaire**), ou à l'échelle du neurone unique (**activité neuronale unitaire**), parfois même avec une **caractérisation du type cellulaire** potentiel. De plus, les avancées technologiques ont facilité l'essor des microélectrodes intracrâniennes, en permettant d'améliorer la visualisation de l'activité cérébrale sur plusieurs échelles simultanément offrant ainsi un nouvel espoir d'approcher des mécanismes cellulaires sous-jacents à la genèse des crises épileptiques (**Figure 6**).

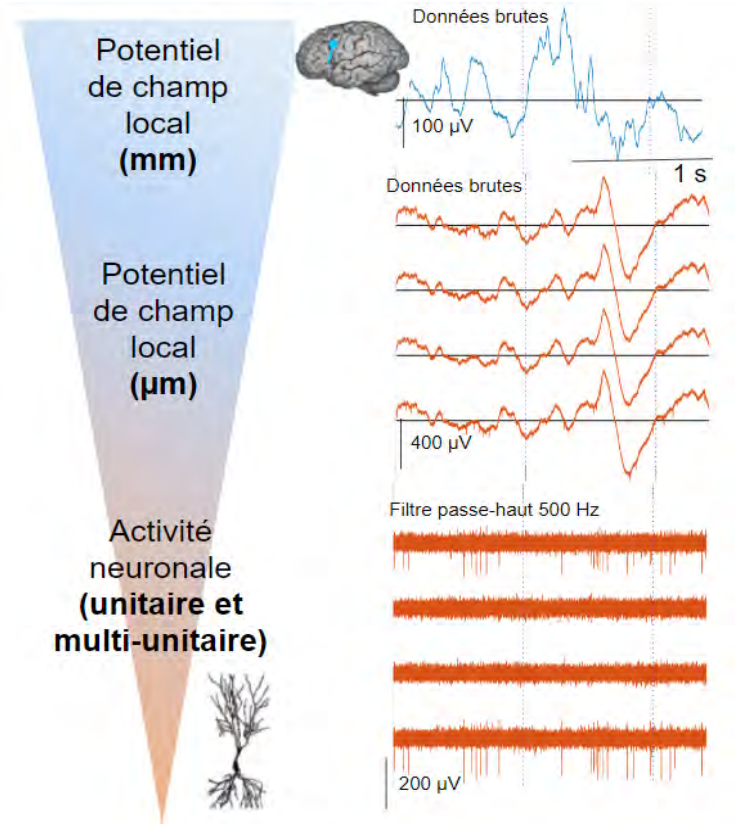


Figure 6. Les macrocontacts permettent de visualiser les potentiels de champs locaux (LFP) extracellulaires à l'échelle millimétriques, reflet d'une sommation des activités locales*. Les microcontacts permettent d'enregistrer les LFP à une échelle micrométrique, permettant d'approcher des populations neuronales circonscrites. Avec l'application de filtre passe-haut à 500 Hz, les microcontacts révèlent les potentiels d'action neuronaux, ouvrant une fenêtre sur l'activité cellulaire à l'échelle individuelle. Les électrodes hybrides, combinant des macrocontacts et microcontacts, permettent de révéler simultanément ces échelles, afin d'avoir un reflet de l'activité cérébrale selon ces 3 points de vue différents.*

2) Microélectrodes profondes

Les microélectrodes profondes, initialement étudiées chez le singe avant d'être appliquées chez l'homme, ont marqué les premières avancées dans ce domaine. Elles se composent le plus souvent d'une électrode classique avec des macrocontacts répartis régulièrement le long de la tige. En son cœur circulent 9 microfilaments qui émergent à l'extrémité distale de l'électrode, se déployant telles les branches d'un parapluie à distance du dernier macrocontact. Chacun de ces microfilaments, constitué de platine/iridium mesure 5mm de long et 40µm de diamètre (**Figure 7**). Ce modèle d'électrodes est nommé **Behnke-Fried**, d'après les chercheurs qui l'ont conçu. Ces microélectrodes trouvent une application privilégiée dans l'exploration de structures profondes telles que l'hippocampe, l'amygdale ou encore le cortex cingulaire (Babb, Carr, and Crandall 1973; Fried et al. 1999; Misra et al. 2018; Verzeano, Crandall, and Dymond 1971).

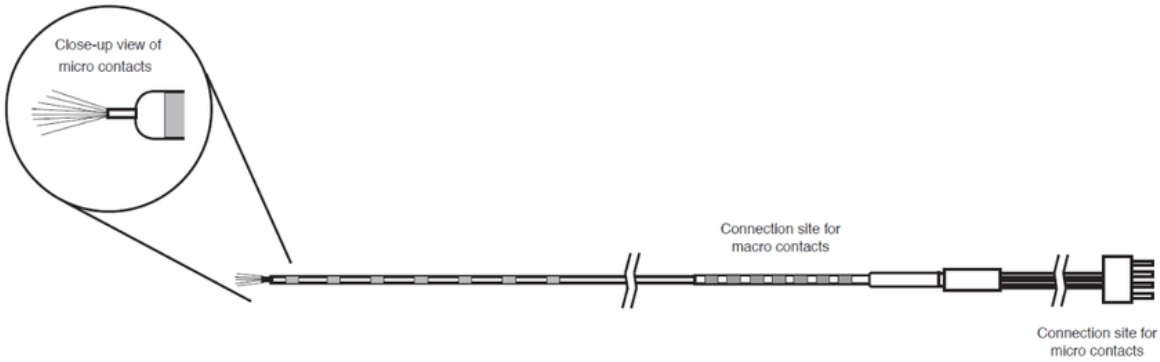


Figure 7. Illustration schématique d'une microélectrode profonde de type « Behnke-Fried », *caractérisée par une structure en deux couches distinctes. La partie externe de la tige contient des macrocontacts, répartis uniformément le long de l'électrode. En son centre, se trouvent les microfils qui émergent en faisceau à l'extrémité distale de l'électrode (généralement 9 microfils au total, dont 1 dédié à la référence), chacun mesurant 40 µm de diamètre.*

3) Grilles néocorticales

Les microélectrodes en grille (*microelectrode array*, MEA) ont vu le jour dans les années 2000, initialement étudiées dans le domaine de l'interface cerveau-machine (Donoghue 2002), avant de trouver leur application dans le domaine de l'épilepsie (House et al. 2006). Elles sont constituées d'une matrice de 10 x 10 microélectrodes, exception faite des quatre coins, totalisant ainsi 96 microélectrodes, réparties sur une surface carrée de 4mm², d'une longueur de 1mm (**Figure 8**). En raison de leur configuration, elles se cantonnent à l'exploration des **régions superficielles du néocortex**, au niveau des **couches corticales III**

à V. Elles sont combinées avec des électrodes sous-durales utilisées en pratique clinique en ECoG, réparties en grilles sur la surface corticale. L'agencement des microélectrodes en deux dimensions offre une perspective nouvelle pour analyser les crises, notamment pour visualiser leur propagation bidirectionnelle. Elles ont ainsi permis la mise en évidence d'**ondes de déplacement ictales progressives** (Schlafly et al. 2022; Smith et al. 2016). Cependant, du fait de leur configuration, ces microélectrodes ne peuvent couvrir qu'une région corticale très limitée, avec en général une seule grille de microélectrodes par patient.

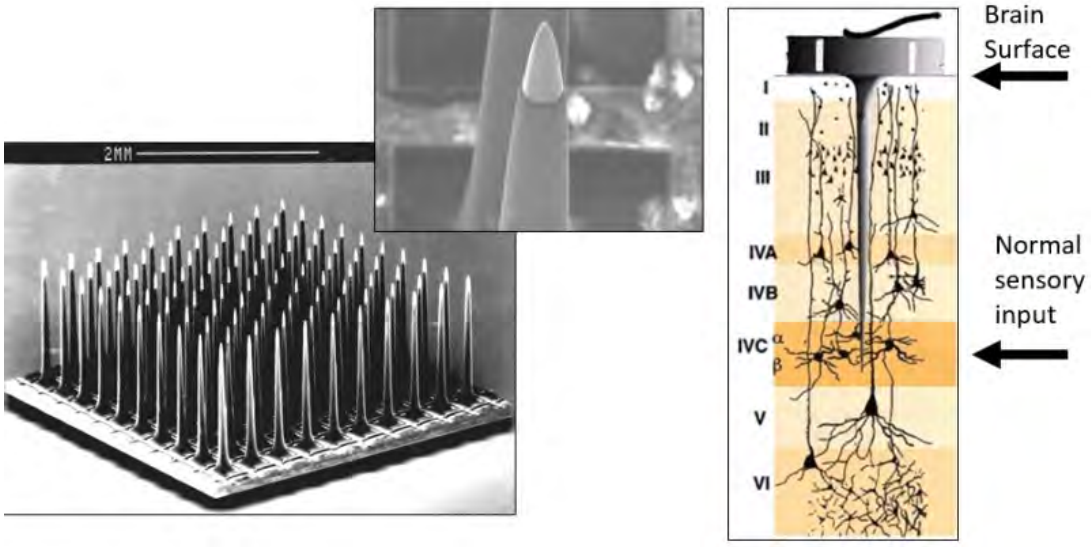


Figure 8. Les grilles de microélectrodes néocorticales (MEA) *sont composées de 96 électrodes en titane alignées sur une grille. Les pointes en silicone sont revêtues de platine à leur extrémité. L'extrémité des microélectrodes pénètre généralement dans les couches corticales IV ou couche granulaire interne, abritant des neurones pyramidaux et étoilés, qui reçoivent notamment des afférences thalamiques et de l'hémisphère controlatéral (Dunlap et al. 2020).*

4) Les tétrodes

Les **tétrodes** ont été utilisées pour la première fois chez l'être humain à la fin des années 1990 (Howard et al. 1996). Dans le domaine de l'épilepsie, leur développement a d'abord débuté avec des expérimentations chez le chat avant d'être adapté à l'homme (Buzsáki 2004; Gray et al. 1995). Les tétrodes, les « triodes » ou « stéréotrodes » sont constituées sur le même principe de plusieurs microcontacts adjacents, respectivement quatre, trois ou deux. La détection repose sur le principe selon lequel les cellules présentant des rapports de distance différents par rapport aux microcontacts auront des rapports d'amplitude de potentiel d'action différents lorsqu'elles sont enregistrées sur deux canaux.

Le rapport d'amplitude entre les deux canaux reste constant, quelle que soit la variation intrinsèque de l'amplitude absolue des signaux (**Figure 9**). Cet agencement permet ainsi d'améliorer significativement les performances de détection des activités neuronales unitaires (Harris et al. 2000).

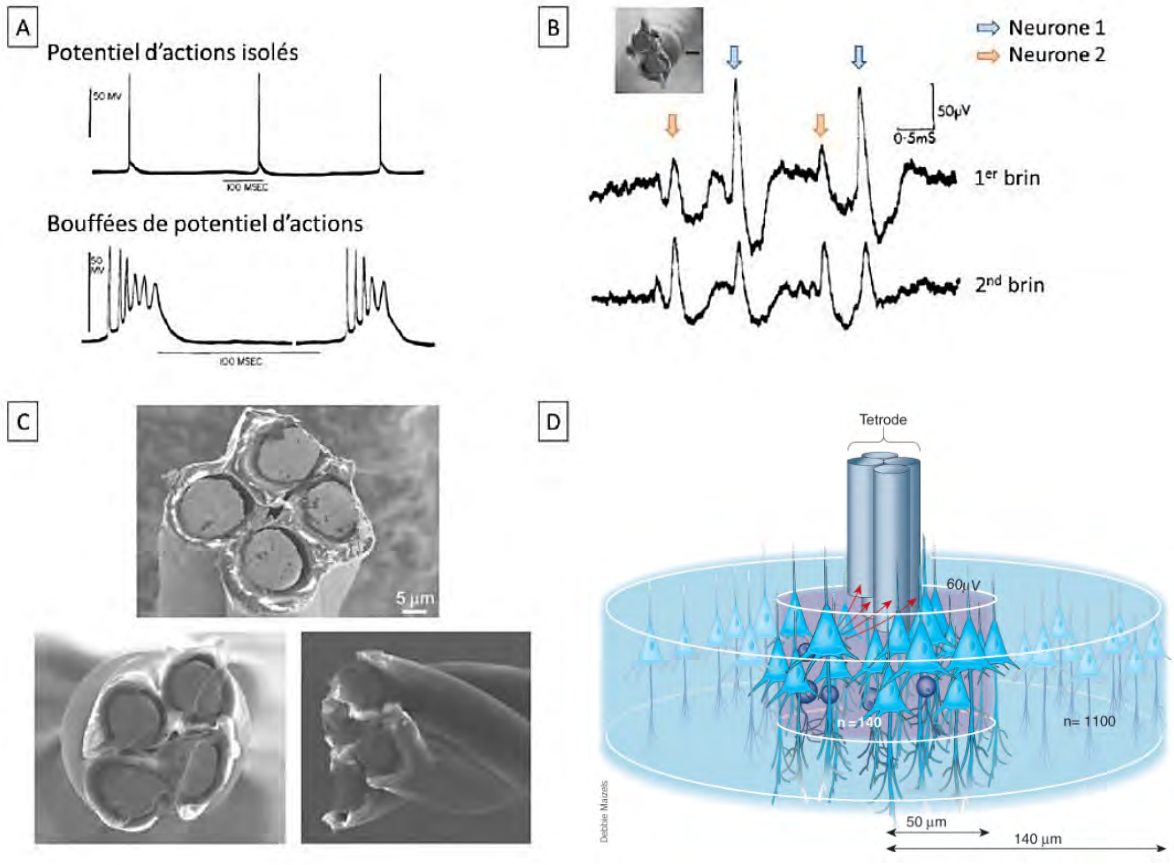


Figure 9. Illustrations de tétrodes et de leur utilité dans l'isolation des neurones. *(A) Exemples de potentiels d'action illustrant des décharges isolées ou en bouffées, enregistrés dans l'hippocampe d'un chat. Lors de bouffées de décharges, l'amplitude des potentiels d'action peut varier jusqu'à 50% (adapté de Kandel et Spencer, 1961). (B) Enregistrements obtenus à l'aide d'une stéréotrode chez le rat. Sur le premier brin isolé, on observe des décharges émanant présumément de deux neurones différents. Lors de l'observation du deuxième fil isolément, ces quatre décharges neuronales pourraient erronément être attribuées au même neurone. Par conséquent, l'ajout d'un deuxième fil permet de différencier distinctement les deux neurones en orange et en bleu (adapté de McNaughton et al., 1983). (C) Vue en microscopie électronique d'une tétrode composée de quatre microfilaments torsadés ensemble isolés entre eux par du téflon (Ferguson et al., 2009 et Liao et al., 2011). (D) Schématisation de la détection des activités cellulaires par les tétrodes. La qualité de l'isolement cellulaire varie en fonction de la distance entre l'électrode et la cellule pyramidale (flèches rouges). Les potentiels de neurones présentent une amplitude significative (>60 µV) dans un cylindre gris d'environ 50 µm de rayon, contenant environ 100 neurones. Bien que l'amplitude des décharges enregistrées diminue avec la distance, grâce à la méthode de triangulation, il est possible de détecter théoriquement les neurones dans un rayon de 140 µm, contenant environ 1 000 neurones dans le cortex de rat (adapté de Buzsáki et al., 2004, Despouy 2019).*

Dans notre équipe, nous utilisons les tétrodes au sein d'électrodes hybrides avec macroélectrodes classiques avec deux à trois tétrodes s'ouvrant entre les deux derniers macrocontacts (**Figure 10**) (Curot et al. 2023; Despouy et al. 2019, 2020). Cette disposition avec les tétrodes nichées entre les macrocontacts, offre la possibilité de visualiser les mêmes activités à plusieurs niveaux avec une excellente corrélation spatiale entre ces deux échelles.

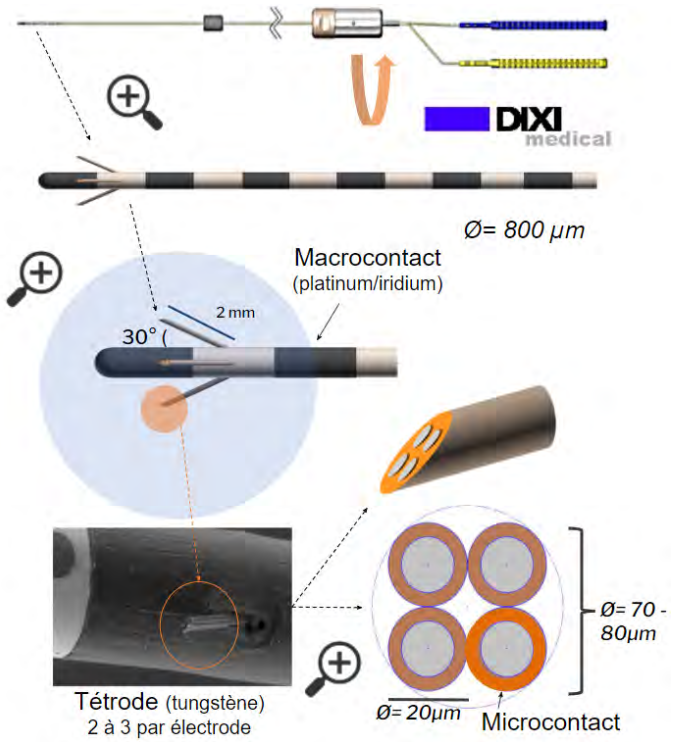


Figure 10. Les électrodes hybrides semi-rigides avec tétrodes ont un diamètre de 0,8 mm avec des longueurs disponibles de 33,2mm, 40,4mm ou 50,8 mm*. Chaque électrode contient 6 à 9 macrocontacts en platine/iridium, mesurant 2 mm de long et espacés de 1,5 mm Chaque électrode est équipée de deux ou trois tétrodes (comprenant chacune quatre microcontacts) qui s'étendent jusqu'à 2 mm de la tige, entre le premier et le deuxième macrocontact le plus médial. Chaque tétrode est fabriquée en tordant ensemble quatre microfilaments de tungstène de 20µm de diamètre. Après l'implantation en salle d'opération, les tétrodes sont extériorisées grâce à la rotation d'une vis micrométrique externe.*

A ce jour, l'efficacité de la chirurgie de l'épilepsie demeure imparfaite, marquée par un taux d'échec persistant qui reste trop important. Toutefois, l'évaluation par le biais des modèles multimodaux et l'introduction de nouvelles technologies d'analyses, ouvrent la voie à des pistes prometteuses. Mieux comprendre les processus physiopathologiques à l'origine des crises épileptiques est indispensable pour progresser. Pour explorer cette question, il nous faut revenir vers l'origine même des crises, en se rapprochant de l'échelle de l'acteur principal de cette scène, le neurone. L'exploitation de nouveaux outils tels que les microélectrodes s'avère prometteuse pour élucider les mécanismes d'ictogénèse, en ciblant des populations neuronales spécifiques.

Dans les deux chapitres suivants, notre démarche s'est orientée vers l'étude des crises épileptiques par le prisme des microélectrodes. Une revue de la littérature détaillant l'état actuel des connaissances sur ce sujet est présentée dans la section à venir. Puis, la section suivante rapporte une étude s'intéressant à l'analyse des crises épileptiques grâces aux tétrodes, sur une cohorte de 64 patients épileptiques pharmaco-résistant issus des Centre Hospitalo-Universitaires (CHU) de Toulouse et de Lyon.

REVUE DE LA LITTÉRATURE

« A persistent but surmountable gap in microelectrode recordings for multiscale synthesis of epileptic seizures in human »

Les travaux présentés ci-dessous sont les avancées préparatoires en vue de la soumission d'une revue de la littérature concernant les crises épileptiques vues par le prisme des microélectrodes. Cette démarche s'inscrit en réponse à une demande d'article de synthèse de la part du comité de rédaction de la Revue Neurologique.

A persistent but surmountable gap in microelectrode recordings for multiscale synthesis of epileptic seizures in humans

Authors

Pauline Calvat[1, 2, 3, 4], Emmanuel Barbeau[1, 2, 4], Marie Denuelle[1, 2, 3], Luc Valton[1, 2, 3], Jonathan Curot[1, 2, 3, 4]

Affiliations

1. Centre de Recherche Cerveau et Cognition, Université de Toulouse, Université Paul Sabatier, Toulouse, France
2. Centre National de la Recherche Scientifique, CerCo (UMR5549), Toulouse, France
3. Electrophysiologie cérébrale, Epilepsie, Sommeil, Département de Neurologie, Centre Hospitalier Universitaire de Toulouse, Toulouse, France
4. Faculté de Santé, Université de Toulouse, Toulouse, France

Keywords

seizure, microelectrode, tetrode, single-unit activity, multiunit activity, seizure onset pattern

Abbreviations

ECoG: electrocorticography; EZ: epileptogenic zone; FR: fast ripple; HFO: high-frequency oscillations; HYP: hypersynchronous seizure onset; IBS: ictal baseline shift; IED: interictal epileptiform discharge; iEEG: intracranial EEG; LFP: local field potential; LVF: low-voltage fast activity; MEA: microelectrode array; MUA: multiunit activity; SEEG: stereo-electroencephalography; SOP: seizure onset pattern; SOZ: seizure onset zone; SUA: single-unit activity.

Introduction

Linking neurons, the cellular target of antiseizure medications, to the large-scale network dynamics leading to epileptic seizures and their clinical consequences is still not entirely possible at present. The cascade of events from local circuits to global dynamics that occur in the brain is barely understood in humans. Although models coexist at different spatial scales, bottom-up synthesis for understanding human epilepsy is sorely lacking, from the cell to the large-scale networks at the fast time scale of a seizure.

Ictogenesis in humans has been described in relation to “key electrophysiological concepts'' based on electroencephalographic recordings, with an evolutionary turn with intracranial EEG (iEEG) (Bancaud & Talairach, 1965). Several of these concepts have become operational information in clinical reasoning to determine the organization of the epileptogenic network: (1) **seizure-onset patterns** (Lagarde et al., 2016; Perucca et al., 2014), (2) **infraslow activity or ictal baseline shifts** (Gnatkovsky et al., 2014; S. Lee et al., 2020; Thompson et al., 2016), more recently (3) **the fingerprint of the epileptogenic zone** (Grinenko et al., 2018), and (4) **interictal dynamics** (Diamond et al., 2021, 2023). The primary electrophysiological indicator of epilepsy and identification of the earliest and rapid components of ictal discharges are crucial to determine the seizure-onset zone (SOZ). This has been acknowledged since the beginning of stereoelectroencephalography (SEEG) (Bancaud & Talairach, 1965).

Of course, this is not an exhaustive list of the electrophysiological concepts that have shaped epileptology. But they are among those used routinely by clinicians as tools to define the epileptogenic zone (EZ), the irritative zone and the propagation zone. They drive presurgical workups and hypotheses on seizure genesis. Each of these

concepts is based on iEEG in local field potentials (LFP) recorded by standard macroelectrodes (grids or deep macroelectrodes), thus covering large neuronal populations (macroLFP).

However, only medical devices such as **microelectrodes** that enable micrometric recordings provide the possibility to reach the cellular scale. There are several types of microelectrodes, but their most common characteristic is small contact pads at the tip of isolated wires, with a small diameter (approximately 40 μm) (Babb et al., 1973; Fried et al., 1999). These microcontacts record LFP on a submillimeter scale (microLFP) with a higher spatial resolution than any macrocontact (diameter: approximately 1.5 mm, surface: 1-10 mm^2) within a smaller sample of neurons on a micrometer scale. Simultaneously, they detect action potentials of neurons: mostly multiunit activities (Pedreira et al., 2012; Stacey et al., 2013) but also single units (Despouy et al., 2019).

At first glance, microelectrodes are promising devices to understand the seizure "cascade" from the cell to the network level, *in vivo* in humans. Yet, despite more than 65 years of microelectrode use in humans (Ward & Thomas, 1955) and more than 4 decades of seizure recordings with microelectrodes in epileptic patients (Babb & Crandall, 1976), there remains a major gap between these different scales to synthesize ictogenesis. Seizure analysis remains fragmented across different scales of the human brain, and the use of new medical devices is now essential for a multiscale synthesis. Very few studies have attempted to analyze the three scales simultaneously: single unit, microLFP and macroLFP, while this is the key to providing a synthesis. Moreover, scientific reports often propose multiscale analyses that involve spatial shifts (microelectrodes are not perfectly colocalized with macroelectrodes, and multiunit activities and microLFP are not spatially nested in macroLFP), which does not enable proper synthesis of the neuronal scale and the large-scale network.

To address these gaps, let us proceed in reverse. How are the "key concepts" defined by macroelectrode recordings of epileptic seizures viewed through the prism of microelectrodes in humans? Comprehensive reviews have already demonstrated the importance of multiscale recordings (Schevon et al., 2012) and the panel of microelectrode recording types in humans (Chari et al., 2020). Therefore, our aim is different. We investigated how the influential electrophysiological concepts described in macroLFP and cited below have been explored, if at all, via microelectrodes. We voluntarily considered only *in vivo* recordings in humans. Animal studies, and *in silico* or *in vitro* models were considered for discussion purposes only. We focused on ictal activity in humans *in vivo*, specifically the transition from interictal to ictal states as well as seizure onset patterns.

Methods

Babb et al. (Babb & Crandall, 1976) were the first to record seizures in humans with microelectrodes in 1976. These electrodes consisted of a bundle of flexible wires that protruded in a spray from the tip of a 30-62.5 µm diameter cannula and were made of pure metals and alloys. They showed an increasing firing rate of neuronal discharges which varied according to the seizure onset pattern. Since then, several studies have analyzed epileptic seizures using microelectrodes, in terms of LFP or neuronal activity.

We used the following keywords in isolation or in combination in Google Scholar and PubMed databases: "seizure", "ictal", "epilepsy", "microelectrode", and "tetrode". These keywords were also combined with others ("MEA", "array", "multiscale" or "ictogenesis", "single unit", and "multiunit"). We voluntarily considered only *in vivo* recordings in humans. We excluded microelectrode studies in animal models.

Results

1. Very few studies that track seizure onset with microelectrodes *in vivo* in humans

Some twenty-five studies in five decades of intracranial microelectrode use is the main illustration of the current shortcomings in our understanding of the mechanisms of ictogenesis and of the remaining challenges. Finally, we surveyed 24 (23 articles and 1 review) studies designed to analyze epileptic seizures using microelectrodes or designed to analyze interictal epileptic discharges (IEDs) in apparent seizures in humans. The main methodological features of each of these studies are summarized in **Table 1** and their main results in **Table 2**.

These studies, published between 1976 and 2023, included 1 to 27 subjects (a total of 214 patients), which is a total of 449 seizures and more than 240 microseizures (except 1 study that did not mention the number of seizures analyzed (Merricks et al., 2015), see details in **Table 1**).

They include heterogeneous populations: different types of pharmacoresistant focal epilepsy, with or without identifiable brain lesions which is a major bias for comparison. Multiple histological lesions were reported: mostly medial temporal sclerosis and gliosis. More rarely, electrodes were implanted in cortical development abnormalities (polymicrogyria, periventricular nodular heterotopia, focal cortical dysplasia, tubers in a tuberous sclerosis complex, cortical atrophy, encephalomalacia), low-grade glioneuronal tumor and stroke. Microelectrode recordings were also available when there was no visible lesion.

Almost every brain lobe has been explored, but mainly the temporal lobe. Twenty-two (22) studies implanted microelectrodes in the temporal lobe (mostly in the hippocampus, and less frequently in the fusiform gyrus, amygdala, uncus, entorhinal and perirhinal cortices), 12 in the frontal lobe, 6 in the parietal lobe, 1 in the

insula and 3 in the cingulum. None explored the occipital lobe or deep gray nuclei (such as the thalamus, while implantations in such structures are now done in several epilepsy centers) (Pizzo et al., 2021). There is an overrepresentation of hippocampal recordings although cytoarchitectonics may differ according to the structure. We identified 15 studies with recordings on the neocortex mainly using microelectrode arrays (MEA) and 10 on the allocortex with hybrids with microfilaments at the tip or microcontacts flush against the macroelectrode. In one study, the location of the microelectrode recording was not clearly specified (Weiss et al., 2013).

Several types of microelectrodes were used: MEA in 14 studies (Basu et al., 2015; Martinet et al., 2017; Merricks et al., 2015, 2021; Schevon et al., 2008, 2010, 2012; Schlafly et al., 2022; Smith et al., 2016; Stead et al., 2010; Truccolo et al., 2011, 2014; Wagner et al., 2015; Weiss et al., 2013) and hybrid depth electrodes with microwires at the tip in 10 studies (Behnke-Fried hybrid electrodes or a similar design: (Agopyan-Miu et al., 2023; Babb et al., 1987; Babb & Crandall, 1976; Bower et al., 2012a, 2012b; Elahian et al., 2018; Lambrecq et al., 2017; Merricks et al., 2021; Misra et al., 2018; Stead et al., 2010; Weiss et al., 2016; Wyler et al., 1982). Wyler and colleagues used a specific design (electrolytically etched tungsten microelectrodes coated with epoxylite), and Stead's team provided recordings with microcontacts (single microwires flush against one macrocontact on either side) (1 study: Stead et al., 2010). No study implanted tetrodes in humans to specifically record seizures despite common usage in animal models (Buzsáki, 2004). Only one study analyzed neuronal activity during IED and focused on LFP during seizure using micro-macroelectrodes with tetrodes (Despouy et al., 2019).

Nearly all these studies provide an analysis or a description of LFP recorded on a microscale. A visual comparison of the onset of seizures in macro and microLFP can be found in 8 articles (Despouy et al., 2019; Lambrecq et al., 2017; Martinet et al., 2017;

Misra et al., 2018; Schevon et al., 2008, 2012; Stead et al., 2010; Truccolo et al., 2011; Weiss et al., 2016).

Of the 24 studies referenced, a majority incorporated single-unit or multiunit analyses, with the indispensable contribution of MEA and depth electrodes. A total of 21 studies were dedicated to examining neuronal firing during seizures in humans. These studies encompassed various aspects of neural activity, including **multiunit activity** (MUA) in 4 studies (Basu et al., 2015; Bower et al., 2012a; Schlafly et al., 2022; Weiss et al., 2013), **single-unit activity** (SUA) in 3 studies (Schevon et al., 2010; Weiss et al., 2016; Wyler et al., 1982), and the combined phenomena in 12 studies (Agopyan-Miu et al., 2023; Babb & Crandall, 1976; Elahian et al., 2018; Lambrecq et al., 2017; Merricks et al., 2015, 2021; Misra et al., 2018; Schevon et al., 2012; Smith et al., 2016; Truccolo et al., 2011, 2014; Wagner et al., 2015). According to the experiment, a total of 143 patients had a range of 84 to 787 neurons identified (if mentioned). However, most studies did not establish a correlation with the etiology or the histopathological findings. Single-unit dynamics were studied on the basis of cross-correlograms or changes in firing rates with various spike sorting algorithms. No analysis of unit activity has yet been carried out with tetrodes during a seizure.

Twenty-five studies contrast with the comprehensive data of other approaches for studying seizures at a different scale from macroelectrodes, such as *in vitro* models on slices (e. g., Gnatkovsky et al., 2008; Huberfeld et al., 2015; Lévesque et al., 2018; Lopantsev & Avoli, 1998; Pallud et al., 2014; Scalmani et al., 2023), optogenetic models in animals (e.g., Chang et al., 2018; Ellender et al., 2014; Rich et al., 2020; Sessolo et al., 2015; Shiri et al., 2015; Wickham et al., 2023; Yekhlef et al., 2015), or more recently, *in silico* models (e.g., Cressman et al., 2009; Depannemaecker et al., 2021; Hashemi et al., 2020; Jirsa et al., 2017; Kuhlmann et al., 2015; Liou et al., 2020). This also contrasts with the large number of LFP analyses of seizures with macroelectrodes (e.g., Di

Giacomo et al., 2019; Grinenko et al., 2018; Lagarde et al., 2016, 2019; Perucca et al., 2014; Pizzo et al., 2021; Rosenow & Lüders, 2001; Velasco et al., 2000).

In these 24 studies, experiments that focus on **interictal or peri-ictal dynamics before seizure onset** were conducted with microelectrodes in humans (De Curtis & Avanzini, 2001; Despouy et al., 2019; Frazzini et al., 2022; Keller et al., 2010; Truccolo et al., 2011). Keller's team focused on the analysis of IEDs using LFP and single-unit analysis and demonstrated activity changes in a small, heterogeneous population of neurons, both inside and outside the EZ, 500 ms to 200 ms before IED. Truccolo and colleagues observed multi- and single-unit activity in the ictal and preictal period and demonstrated an increase or a decrease in firing rate in a few neurons minutes before seizure onset. Navarro's team (Frazzini et al., 2022) identified specific interictal patterns in periventricular nodular heterotopia, with modulation by increasing or decreasing neuronal firing rates, which could have a role in seizure generation.

Our team (Despouy et al., 2019) analyzed IEDs, but also fast ripples (FR), neuronal activity and the epileptogenicity index (Bartolomei et al., 2008) in tuber and peritube tissue of a patient with tuberous sclerosis complex. By combining a 3-scale analysis: single-unit activity, microLFP and macroLFP, we were able to demonstrate a gradient of epileptogenicity within dysplastic lesions, beyond that which can be shown by MRI. We identified 12 other studies that analyzed interictal fast ripples (FRs, 250-600Hz) via microelectrodes in humans (Blanco et al., 2011; Bragin et al., 1999, 2002; Curot et al., 2023; Despouy et al., 2019; Kondylis et al., 2014; Ogren et al., 2009; Schevon et al., 2008; Staba et al., 2002, 2004, 2014; Weiss et al., n.d., 2016, 2020; Worrell et al., 2008). FRs were first detected in humans by microelectrodes (Staba et al., 2002) and are related to the EZ (Crépon et al., 2010; Despouy et al., 2019; Jacobs et al., 2008, 2009; Lévesque et al., 2012; Staba et al., 2002). The study of FRs is the first step in this

multiscale integration between LFP and neuronal activity: microelectrode data highlighted that FRs originate from a very local generator of about one millimeter (Bragin et al., 2002; Curot et al., 2023; Worrell et al., 2012) and are linked to a local increase in neuronal firing rate and large-scale inhibition of neuronal activity (Curot et al., 2023). However, for a multiscale synthesis of FR genesis, experiments that simultaneously combine the three scales (single-unit activity, microLFP and macroLFP) are lacking.

Authors, Year	Type of electrode	Nb of subjects / seizures	Nb of macro-electrodes/macrocontacts	Nb of hybrids or MEA/ microelectrodes	Location	Lesion on MRI	Lesion after histopathology	Seizure onset patterns in macroLFP
Babb et al. (1976)	microwires at the end of a macroelectrode[(a)]	26/33	NS	205/1,453	mesial temporal lobe, unilateral hippocampus	hippocampal sclerosis	hippocampal sclerosis	spike-and-wave activity
Wyler et al. (1982)	tungsten microelectrodes coated with epoxylite	17/3	ECoG[(b)]	NS	lateral temporal cortex, parietal cortex, superior frontal cortex	NS	NS	NS
Babb et al. (1987)	a bundle of 9 fine flexible wires (diam. 40 µm)	13/15 (6 clinical, 9 subclinical)	14/0	182/1,638	amygdala, hippocampus	NS	NS	NS
Schevon et al. (2008)	MEA	5/around 140	ECoG[(b)]	4[(c)]/480	middle temporal gyrus, lateral frontal cortex, parietal cortex, inferior temporal gyrus	NS	focal reactive leptomeningitis, Chaslin's subpial gliosis, mild neuronal loss in the hippocampus	microseizures: runs of repetitive sharp waveforms or continuous rhythmic activity, y focal, semi-rhythmic beta range activity
Stead et al. (2010)	hybrid depth with additional MEA	14[(d)]/66	780/NS	NS	medial temporal lobe (amygdala and hippocampus)	NS	NS	NS
Schevon et al. (2010)	MEA	7/>100 examples of "microdischarges"	ECoG[(b)]	7[(c)]/672	same as Schevon et al. 2008, 2012	same as Schevon et al. 2008, 2012	same as Schevon et al. 2008, 2012	NS
Truccolo et al. (2011)	MEA	4/8	ECoG[(b)]	4[(c)]/384	middle frontal gyrus, middle temporal gyrus	encephalomalacia, diffuse atrophy, glioma, no lesion	hippocampal sclerosis, mild dysplastic changes in the lateral temporal neocortex, gliosis, neuronal loss in the hippocampus, cortical dysplasia, low-grade glioneuronal tumor	- LVF activity - generalized burst of sharp waves followed by sharp wave complexes - generalized epileptiform spiking activity, followed by 1–2 s of generalized attenuation and then prominent spike and wave activity - generalized spike followed by 1–2 s of attenuation and then the onset of a generalized, high-frequency buzz lasting 4 s, followed by spike and wave discharges
Schevon et al. (2012)	MEA	5/72	ECoG[(b)]	5[(c)]/480	posterior parietal to central sulcus, supplementary motor area, lateral frontal cortex, inferior posterior temporal gyrus	NS	nonspecific, mild CA1 neuronal loss	- initial epileptiform discharge followed by rhythmic beta activity that gradually slows to theta - initial monomorphic delta rhythm that gradually increased in

								frequency to theta, then slowed to a 3–4-Hz spike and wave rhythm
Bower et al. (2012)	Ad-Tech particular hybrids[(f)]	7/12	NS	207/NS	medial temporal lobe	hippocampal atrophy, no lesion	gliosis, mesial temporal sclerosis, subpial gliosis, no lesion	
Weiss et al. (2013)	MEA	4/10	ECoG[(b)] (672 subdural electrode recording)	4[(c)]/384 (203 high-quality microelectrode recordings of full seizure activity)	neocortex	NS	NS	NS
Truccolo et al. (2014)	MEA	4/8	ECoG[(b)]	4[(c)]/384	middle or superior temporal gyrus	encephalomalacia, cortical dysplasia, temporal polymicrogyria, no lesion	hippocampal sclerosis with gliosis, neuronal dysgenesis with focal superficial gliosis and areas of encephalomalacia, mild dysplastic changes in the lateral temporal neocortex, gliosis with moderate neuronal loss in hippocampus	- rhythmic spike-wave complexes (~3Hz) - low amplitude gamma (40-60 Hz) activity
Basu et al. (2015)	hybrid grids of 4*4 and strip and depth electrodes	4/7	ECoG[(b)]	Grids: 4/64 Depth electrodes: 9	temporal, amygdala, hippocampus, frontal cortex, cingulate cortex, frontotemporal cortex	NS	NS	NS
Merricks et al. (2015)	MEA	4/NS	ECoG[(b)]	4[(c)]/384	same as Schevon et al. 2008, 2009, 2012	same as Schevon et al. 2008, 2009, 2012	same as Schevon et al. 2008, 2009, 2012	NS
Wagner et al. (2015)	MEA	5/13	ECoG[(b)]	5[(c)]/384	middle or superior temporal gyrus	medial temporal sclerosis, temporal polymicrogyria, nodular gray matter heterotopia, no lesion	hippocampal sclerosis, mild gliosis, FCD, neuronal dysgenesis with focal superficial gliosis and areas of encephalomalacia, gliosis and moderate neuronal loss in the hippocampus	- rhythmic spike-wave complexes - low amplitude gamma activity
Weiss et al. (2016)	Behnke-Fried[(f)]	6/7	NS/410	NS/152	amygdala, hippocampus, entorhinal cortex, fusiform gyrus, cingulate cortex	no lesion, bilateral hippocampal atrophy, medial temporal sclerosis, PCA stroke involving the hippocampus	Chaslin's gliosis	- HYP - rhythmic spike - LVF - polyspike and wave
Smith et al. (2016)	MEA	5/16	ECoG[(b)]	5[(c)]/480	same as Schevon et al. 2009, 2012, Kellis et al. 2015	same as Schevon et al. 2009, 2012, Kellis et al. 2015	same as Schevon et al. 2009, 2012, Kellis et al. 2015	NS

Lambrecq et al. (2017)	Behnke-Fried[(f)]	9/38	8-14/patient	NS/NS	uncus, hippocampus, perirhinal cortex, pregenual anterior cingulate cortex, amygdala, periventricular nodule in the temporal horn	no lesion, periventricular nodular heterotopia, temporo-polar brain injury, hippocampal sclerosis	gliosis, minor cortical modifications, hippocampal sclerosis type 1	- LVF activity - hypersynchronous activity
Martinet et al. (2017)	MEA	3/7	ECoG[(b)]	3[(c)]/288	middle or superior temporal gyrus	same as Wagner et al. 2015	NS	NS
Misra et al. (2018)	Behnke-Fried[(f)]	7/11	NS	1-4 p. patient/8-32 p. patient	frontal cortex, temporal neocortex	encephalomalacia, gliosis in the temporal lobe, T2 hyperintensity within the parietal lobe, temporal encephalocele, gyrus thickening with increased T2 signal and cystic components, no lesion, smaller hippocampus	reactive gliosis with focal parenchymal necrosis, cyst formation and hemosiderin deposition, reactive gliosis, and small foci of parenchymal necrosis, glioneuronal lesion, mild subpial gliosis, neuronal satellitosis, increased white matter cellularity, no lesion	NS
Elahian et al. (2018)	Behnke-Fried[(f)]	9/13		200/NS	medial temporal lobe epilepsy, frontal cortex, temporal neocortex	temporal subcortical T2, scattered T2 signal abnormality, medial temporal sclerosis, no lesion, focal cortical dysplasia and subependymal nodule, parietal and frontal gyrus atrophy, T2 signal in amygdala and temporal pole	hippocampal sclerosis, gliosis, focal cortical dysplasia type 1c, cortical and hippocampal tubers, no lesion	- LVF - spike or polypsike prior to LVF activity
Despouy et al. (2019)	Micromacroelectrode DIXI Medical (tetrode)	1 / 4	15/151	4/48	right insular cortex	tuber (tuberosis sclerosis complex)	NS	- high-amplitude spike-and-wave activity, followed by LVF activity - rhythmic slow wave
Merricks et al. (2021)	MEA and Behnke-Fried [(f)]	27/41	NS	- MEA: 5[(c)]/480 - Behnke-Fried: 1 to 4 per patient/ 8 microwires per hybrid	- MEA: neocortex of frontal convexity, dorsolateral frontal cortex, posterior and inferior temporal gyrus, medial temporal gyrus - Behnke-Fried: hippocampus, anterior frontal cortex, mid- anterior cingulum	NS	- MEA: nonspecific, mild CA1 neuronal loss, lateral temporal nonspecific, medial temporal sclerosis, mild astrocytosis - Behnke-Fried: fibrotic calcified nodules, FCD IB/IC, Chaslin's gliosis, hippocampal sclerosis, astrogliosis, microgliosis, FCD 2B, astrocytosis,	NS

							leptomeningeal inflammation and focal cavitation, ganglioglioma	
Schlafly et al. (2022)	MEA	11/31	ECoG[(b)]	11/1056	medial temporal cortex, temporal neocortex, frontal premotor cortex, prefrontal cortex, supplementary motor area, frontal operculum	NS	medial temporal sclerosis, focal cortical dysplasia type 2a, reactive astrogliosis, medial temporal sclerosis, nonspecific, mild CA1 neuronal loss, lateral temporal nonspecific, mild reactive astrogliosis, patchy microgliosis, Chaslin's marginal sclerosis, diffusely infiltrating low-grade glioma IDH1 negative, mild astrocytosis.	NS
Agopyan-Miu et al. (2023)	Behnke-Fried [(f)]	19/34	NS	52/416	hippocampus, cingulum, amygdala	possible foci of calcification from neurocysticercosis, encephalomalacia and gliosis post resection for choroid plexus carcinoma and resection cavity for ganglioma	fibrotic calcified nodules, moderate astrogliosis with microgliosis, low grade glioma along prior ganglioma resection cavity	NS

Table 1. Studies recording seizures with microelectrodes in humans.

NS = not specified; MEA = microelectrode array; PCA = posterior cerebral arteria; FCD = focal cortical dysplasia; Y=yes; N=no

[(a)] A stainless-steel cannula which serves as an EEG macroelectrode is used as a conduit to introduce a bundle of 9 fine wires, cut bluntly to a length 5 mm beyond the implanted tip of the cannula (diameter 30-62.5 µ), and which spray out at the tip of the cannula (pure metals (e.g., tungsten) and alloys (e.g., Pt 79% ~-Rh 15% ~o-Ru 6%)).

[(b)] For the studies that used ECoG, the number of macrocontacts were usually not specified, but in clinical practice the number is usually 64 to 128 per patient.

[(c)] The MEA consists of 96 individual platinum-coated silicon microelectrodes, protruding 1 mm from the array base and electrically insulated except for the terminal 70 µm platinum microelectrodes (NeuroPort™).

[(d)] 14 patients with epilepsy and 2 control with intractable facial pain.

[(e)] Behnke-Fried special hybrids (with 9 to 18 microcontacts oriented radially on the shaft between macro contacts and a bundle of 9 wires extending from the tip, 40 µm diameter).

[(f)] combined macro and micro depth electrodes (Ad-Tech, Racine, WI), respectively.

Authors, Year	MUA/SUA (N# of units)/ cell type	macro LFP	micro LFP	FR	Main results for neuronal dynamics during seizures
Babb et al. (1976)	Y/Y/Y	N	Y	N	**First observation of a neuronal firing change in humans during spontaneous seizure onset.** Only about 40% of neurons activated at the onset of clinical seizure (a percentage that increases with the development of the seizure). During subclinical seizure, no discernible changes in the firing patterns of neurons.
Wyler et al. (1982)	N/Y(90)/N	N	N	N	**Synchronous firing between single units recorded simultaneously by the same microelectrode at the onset of an ictal event.**
Babb et al. (1987)	Y/Y((90 neurons in, subclinical + 33 and 29 in clinical)/N	N	Y	N	**Various dynamics of seizures, whether clinical or subclinical**. During subclinical SEEG seizures, only 7% of neurons increased firing either at the focus or at propagated sites. During auras with altered consciousness, about 14% of neurons increased firing. During the onset of a clinical seizure, approximately 36% of neurons increased firing. SEEG seizures can be generated focally by synchronous firing of fewer than 10% of neurons, the 'epileptic pool'.
Schevon et al. (2008)	N/N/N	Y	Y	N	**Recordings of discharges within the EZ resembling both IED activity ("microdischarges") and seizures ("microseizures") confined to small cortical regions of 200 µm².**
Stead et al. (2010)	N/N/N	Y	Y	N	**Sparse distribution of "microseizures", more frequent in brain regions that generated seizures**. Sporadic evolution of microseizures into large-scale clinical seizures. Microseizures also present but more rarely in control patients with intractable facial pain.
Schevon et al. (2010)	N/Y/N	N	Y	N	**"Microdischarges" originating at a highly focal source location**, likely within a single cortical macrocolumn, and spreading to local and more distant sites via neural propagation.
Truccolo et al. (2011)	Y/Y(712 SU)/Y	Y	Y	N	**Seizures resulting from heterogeneity in neuronal spiking behaviors that evolve at multiple temporal and spatial scales**. Some putative pyramidal cells increased while others had a decrease in firing rates, suggesting that such heterogeneity does not simply reflect interleaved firing of pyramidal cells and interneurons.
Schevon et al. (2012)	Y/Y/N	Y	Y	N	Recruited areas showing intense, hypersynchronous firing neurons (**the "core territory"**), while surrounding regions showing low-level unstructured firing (**the "ictal penumbra"**).
Bower et al. (2012)	Y/N/N	Y	N	N	**Seizure heterogeneity of neuronal dynamics.** Among microelectrode recordings, only 7.6% of neurons showed increased firing before seizures, and 32.4% displayed seizure-related activity changes. Most microelectrodes (67.6%), even within the SOZ, maintained consistent firing rates during seizures. Changes in firing occurred before and at seizures onset, inside and outside the SOZ and even in the contralateral medial temporal lobe. Increased neuronal synchrony emerged mainly after seizure onset.
Weiss et al. (2013)	Y/N/N	Y[(a)]	Y[(a)]	Y	Repetitive high gamma (80–150 Hz) bursts, linked to phase-locked low-frequency (1–25 Hz) ictal rhythm, were linked multiunit firing bursts in the seizure core region. This synchronization occurred a few seconds after the ictal wavefront passed. Microelectrode recordings with low, heterogenous neural firing showed a lack of HFOs in the adjacent subdural electrode, despite a strong low-frequency signature: a pattern that may suggest a failure of the seizure to invade the area due to a feedforward inhibitory mechanism.
Truccolo et al. (2014)	Y/Y(787 SU)/Y	N	Y	N	**Two seizure types with different neuronal dynamics**. In sustained gamma seizures (around 40-60 Hz), rare fine temporal synchrony (around 10 ms) among neurons, as firing remained irregular and asynchronous. In spike-wave complex seizures at 3 Hz, phase locking of neuronal firing to the initial spike phase that induces synchrony at 50-100 ms level.
Basu et al. (2015)	Y/N/N	N	N	N	A directed transfer function employed to estimate the propagation pattern. Directional changes of the traveling waves occurred over a time frame of 2 to 10 seconds, with a discernible directionality pattern confined within spatial dimensions of approximately 9mm².
Merricks et al. (2015)	Y/Y(305 putative SU)/N	N	N	N	**Unit recordings stable, even beyond 40 hours and through multiples seizures**. During the seizure, in the penumbral zone, most of the spike patterns remained consistent. About 10-20% of neurons displayed notable firing changes, either up or down. After the seizure ended, spike shapes swiftly recovered: reappearance of some units within seconds and not more than three minutes, over 80% resuming their previous activity levels.

Wagner et al. (2015)	Y/Y/N	N	Y	N	**Recruitment of neocortical regions by seizure activity through complex spatiotemporal dynamics, evolving through distinct stages that last seconds.** Stages remained consistent for each patient's seizures. Finer patterns within seizures organized by slower network dynamics that developed across these discrete stages. Some ictal states at finer spatiotemporal scales, such as individual spike-wave discharges or gamma-oscillations, organized by slower time scale network dynamics that developed across these discrete stages.
Weiss et al. (2016)	N/Y/Y	Y	Y	Y	**Limbic seizures that originate from synchronized neuron clusters that grow and reach a critical mass for propagation.** In HYP seizures, FR power, FR, and ripple rate increased during the transition to the ictal state. In LVF activity seizure, evolving HYP LFP discharges, increased single-unit activity, and rising FR power before onset. Heterogeneous shifts in firing rate of excitatory and inhibitory single units during LVF activity.
Smith et al. (2016)	Y/Y/N	Y[(a)]	Y[(a)]	N	**Seizure progression and termination stemming from a small, migrating cortical area that matches cellular-scale mechanisms.** Seizures that develop into self-organized structures where a compact seizing area emits powerful signals widely across the cortex. A migrating edge of the seizure as the source of traveling waves of synaptic activity propagate into adjacent cortical areas and gradually weaken.
Lambrecq et al. (2017)	Y/Y(173 SU)/N	Y	Y	N	**Only specific neuron subsets that initiate seizure onset within submillimeter scale microdomains.** Highly heterogeneous neuronal activity at seizure onset, but not hypersynchronous. Groups of neurons that display significant changes minutes before seizures.
Martinet et al. (2017)	N/N/N	Y	Y	N	**Inter-scale coupling revealed as rapidly propagating activity waves**. Seizures that involve large neural populations spanning cortical regions that coordinate with small groups within cortical columns. Increased extracellular potassium diffusion as a potential mechanism (suggested by a computational model).
Misra et al. (2018)	Y/Y(125SU)/Y	Y	Y	N	**A mechanism for seizure propagation**: the seizure focus initially synchronized LFP in downstream networks affecting interneuron activity with a diminution of their firing rate and potentially contributing to seizure propagation. Neocortical seizure origin with increased synchrony before spreading into the medial temporal lobe. MTL networks that display an increase in unit-field coherence and reduced neuronal firing rates, particularly in inhibitory interneurons but not pyramidal cells**.**
Elahian et al. (2018)	Y/Y(202 SU)/Y	N	Y	N	**Interneurons play a role in the initiation and propagation of LVF seizures**. During LVF seizure onset, inhibitory interneurons in medial-temporal structures exhibited an increase in firing rate preceding an increase in excitatory neuron firing. Excitatory neuron firing rates peaked ten seconds after the inhibitory neurons. As LVF seizures extended to the opposite medial temporal lobe, the firing rate of inhibitory neurons increased.
Despouy et al. (2019)	N/Y(84 neurons)/N	Y	N	Y	**An epileptogenicity gradient from the tuber to the perituber.** In the interictal period in a patient with tuberous sclerosis complex, FR recorded in the tuber but not the perituber. More neurons in the tuber (57%) exhibiting firing-rate modulation around IEDs compared to the perituber (17%). No analysis of microLFP or neuronal activity during seizure.
Merricks et al. (2021)	Y/Y (1239 neurons/N	N	Y	N	**Two distinct activity patterns that align with the "dual territory" model of seizure dynamics.** In the cortex that is recruited in the seizure, an increase in neuronal firing and an elongation of waveform duration and reduced amplitude. In the penumbral tissue, action potentials remained consistent.
Schlafly et al. (2022)	Y/N/N	N	N	N	**A transient relationship between the ictal wavefront and the traveling wave,** which occurs in multiple stable directions. Using a computational model, a unified explanation that reproduces the wave dynamics observed *in vivo*.
Agopyan-Miu et al. (2023)	Y/Y(156 neurons)/Y	N	Y	Y	**A major global reduction or extinction of excitatory and inhibitory neuronal firing, but with evidence of intact inhibition in medial temporal structures.** Through a quantitative clustering approach and multiunit data, three distinct activity patterns noted during limbic seizure: (1) high-gamma entrainment at seizure onset; (2) evidence of feedforward effects and (3) regions unaffected by the seizure.

Table 2. Main results provided by microelectrode recordings.

Y: Yes; N: No; FR: Fast ripples; HYP: Hypersynchronous seizure onset, LVF: Low voltage fast activity.

[(a)] but no direct macroLFP vs microLFP comparison on the same seizure

2. MicroLFP vs macroLFP scales

2.1. Highly similar seizure onset patterns in microLFP and macroLFP

Different seizure onset patterns (SOP) of iEEG have been defined with macroelectrode recordings (macroLFP). They have been associated with the ability to guide successful surgical resections and long-term prognosis (Bartolomei et al., 2010; David et al., 2011; Doležalová et al., 2013; Faught et al., 1992; Wetjen et al., 2009). Eight seizure-onset patterns have been identified using visual and time-frequency analysis of iEEG, 83% of which include low-voltage fast activity (LVF activity). From the most to the least frequent (Lagarde et al., 2016, 2019; Perucca et al., 2014) are: LVF activity, preictal spiking with rhythmic spikes, bursts of polyspikes, slow wave or DC shift, rhythmic spikes, or low frequency spike waves, sharp beta activity with sinusoid activity of beta-band frequency (see **Table 3 for details**). For reasons of simplification and standardization, we decided to group some of these patterns. We propose grouping the fast activity with the fast low-voltage activity (Di Giacomo et al., 2019). A slow burst is associated with preictal spiking with rhythmic spikes of high amplitude, and repetitive fast spike bursts with delta brush SOP (Di Giacomo et al., 2019). Hypersynchronous seizure onset (HYP) seems similar to rhythmic spikes and waves, although there is a lack of consensus (Weiss et al., 2016).

While there is no clear association between SOP and the extension of EZ (Faught et al., 1992; Holtkamp et al., 2012; Jung et al., 1999; Lagarde et al., 2019), an association between several SOPs and histological types has been described. Seizures beginning with LVF activity are associated with a better postsurgical outcome (Holtkamp et al., 2012; Jiménez-Jiménez et al., 2015; Jung et al., 1999; Lagarde et al., 2016, 2019; S. A. Lee et al.,

2000; Spanedda et al., 1997; Wennberg et al., 2002). Conversely, SOPs with lower frequencies are associated with a poorer prognosis (theta/alpha sharp waves, rhythmic spikes, or spike-waves), with about one-third of patients being seizure-free after surgery (Jiménez-Jiménez et al., 2015; Jung et al., 1999; Kutsy et al., 1999; Lagarde et al., 2016, 2019; S. A. Lee et al., 2000; Singh et al., 2015; Wetjen et al., 2009). For instance, considering lesion type, a repetitive fast spike burst pattern is a marker for a good prognosis in focal cortical dysplasia type IIa, whereas it is a sign of poor outcome in focal cortical dysplasia type IIb (Di Giacomo et al., 2019).

The clinical and prognostic value of these SOP are not being questioned. However, they are insufficiently considered in microelectrode analyses. IED exist at different scales with strong similarities (Despouy et al., 2019), and it is therefore legitimate to wonder whether these SOPs are reproducible or completely different at the micrometric scale. While the majority of studies of seizures recorded with microelectrodes do not define the SOP, the figures provided in each article and the data presented suggest that certain patterns are found in microLFP, although in the majority of cases, there is no direct comparison at the different scales.

Initially, Babb and Crandall (Babb & Crandall, 1976) presented seizures starting with LVF activity and spike-and-wave activity with deep implanted microwires in a bundle, but without a comparison with macroLFP. With Behnke-Fried microelectrodes, examples of LVF activity and HYP seizure similar in macroLFP and microLFP are available, which illustrates that the same pattern can be detected at different scales (Lambrecq et al., 2017). We present an example of a similar seizure onset pattern with tetrodes in macroelectrodes versus microelectrodes (**Figure 1**).

Truccolo and colleagues (Truccolo et al., 2014) analyzed two types of highly similar SOP, in microLFP recorded by MEA and macroLFP recorded by electrocorticography (ECoG): sustained gamma (40–60 Hz) activity or spike-wave complexes (SWCs; 3 Hz). Also using MEA and ECoG simultaneously, at both scales Schevon and colleagues recorded an initial epileptic discharge followed by a rhythmic beta activity that gradually slows to the theta range with a rising amplitude, and an initial monomorphic delta rhythm with a gradually increasing frequency to the theta range, before slowing to a 3–4-Hz spike and wave rhythm before offset (Schevon et al., 2012).

Therefore, some seizures may share similar patterns at different scales, regardless of electrode type and regardless of the volume of neuronal populations that are recorded. The previous analyses lack a complete multiscale analysis and spatial correlation between scales. What is needed is a precise study to demonstrate to what degree seizures can share identical patterns at varying levels, as well as their significance.

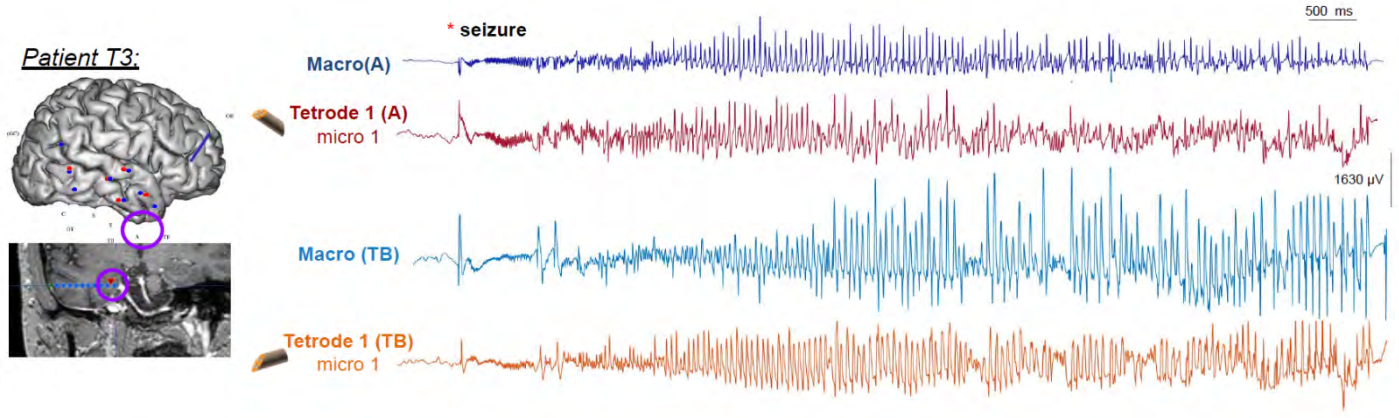


***Figure 1**. In dark and light blue, raw signal of bipolar mounting of the two more distal macrocontact located in the left amygdala (A) and right basal temporal lobe (TB). In red (tetrode 1), the monopolar mounting (raw signal) of the corresponding microcontact between the two most distal macrocontacts in amygdala, and similar for the right basal temporal lobe in orange. We note the same seizure onset pattern, characterized by a spike-and-wave followed by a LVFA, that appears similar in the macro-LFP and the micro-LFP. The seizure onset is tagged with a red star.*

Name	Description	Histology	Location	Prognosis & meaning	Also in microLFP?
Low voltage fast activity (LVF activity)	rhythmic fast oscillations > 14 Hz (median: 36 Hz, range: 14-97), with low initial amplitude <30 µV, starting without initial apparent changes	in all histological types but significantly associated with polymicrogyria at high frequencies (>100 Hz), and with periventricular nodular heterotopia at lower frequencies (13 to100 Hz)	most commonly reported in neocortical epilepsy	associated with a favorable surgical outcome (Singh et al. 2015), in particular in polymicrogyria (Spanneda et al. 1997, Lee et al. 2000, Wennberg et al. 2002, Faught et al. 1992) and associated with a larger EZ (Perucca et al. 2014)	yes Weiss et al. 2016; Schevon et al. 2012; Truccolo et al. 2011, 2014; Lambrecq et al. 2017; Elahian et al. 2018
Preictal spiking with rhythmic spikes	high amplitude (median: 660µV, range: 450-1,400) and low frequency (classically ≤ 3 Hz, median: 1.5 Hz, range: 1-3), prolonged duration (classically > 5s, median: 20 s, range: 4-130) followed by LVF activity, with lower frequency than isolated LVF activity (median: 23 Hz, range: 19.5-32)	found in neurodevelopmental tumors (NDT) and hippocampal sclerosis	not found in the insula, occipital or parietal lobe (Spencer et al. 1992, Velasco et al. 2000, Bartolomei et al. 2004)	-	yes Weiss et al. 2016; Truccolo et al. 2011; Despouy et al. 2019; Schevon et al. 2012.
Polyspike burst	high frequency (typically > 12 Hz, median: 19.3 Hz, range: 12.5-24.5) and amplitude (median: amplitude 420µV, range: 260-800) and short duration (classically < 5s, median: 3.3 s, range: 0.5-6), followed by LVF activity (median frequency: 28 Hz, range: 15.5-3)	not found in NDT (Faught et al. 1992, Wennberg et al. 2002)	-	-	yes Weiss et al. 2016; Elahian et al. 2018.
A slow wave or baseline shift	median amplitude: 400µV, range: 250-500) followed by LVF activity (median frequency: 31 Hz, range: 20-108	periventricular nodular heterotopia and polymicrogyria frequently begin with IBS followed by LVF activity. Rare in FCD type IIa or IIb (Di Giacomo et al. 2019)	-	-	not found
Rhythmic spikes or low-frequency spike waves	usually > 6 Hz and constantly < 14 Hz, median: 3.5 Hz, range: 4-18), with high amplitude (median: 1,200µV, range: 900-1,500)	-	most prevalently reported in medial temporal lobe epilepsy (Wennberg et al. 2002, Perucca et al. 2014, Schuh et al. 2000)	associated with good post-surgical outcome (Singh et al. 2015)	yes Weiss et al. 2016; Lambrecq et al. 2017; Truccolo et al. 2014; Wagner et al. 2015; Babb et al. 1976.
Sharp theta or alpha activity with low-frequency sinusoidal activity	lower than LVF activity (median = 9.5 Hz), median initial amplitude (higher than LVF activity, median: 400µV, range: 80-750), and progressively increasing amplitude	associated with FCD I, although all other patterns can be found with this type of lesion (Di Giacomo et al. 2019, Wennberg et al. 2002, Spanneda et al. 1997, Schiller et al. 1998)	-	-	yes Schevon et al. 2012
Sharp beta activity with beta band-frequency sinusoid activity	lower than LVF activity, median initial amplitude (higher than LVF activity), and progressively increasing amplitude	-	-	-	yes Truccolo et al. 2011
Delta-brush	bursts of low-amplitude rapid activity (within gamma frequency bands) superimposed on low-frequency (delta) sinusoidal activity	associated with FCD IIa	found in the frontal lobe	-	not found

Table 3. Nomenclature of seizure onset pattern identified in macroLFP.

EZ: epileptogenic zone; FCD: focal cortical dysplasia; IBS: ictal baseline shift; LVF: low-voltage fast activity; NDT: neurodevelopmental tumors. We voluntarily chose to classify the HYP onset in the rhythmic spikes and waves category, although there is a lack of consensus.

2.2. The need for a specific nomenclature of seizure onset pattern in microLFP

As the previous examples show, a wide range of highly similar SOP are detected both in microLFP and macroLFP. However, with scaling up different patterns are intuitively detected, as was observed by comparing scalp EEG and iEEG patterns (Tanaka et al., 2018). To our knowledge no classification of SOP at a micrometer scale has yet been established. It is likely that a specific nomenclature for microelectrodes will be necessary since microelectrodes could also provide new information about SOP.

With examples of different SOP according to the microelectrode Weiss and colleagues (Weiss et al., 2016) introduced this notion. They demonstrated an incrementally increasing power of FR in microLFP of around 11-14 sec before seizure onset in macroLFP, at LVF and HYP seizure onset but not when seizures began with rhythmic spiking or a polyspike onset pattern. They observed a similar increase in the power of FR in the microLFP before a HYP seizure, associated with a gamma oscillation before and after the FR. During the transition from rhythmic spiking onset to LVF activity, the power of FR also increased for around 10 seconds, whereas polypsike onset seizure was not accompanied by any increase in FR power. With a pattern resembling HYP in microLFP preceding the seizure onset, they suggest reclassifying a LVF seizure in macroLFP as a HYP. Therefore, in addition to pattern dissimilarity, the onset of the seizure may occur at a different time in the microelectrodes, notably earlier.

However, it is risky to ascribe the same properties to SOP recorded with microLFP as to patterns recorded in macroLFP. No relationship has been noted between the different patterns in microLFP and the histology, the postoperative prognosis, or the EZ. The heterogeneity of the SOP between the different authors, as

well as the heterogeneous locations, histopathologies, and microelectrode types raise the question of extrapolation and interpretation concerning their predictive and prognostic value. Recently, another type of classification, using computer assistance for the analysis of the LFP at seizure onset led to a more functional categorization (Gnatkovsky et al., 2019). The L-type seizure pattern is characterized by an LVF activity superimposed on a slowly developing slow potential shift, followed by an irregular spiking activity that gradually organizes into rhythmic bursting discharges. It has been specifically found in medial temporal lobe epilepsy and is associated with a longer seizure. The P-type seizure, typical of the neocortex of all cerebral lobes, is characterized by LVF activity with subharmonic bands superimposed on a fast-rising and fast-closing slow potential shift. A lack of consensus regarding the naming of patterns in macro (e.g., HYP vs burst of polyspikes) adds to the confusion and the low reproducibility.

Finally, most of these patterns detected in microLFP have also not been linked to any specific neuronal dynamics. For instance, in animals, °an increase in ripples and interneuron spike firing before LVF activity onset was demonstrated in LVF activity onset seizure (Shiri et al., 2015). No study in humans has investigated the differences in LFP amplitudes in micro vs. macro, which could provide information on neuronal generator size. A key step is to develop a specific investigation aimed at thoroughly exploring the differences between microLFP and macroLFP seizures. This study should include aspects such as latency of onset, amplitude, and potential correlations with high-frequency oscillations (HFOs) and neuronal dynamics. These findings should be compared with the histopathology and postoperative outcome.

2.3. Ictal baseline shift

The graphic element known initially as DC shifts, also called paroxysmal depolarizing shifts, initial slow wave, infraslow activity, or ictal baseline shifts (IBS), involves a subdelta oscillation lasting over one second. This distinctive feature has been associated with the SOZ (Bragin et al., 2007; Gumnit & Takahashi, 1965; Kanazawa et al., 2015; S. Lee et al., 2020; Rampp & Stefan, 2012; Wu et al., 2014). Predominantly observed in single cells in animal studies (De Curtis & Avanzini, 2001; Matsumoto & Ajmone, 1964; McCormick & Contreras, 2001; Steriade et al., 1998; Steriade & Contreras, 1998), it is one of the electrographic hallmarks of an established seizure, with hypersynchronous discharges recorded across neuronal populations (Steriade et al., 1994). Furthermore, IBS is one of the potential biomarkers that colocalize with the EZ in humans, alongside features such as fast activity and signal flattening (Gnatkovsky et al., 2014). The IBS has been colocalized with HFO but could appear in more restricted areas than ictal discharges (Ikeda, 2008; S. Lee et al., 2020; Mader et al., 2005; Rampp & Stefan, 2012; Rodin & Modur, 2008). This slow polarizing shift at seizure onset could help to determine the EZ when associated with an increase in the power of a specific fast activity band and electrographic “flattening” (Gnatkovsky et al., 2014).

Anatomically widespread IBS have been described, with an increasing peak at the onset and offset of seizure (Thompson et al., 2016). Therefore, IBS display characteristics of being both anatomically distributed and focal, forming a closed electric field. Rather than solely representing a localized area of abnormal activity, this infraslow spatiotemporal pattern that occurs during seizures suggests the involvement of a network process as a component of ictal dynamics. In *in vivo* (Ayala et al., 1973) or *in vitro* (Buzsáki et al., 1991) animal models, it has been assumed that the slow wave

reflects the inhibitory postsynaptic potentials generated by a wide interneuron network in response to a discharge of clusters of pathologically interconnected neurons which form the initial part of EEG spikes (Bragin et al., 2007; De Curtis & Avanzini, 2001).

Unfortunately, to our knowledge, such neuronal dynamics or even IBS analyses have not been reproduced with microelectrode recordings in humans. Studies should be designed to compare IBS simultaneously at the macro- and micro-LFP scales, in addition to using single units and different brain locations.

2.4. Chirps & fingerprint: spectrographic signatures of seizures in macroLFP only?

A “chirp” is a brief pseudo-periodic signal in which the frequency changes rapidly. In nature, a chirp is the sound of a bird's songs, the vocalization of cetaceans and is commonly used in sonar and radar terminology. But a chirp could also be a spectral signature of seizure onset, as shown at the onset of seizures on cortical grids, with a high sensitivity and specificity (respectively 83% and 100% in 43 seizures across six patients (Schiff et al., 2000).) The intensity of the chirp, and more particularly its earlier onset, could localize the source of a seizure and also provide information about its spread as it can be automatically detected. To our knowledge, chirps have not been investigated with microelectrode recordings.

Another specific time-frequency pattern of seizure onset, recently identified in macroLFP and which could be specific to the EZ (Grinenko et al., 2018) is the fingerprint. It associates 3 features: (i) **single or multiple pre-ictal sharp transients or spikes** (depending on their slow component duration); (ii) **narrow frequency bands of fast activity**; (iii) **simultaneous suppression of slow pre-ictal**

frequencies. Identifying the fingerprint could help the clinician to classify a macrocontact as being inside or outside the EZ.

Fingerprints have not yet been explicitly reproduced with microelectrodes. However, several time-frequency maps available in figures of some microelectrode research work suggest that the existence of a fingerprint is also worth exploring on a micrometric scale (Lambrecq et al., 2017; Schevon et al., 2012; Truccolo et al., 2011). Further work is needed to propose power spectral distribution and time-frequency analyses that allow a more accurate comparison of microLFP and macroLFP seizures to determine whether fingerprints also exist at the microscale and whether they can be used to identify the epileptic network. The use of the same machine-learning methods that have been applied to macroLFP for the automatic extraction of the fingerprint from the time-frequency data should also be explored in microLFP (Grinenko et al., 2018).

2.5. Electrophysiological concepts only identified in microLFP: microseizures

In vivo studies, and more recently human surface and depth microelectrode recordings, have uncovered synchronous firing patterns concentrated in small micro-domains with diameters of less than 1 mm, with a morphology, frequency, and periodicity similar to seizure discharges. These highly localized EEG events termed "**microseizures**" as well as "**micro periodic epileptiform discharges**", which are clinically silent, appear most prominently in the SOZ, and precede the ictal onset in 20% of seizures (Schevon et al., 2008, 2010; Stead et al., 2010).

Microseizures are suspected to have a role in ictogenesis. However, their physiological or pathological nature is yet to be established because they may also happen in nonepileptic control patients (Stead et al., 2010). *In vivo* models of seizure of

hippocampal slices in mice, using two-photon calcium imaging have demonstrated that microseizures precede the visible ictal activity in microLFP as the earliest step of seizure emergence and could be caused by a microdomain of pathologically interconnected neurons (Wenzel et al., 2019). This imaging technique also revealed that epileptic networks might consist of several distinct functional clusters comprised of neurons localized within specific spatial regions (Muldoon et al., 2013).

Microseizures provide evidence of the presence of microLFP events that might escape detection through macroLFP patterns. Additional investigation is required to explore the degree of disparity between micro- and macro-scale LFP seizures, focusing particularly on factors such as onset latency and propagation dynamics at each level. Furthermore, it is essential to ascertain whether alternative devices to MEAs can identify microseizures.

3. MacroLFP vs neuronal scales

Some concepts only emerged through the detection of neuronal activity with microelectrodes during seizures recorded with the clinical devices in macroLFP. They helped to update traditional dogma on ictogenesis.

3.1. The traditional view: hypersynchronization at seizure onset

Based on macroLFP signals, Penfield and Jasper first hypothesized that seizures are a manifestation of synchronous brain activity characterized by decreased inhibition and enhanced excitation resulting in a transient state of intense, high-amplitude, hypersynchronous neuronal activity (Penfield & Jasper, 1954). It was acknowledged that epileptic seizure resulted from a hypersynchronous activation of most or all neurons in an epileptic “focus” (Kandel, 1991). Thereafter, functional

connectivity analysis showed that seizures are associated with abnormal synchronization of distant structures before seizure onset (Bartolomei et al., 2004; Gotman & Levtova, 1996; Guye et al., 2006; Ponten et al., 2007; Wendling et al., 2003). For many years, this concept of hypersynchronous activity has been the prominent, commonly accepted hypothesis (Bancaud et al., 1970; Fisher et al., 2005; Margineanu, 2010; Westbrook, 1991).

However, microwire recordings suggested that seizure activity could not be entirely due to hypersynchrony. The issue of neural synchrony seems more complex than previously imagined (Bower et al., 2012a; Jiruska et al., 2013; Kramer et al., 2010; Mormann et al., 2003; Truccolo et al., 2011), see **Table 2**.

3.2. Heterogeneous neuronal dynamics (neuronal scale) vs hypersynchronization (macroLFP)

While human studies had shown activation of neuronal firing both inside and outside the epileptic "focus" in the pre-ictal period (Rayport & Waller, 1967; Verzeano et al., 1971; Wyler et al., 1982), hybrid depth electrodes introduced the concept of **heterogeneous firing**, confirmed by MEA at the beginning of seizures recorded in macroLFP. In fact, it would appear that the majority of neurons are not involved in the ictal onset of clinical seizures. The first studies by Babb and colleagues in 1976 and 1987 with depth microelectrodes recorded only 35-40% of neurons that increase their firing at ictal onset, and not in all seizures. The involvement of neurons increased during the seizure. Such neuronal dynamics were observed consistently in the cat model (Matsumoto & Ajmone, 1964) and in the kainic acid-treated rodent model (Bragin et al., 1999).

They also showed the involvement of only 7% of neurons recorded in subclinical seizures (discharge visible on macroLFP without concomitant clinical

manifestation), with no modification of single or multiunit firing for the majority; and 14% in auras, known as clinical focal seizures in modern terminology. This minority neuronal ensemble which can generate seizures focally has been called the "**epileptic pool**". No fixed “epileptic” neuron that could act as a pacemaker has ever been recorded, which invalidates the “epileptic neurons'' hypothesis by Wyler (Wyler et al., 1982). Nevertheless, they proved that when examined at the cellular level recurrent seizures in individual patients exhibit a consistent and stereotypical “pattern” characterized by distinct neuronal activation preceding and persisting throughout seizures.

These results were confirmed with MEA, with an increase of firing rate in 11.8% of the recorded neurons and a 7.5% decrease in the preictal period, with some neurons firing consistently throughout different seizures (Truccolo et al., 2011). In the ictal period, they observed an increase in firing rates in 45.4% of the recorded neurons and a diminution in 9.9% of the neurons, with great heterogeneity between patients. It is important to note that these heterogeneous dynamics were recorded in a restricted patch of cortex of 4 x 4 mm^2, which was not necessarily in the EZ.

In cases of medial temporal epilepsy, 67.6% of recorded neurons did not modify firing during seizure, while 7.6% showed a preictal increase, 9.5% a preictal decrease, and 15.3% an ictal increase (Bower et al., 2012). These results observed inside and outside the SOZ are additional evidence that the ‘‘epileptic ensemble” or “network’’ responsible for seizure generation is more complex and heterogeneous than previously thought. Such heterogeneity, although in different proportions, was confirmed with depth electrodes during low voltage fast activity in deep medial temporal structures: around 30% of the neurons significantly modified their firing rate at seizure onset, whether by a decrease or an increase, with a majority of stable units (Lambrecq et al., 2017). This heterogeneity becomes even more complex when cell type is taken account

of. During seizures, recent data with Behnke-Fried electrodes showed that the firing rate of the majority of both excitatory and inhibitory neurons decreased (69.2%) or ceased firing (21.8%), while interneuronal firing rates rarely increased (13.5%). Recently, Agopyan and colleagues (Agopyan-Miu et al., 2023) observed an overall increase in firing rates in SUA but the SUA results showed a downward trend during seizure. The diminution were observed in 69.2% and was greater than 3 standard-deviation in 24.4% of the neurons, whereas 5.1% increased their firing rate by 3 standard-deviation. Curiously, no difference was found between recruited and non-recruited groups overall or by cell-type.

In summary, these observations of seizure by microelectrodes at the neuronal scale have challenged the conventional belief of a hypersynchronous ictal onset (Bower et al., 2012a; Truccolo et al., 2011). Instead, they introduced the concept of heterogeneity and asynchronous activity. In fact since the first analyses of single-unit neurons during human seizures, the diversity of neuronal activity has been highlighted, with a large proportion of neurons remaining inactive or "**passive**" during seizure, whether using depth microelectrodes (Babb et al., 1987; Wyler et al., 1982; Wyler & Ward, 1986), or the 96-electrode Utah array (Truccolo et al., 2011). Only a minority of the epileptic pool consists of "active neurons" which increase their firing rate at seizure (Lambrecq et al., 2017).

3.3. The ictal penumbra (neuronal scale) vs high gamma activity (macroLFP)

The concept of an "**ictal penumbra**" that surrounds the ictal core was introduced with MEA studies (Schevon et al., 2012), confirmed in animal models, including cats, rodents, and ferrets (Dichter & Spencer, 1969; Prince & Wilder, 1967;

Schwartz & Bonhoeffer, 2001; Timofeev & Steriade, 2004) and in vitro (Trevelyan, 2009; Trevelyan et al., 2006, 2007). In humans iEEG recordings, the combination of an ictal high gamma signal in the macroLFP and a phase-locking value (phase-locked high gamma) was developed to determine the ictal core and the adjacent penumbra.

Ictal penumbra is characterized by desynchronized and low rates of neuronal firing, which contrasts with the wide-amplitude low-frequency signals recorded during a seizure. The ictal core is surrounded by an intense inhibitory signal that originates from the recruited areas and propagates into non-recruited regions ahead of the ictal wavefront. Within the recruited regions, there is a significant surge in MUA, which can be up to 30 times higher than baseline levels. Subsequently, there is a synchronization of low-frequency firing patterns across these areas. In contrast, the neurons within the ictal penumbra exhibit diminished firing rates, increased variability, inconsistent firing patterns, without any phase-locking with macroLFP oscillations (Schevon et al., 2012).

In essence, the ictal penumbra acts as a synaptic barrage, actively limiting ictal discharge and its spread. This concept of surround inhibition, which extends largely beyond the seizure core, may explain why many microelectrode studies have not revealed the expected neural signature of seizures (Babb et al., 1987; Bower et al., 2012a; Truccolo et al., 2011; Wyler et al., 1982). However, such hypotheses should be approached with a strict multiscale analysis combining neuronal, microLFP and macroLFP scales, without any spatial shifts.

3.4. Neuronal clusters in relation to macroLFP seizures

A crucial point to highlight is neuronal dynamics recorded on a limited cortical area of 4 x 4 mm^2 in MEA studies. It is also possible that these patches of neocortex are not located exactly within the EZ (Truccolo et al., 2011), which underscores the fact

that heterogeneous neuronal dynamics might not be confined. Indeed, seizures may not necessarily originate from a single constrained cortical site but from the coalescing of distinct epileptic microdomains spatially located apart (Bikson et al., 2003; Bragin et al., 2000; Jiruska et al., 2010). This has been suggested in non-human models as a potential mechanism that drives the shift towards more intense ictal discharges and the progression from microseizures to the manifestation of a macroseizure at a larger scale (Jiruska et al., 2010; Stead et al., 2010).

A comparison of metrics at neuronal and LFP scales could make it possible to distinguish different groups of neurons (microdomains or clusters). Very recently hybrid depth electrodes in limbic structures identified neuronal clusters that generate distinct ictal activity patterns in relation to high gamma and low-frequency activity in macroLFP (Agopyan-Miu et al., 2023). One cluster exhibited an increase in synchronous multiunit firing that was entrained to the ictal rhythm. This group was strongly associated with the clinical assessment of the EZ and a higher interictal HFO rate. A group of non-recruited neurons was not significantly affected by the ongoing seizure. The last group without any ictal recruitment had multiunit metrics (e.g., firing rate, firing entrainment to frequencies, waveform, high-gamma phase-amplitude coupling to the low frequency) similar to those observed in the recruited group, suggesting a probable conversion to an ictal state and feedforward effects originating from the seizure. This would be consistent with the expected neuronal activity in penumbral territories that receive synaptic barrages from the seizure core (Schevon et al., 2012). Among the different patterns of neuronal activity, phase-locking with high-gamma activity from the macroLFP could effectively discriminate between the two distinct groups of neurons with similar multi-unit metrics. This result reinforces the interdependence of different scales for analyzing ictogenesis.

3.5 The propagation of seizures through traveling waves (neuronal scale) vs macroLFP

The concept of **traveling waves**, a propagation of fast organized waves, as a theory of seizure propagation was established thanks to multiscale recordings with MEA and macroLFP during ECoG. However, the origin of these traveling waves remains unclear.

The "**ictal wavefront model**" suggests that waves arise from slowly advancing regions of high-firing multi-units known as the **ictal wavefront**, and propagate at 1mm/sec. As it spreads, it generates fast-propagating waves that move radially in two directions: inwards to a recruited core and outwards into a non-recruited zone or penumbra (Liou et al., 2020; Schevon et al., 2019; Smith et al., 2016). Coherence analyses suggest other dynamics of propagation. Coupling between large-scale neuronal populations in macroLFP with small neuronal groups spanning cortical columns was observed during seizures, with a greater increase in coupling at shorter distances (Martinet et al., 2017). Rapidly propagating waves of activity could support this multiscale coupling. Using a computational model compared to these *in vivo* recordings, the authors attempt to explain that a fixed source leads to an increase in the concentration of extracellular potassium. As this potassium diffuses through the cortex, it gradually increases the excitability of the overall system. Due to this increase in excitability, activity at the fixed source travels as waves across the surface of the cortex. According to this theory, fast-traveling waves propagates radially outwards from **stationary sources** (Martinet et al., 2017).

Individually, these theories fail to fully describe the range of spatiotemporal dynamics observed. It should be borne in mind that despite multiscale recordings, they remain limited to small areas of the cortex due to the sampling limitations of ECoG and

MEA. By simulating both the ictal wavefront and the fixed source, recent computational models have succeeded in replicating some of the features observed *in vivo* (Schlafly et al., 2022). Pursuing multiscale analyses by introducing the microLFP scale and more complex brain sampling (not only the neocortex) remains fundamental. Localizing these traveling wave sources has been found to help determine the EZ (Diamond et al., 2021). Consequently, these sources could be targeted for resection in epilepsy surgery (Lüders et al., 2006).

4. MacroLFP vs MicroLFP vs neuronal scales

How can concepts such as epileptic pool (Babb et al., 1987), small cortical patches (Truccolo et al., 2011) and neuronal clusters be integrated with large-scale clinically relevant seizure dynamics recorded by macroLFPs, when pieces of the puzzle are missing? Indeed, many papers claim to be multiscale, but multiscale does not mean that all the levels are present in the scale. “Pure” multiscale analyses require high spatial correspondence between the neuronal populations recorded by macrocontacts and microwires, which is not permitted by the design of MEAs and Behnke-Fried micro-macroelectrodes.

4.1. Is a combination of the 3 scales really possible?

The work by Truccolo and colleagues (Truccolo et al., 2014) is one of the rare comparisons of macroLFP (ECoG), microLFP (in MEA), and neuronal activity during seizures. They demonstrated that the degree of hypersynchrony can be highly dependent on the type of seizure: synchrony mostly occurs during the initial phase of the spike-and-wave complex pattern (~3 Hz), but not in gamma onset or LVF activity (~40–60 Hz). In gamma seizure onset patterns, the neuronal firing rate remained

irregular and asynchronous, while in the spike-wave pattern, they noticed phase-locking neuronal firing during the spike phase, leading to a coarse level of synchrony (50-100ms). The spike-and-wave complex pattern could be due to the existence of strong phase-locking discharges of neurons firing only during the spike-and-wave phase, with coarse temporal synchrony (50-100ms), suggesting a strong connection for synchronizing these neurons. Interestingly, EEG patterns, in particular LVF, were similar in macroLFP and corresponding microLFP.

These results support the idea of desynchronization during LVF activity, as described in LVF activity seizures that originate from the neocortex and entorhinal cortex in epileptic animal models (de Curtis & Gnatkovsky, 2009; Gnatkovsky et al., 2008; Wendling et al., 2003). During seizure onset, there is a preictal hypersynchronization followed by the suppression of action potential firing. Meanwhile, local somatic-projecting interneurons show sustained intense discharges, leading to strong fast inhibitory postsynaptic potentials in principal cells that increase later before seizure termination (de Curtis & Gnatkovsky, 2009; Wendling et al., 2002). These findings support the existence of an "inhibitory veto" or "**ictal penumbra**" in regions ahead of the ictal wavefront (Trevelyan et al., 2006, 2007). The most significant changes in increased network synchrony occur during seizure spread and termination (Evangelista et al., 2015; Guye et al., 2006; Ponten et al., 2007; Schindler et al., 2007).

Analysis at all three scales is possible, simultaneously and with high spatial correspondence as demonstrated by work on intercritical epileptic activity. *In vivo* rodent and *in vitro* models of epileptic seizures have revealed tiny microdomains (<1mm in diameter) with synchronous firing clustered during epileptogenesis and ictogenesis, and reported as HFO (Bragin et al., 2000; Jiruska et al., 2010). Our team confirmed these data in humans with tetrodes (Curot et al., 2023) and demonstrated that FR are associated with increased neuronal activity in the local network, but with

inhibition in brain-wide networks. These pathologically interconnected clusters could act as an internal kindling generator. In fact, the emergence of seizures may not necessarily originate from a single constrained cortical site but rather from coalescing distinct epileptic microdomains spatially located apart (Bikson et al., 2003; Bragin et al., 2000; Jiruska et al., 2010). This has been suggested as a potential mechanism that drives the shift towards more intense ictal discharges and the progression from microseizures to the manifestation of a “macroseizure” at a larger scale (Jiruska et al., 2010; Stead et al., 2010).

4.2. Adding a fourth scale: multiunit vs single unit activities

4.2.1. The single-unit scale and discrimination of cell types in humans

It should be noted that many of the studies cited above misuse the term "single unit", whereas the results presented concern above all "multiunits". Many synaptic connections occur between nearby neurons and are often detectable on the same electrode. This can pose challenges for accurate spike sorting and discriminating temporally overlapping action potentials (English et al., 2017; Fujisawa et al., 2008).

Initially applied in animal investigations, the use of stereotrodes, formed by intertwining two microwires with contact at the tip, and particularly tetrodes, marks a remarkable progression in the identification of individual neuronal units compared to the use of microwires (Buzsáki, 2004). This configuration offers notable advantages in assessing neuronal activity. For instance, neurons situated at varying distances from the two electrode tips exhibit distinct spike amplitude ratios when captured through two separate channels (McNaughton et al., 1983). Furthermore, employing tetrodes, which involve the bundling of four microwires, has been shown to notably enhance the

yield of single neuronal units at specific recording sites (Buzsáki & Draguhn, 2004; Gray et al., 1995; O'Keefe & Recce, 1993; Wilson & McNaughton, 1993), thereby expanding the scope of insights gained from neural recordings. However, challenges arise in brain regions with high cell densities, where closely clustered cell bodies and intricate firing patterns complicate the analysis (Buzsáki, 2004). Moreover, action potential amplitudes can increase during burst firing, adding complexity to recorded signals (Kandel & Spencer, 1961; Ranck, 1973).

Despite this bias, some studies go so far as to suggest a cell type-based analysis. First, better identification of interneurons and pyramidal cells would be necessary. So far, a superficial approach has been proposed with very small patient cohorts and low numbers of neurons with identified cell types. Recent studies with different microelectrodes in humans have highlighted a consistent progressive increase in a rate of fast-discharging interneurons. (De Curtis & Avoli, 2016; Mormann & Jefferys John G R, 2013; Schevon et al., 2012; Truccolo et al., 2014; Weiss et al., 2016). This happens while slow activity from pyramidal cells still persists.

During LVF activity, hybrid depth electrodes suggest an increase in neuronal firing of putative excitatory neurons during the increasing power of HFO, in about half of the recorded excitatory neurons (Weiss et al., 2016). They observed a diminution in the firing rate of putative principal cells, which is consistent with *in vitro* data (Gnatkovsky et al., 2008). Concerning the few putative interneurons detected, no specific propensity was identified. These data support the theory that some interneurons play a role in inhibition and might serve as synchronizers of principal cell spikes. In LVF seizures, a variability in firing rates within populations of pyramidal cells and a preictal increase more striking in putative interneurons were also observed (Truccolo et al., 2011). In fact, interneuron firing rate increases, while pyramidal cell activity slows down or stops, without evidence of synchronization at the neuronal level

(Truccolo et al., 2014). The slowdown of principal cells could explain the suppression of lower frequencies in the macroLFP at seizure onset. This increasing activity of inhibitory neurons could affect the membrane potential of pyramidal cells and explain the narrow band of fast activity in the macroLFP or microLFP (Ray & Maunsell, 2011; Sedley & Cunningham, 2013). The increase in rapid inhibitory interneuron activity could be due to reduced inhibition from slower inhibitory neurons. *In vitro* studies have suggested that slow inhibitory dendritic activity could impact fast inhibitory perisomatic interneurons (Banks et al., 2000).

In *in vitro* work (Gnatkovsky et al., 2008), principal neurons of superficial and deep layers were inhibited at the onset of seizure whereas putative interneurons had sustained firing, which is consistent with these human recordings. A slow increase in extracellular potassium concentration could promote ictal progression by diminution of inhibitory postsynaptic potentials. Rat models of chronic temporal lobe epilepsy reveal a selective implication of fast-spiking interneurons during IED and spontaneous seizure. These findings suggests that GABAergic inhibition may play a key part in seizure onset, possibly through parvalbumin-expressing interneurons. These interneurons exert strong inhibitory regulation by perisomatic and proximal dendrites in the normal brain (Neumann et al., 2017).

Regarding the termination of epileptic seizures, only one study identified an abrupt and widespread suppression of neuronal activity at the end of seizure, in principal cells as well as putative interneurons (Truccolo et al., 2011). There was no elaboration of conceptual principles, as opposed to *in vitro* studies in animals or humans with macroelectrodes (Bragin et al., 1997; Lado & Moshé, 2008; Salami et al., 2022).

It should be borne in mind that distinguishing cell subtypes in humans remains a real challenge. A comprehensive classification of neurons based on their properties available in extracellular recordings (e.g., waveform features, spike train dynamics as firing rate, refractory period, burst index, auto-correlograms) is still not available, while short timescale cross-correlograms require careful examination, (Ostojic et al., 2009; Peyrache & Destexhe, 2019).

Conclusions

By focusing too closely on neuronal activity, researchers often forget about microLFPs and, above all, their large-scale dynamics. To date, analyses of seizures have been coarse, incomplete, and based on small numbers of patients, and multiscale seizure analyses have not included all these levels (Schevon et al., 2019).This review highlights the various challenges that researchers using microelectrodes will need to overcome in the quest for a better understanding of epileptic seizures:

1st challenge: microLFP

The first challenge will be to carry out a systematic descriptive analysis of the microLFP seizure signal, which can then be compared with the macroLFP signal.

2nd challenge: high spatial correspondence

The second challenge is to improve the spatial correspondence between a macroelectrode and a microelectrode in order to achieve better comparability between the two scales. Conducting multiscale recordings requires a significant level of spatial alignment to effectively merge the information from neuronal and large-scale network perspectives. This can be done with hybrid electrodes using tetrodes, as well as with microcontacts along the macroelectrodes. Regrettably, many scientific studies

frequently present multiscale analyses that incorporate spatial discrepancies because microelectrodes are not consistently collocated with macroelectrodes.

3rd challenge: improving brain sampling

At this stage, this remains very limited within individuals and across individuals. The primary limitation of using microelectrodes is restricted spatial sampling, which naturally stems from the size of the electrode. We have noted that the use of deep electrodes, compared to MEA, enables a wider exploration of the brain volume, with the possibility of implanting a more electrodes containing microcontacts. New devices with lateral contact should also be available in the near future.

4th challenge: long duration recordings

Obtaining stable recordings over days is a technical challenge which requires similarity in receiving signal, especially when detecting multi and above all single unit activity and particularly when seizures occur (Brinkmann et al., 2009).

MEA are useful tools for studying propagation dynamics. However, they have limited spatial sampling of cortical surface and can analyze only one or two cortical layers, which makes them insufficient for the analysis of local generators. On the other hand, new devices that combine tetrode and macrocontacts, enable the exploration of the neocortex as well as the allocortex, and provide a microelectrode exploration (microLFP and single-unit analysis) with a strong spatial correspondence with the macroLFP signal, seem to be a promising tool for the future. In fact, the networked organization of the EZ requires brain sampling at multiple sites to determine the boundaries more precisely (Bartolomei et al., 2017). Tetrodes have already demonstrated their potential in the multiscale analysis of brain activity (macroLFP, microLFP, single-unit activity) for the study of FRs, by showing changes in neuronal activity on both a local and a global scale (Curot et al., 2023).

The most complete and informative multiscale vision would be a systematic 4-level comparison and synthesis: with macroLFP analysis, which shows extracellular potential over a large area, microelectrodes, which offer a more local field potential, multiunit analysis, and finally single-unit analysis with a combination of different metrics for cell type classification for a comprehension of seizures at the cellular level.

References

Agopyan-Miu, A. H., Merricks, E. M., Smith, E. H., McKhann II, G. M., Sheth, S. A., Feldstein, N. A., Trevelyan, A. J., & Schevon, C. A. (2023). Cell-type specific and multiscale dynamics of human focal seizures in limbic structures. *Brain*, *Online ahead of print.* https://doi.org/10.1093/brain/awad262

Ayala, G. F., Dichter, M., Gumnit, R. J., Matsumoto, H., & Spencer, W. A. (1973). Genesis of epileptic interictal spikes. New knowledge of cortical feedback systems suggests a neurophysiological explanation of brief paroxysms. *Brain Research*, *52*(C). https://doi.org/10.1016/0006-8993(73)90647-1

Babb, T. L., Carr, E., & Crandall, P. H. (1973). Analysis of extracellular firing patterns of deep temporal lobe structures in man. *Electroencephalography and Clinical Neurophysiology*, *34*, 247–257.

Babb, T. L., & Crandall, P. H. (1976). Epileptogenesis Of Human Limbic Neurons In Psychomotor Epileptics. *Electroencephalography and Clinical Neurophysiology*, *40*, 225.

Babb, T. L., Wilson, C. L., & Isokawa-Akesson, M. (1987). *Firing patterns of human limbic neurons during stereoencephalography (SEEG) and clinical temporal lobe seizures*.

Bancaud, J., Angelergues, R., Bernouilli, C., Bonis, A., Bordas-Ferrer, M., Bresson, M., Buser, P., Covello, L., Morel, P., Szikla, G., Takeda, A., & Talairach, J. (1970). Functional stereotaxic exploration (SEEG) of epilepsy. *Electroencephalography and Clinical Neurophysiology*, *28*(1).

Bancaud, J., & Talairach, J. (1965). *La stéréo-encéphalographie dans l'épilepsie* (Masson et Cie, Ed.).

Banks, M. I., White, J. A., & Pearce, R. A. (2000). Interactions between distinct GABA(A) circuits in hippocampus. *Neuron*, *25*(2). https://doi.org/10.1016/S0896-6273(00)80907-1

Bartolomei, F., Chauvel, P., & Wendling, F. (2008). Epileptogenicity of brain structures in human temporal lobe epilepsy: A quantified study from intracerebral EEG. *Brain*, *131*(7), 1818–1830. https://doi.org/10.1093/brain/awn111

Bartolomei, F., Cosandier-Rimele, D., McGonigal, A., Aubert, S., Régis, J., Gavaret, M., Wendling, F., & Chauvel, P. (2010). From mesial temporal lobe to temporoperisylvian seizures: A quantified study of temporal lobe seizure networks. *Epilepsia*, *51*(10). https://doi.org/10.1111/j.1528-1167.2010.02690.x

Bartolomei, F., Lagarde, S., Wendling, F., McGonigal, A., Jirsa, V., Guye, M., & Bénar, C. (2017). Defining epileptogenic networks: Contribution of SEEG and signal analysis. In *Epilepsia* (Vol. 58, Issue 7, pp. 1131–1147). Blackwell Publishing Inc. https://doi.org/10.1111/epi.13791

Bartolomei, F., Wendling, F., Régis, J., Gavaret, M., Guye, M., & Chauvel, P. (2004). Pre-ictal synchronicity in limbic networks of mesial temporal lobe epilepsy. *Epilepsy Research*, *61*(1–3). https://doi.org/10.1016/j.eplepsyres.2004.06.006

Basu, I., Kudela, P., Korzeniewska, A., Franaszczuk, P. J., & Anderson, W. S. (2015). A study of the dynamics of seizure propagation across micro domains in the vicinity of the seizure onset zone. *Journal of Neural Engineering*, *12*(4). https://doi.org/10.1088/1741-2560/12/4/046016

Bikson, M., Fox, J. E., & Jefferys, J. G. R. (2003). Neuronal aggregate formation underlies spatiotemporal dynamics of nonsynaptic seizure initiation. *Journal of Neurophysiology*, *89*(4). https://doi.org/10.1152/jn.00764.2002

Blanco, J. A., Stead, M., Krieger, A., Stacey, W., Maus, D., Marsh, E., Viventi, J., Lee, K. H., Marsh, R., Litt, B., & Worrell, G. A. (2011). Data mining neocortical high-frequency oscillations in epilepsy and controls. *Brain*, *134*(10). https://doi.org/10.1093/brain/awr212

Bower, M. R., Stead, M., Meyer, F. B., Marsh, W. R., & Worrell, G. A. (2012a). Spatiotemporal neuronal correlates of seizure generation in focal epilepsy. *Epilepsia*, *53*(5), 807–816. https://doi.org/10.1111/j.1528-1167.2012.03417.x

Bower, M. R., Stead, M., Meyer, F. B., Marsh, W. R., & Worrell, G. A. (2012b). Spatiotemporal neuronal correlates of seizure generation in focal epilepsy. *Epilepsia*, *53*(5), 807–816. https://doi.org/10.1111/j.1528-1167.2012.03417.x

Bragin, A., Claeys, P., Vonck, K., Van Roost, D., Wilson, C., Boon, P., & Engel, J. (2007). Analysis of Initial Slow Waves (ISWs) at the seizure onset in patients with drug resistant temporal lobe epilepsy. *Epilepsia*, *48*(10), 1883–1894. https://doi.org/10.1111/j.1528-1167.2007.01149.x

Bragin, A., Csicsvári, J., Penttonen, M., & Buzsáki, G. (1997). Epileptic afterdischarge in the hippocampal-entorhinal system: Current source density and unit studies. *Neuroscience*, *76*(4). https://doi.org/10.1016/S0306-4522(96)00446-0

Bragin, A., Engel, J., Wilson, C. L., Vizentin, E., & Mathern, G. W. (1999). Electrophysiologic analysis of a chronic seizure model after unilateral hippocampal KA injection. *Epilepsia*, *40*(9), 1210–1221. https://doi.org/10.1111/j.1528-1157.1999.tb00849.x

Bragin, A., Mody, I., Wilson, C. L., & Engel, J. (2002). Local generation of fast ripples in epileptic brain. *Journal of Neuroscience*, *22*(5). https://doi.org/10.1523/jneurosci.22-05-02012.2002

Bragin, A., Wilson, C. L., & Engel, J. (2000). Chronic epileptogenesis requires development of a network of pathologically interconnected neuron clusters: A hypothesis. *Epilepsia*, *41*(SUPPL. 6). https://doi.org/10.1111/j.1528-1157.2000.tb01573.x

Brinkmann, B. H., Bower, M. R., Stengel, K. A., Worrell, G. A., & Stead, M. (2009). Large-scale electrophysiology: Acquisition, compression, encryption, and storage of big data. *Journal of Neuroscience Methods*, *180*(1). https://doi.org/10.1016/j.jneumeth.2009.03.022

Buzsáki, G. (2004). Large-scale recording of neuronal ensembles. In *Nature Neuroscience* (Vol. 7, Issue 5, pp. 446–451). https://doi.org/10.1038/nn1233

Buzsáki, G., & Draguhn, A. (2004). Neuronal Oscillations in Cortical Networks. In *Source: Science, New Series* (Vol. 304, Issue 5679).

Buzsáki, G., Masliah, E., Chen, L. S., Horváth, Z., Terry, R., & Gage, F. H. (1991). Hippocampal grafts into the intact brain induce epileptic patterns. *Brain Research*, *554*(1–2). https://doi.org/10.1016/0006-8993(91)90168-U

Chang, M., Dian, J. A., Dufour, S., Wang, L., Moradi Chameh, H., Ramani, M., Zhang, L., Carlen, P. L., Womelsdorf, T., & Valiante, T. A. (2018). Brief activation of GABAergic interneurons initiates the transition to ictal events through post-inhibitory rebound excitation. *Neurobiology of Disease*, *109*. https://doi.org/10.1016/j.nbd.2017.10.007

Chari, A., Thornton, R. C., Tisdall, M. M., & Scott, R. C. (2020). Microelectrode recordings in human epilepsy: a case for clinical translation. In *Brain Communications* (Vol. 2, Issue 2). Oxford University Press. https://doi.org/10.1093/braincomms/fcaa082

Crépon, B., Navarro, V., Hasboun, D., Clemenceau, S., Martinerie, J., Baulac, M., Adam, C., & Le Van Quyen, M. (2010). Mapping interictal oscillations greater than 200 Hz recorded with intracranial macroelectrodes in human epilepsy. *Brain*, *133*(1). https://doi.org/10.1093/brain/awp277

Cressman, J. R., Ullah, G., Ziburkus, J., Schiff, S. J., & Barreto, E. (2009). The influence of sodium and potassium dynamics on excitability, seizures, and the stability of persistent states: I. Single neuron dynamics. *Journal of Computational Neuroscience*, *26*(2). https://doi.org/10.1007/s10827-008-0132-4

Curot, J., Barbeau, E., Despouy, E., Denuelle, M., Sol, J. C., Lotterie, J. A., Valton, L., & Peyrache, A. (2023). Local neuronal excitation and global inhibition during epileptic fast ripples in humans. *Brain : A Journal of Neurology*, *146*(2), 561–575. https://doi.org/10.1093/brain/awac319

David, O., Blauwblomme, T., Job, A. S., Chabards, S., Hoffmann, D., Minotti, L., & Kahane, P. (2011). Imaging the seizure onset zone with stereo-electroencephalography. *Brain*, *134*(10). https://doi.org/10.1093/brain/awr238

De Curtis, M., & Avanzini, G. (2001). Interictal spikes in focal epileptogenesis. In *Progress in Neurobiology* (Vol. 63). www.elsevier.com/locate/pneurobio

De Curtis, M., & Avoli, M. (2016). GABAergic networks jump-start focal seizures. In *Epilepsia* (Vol. 57, Issue 5, pp. 679–687). Blackwell Publishing Inc. https://doi.org/10.1111/epi.13370

de Curtis, M., & Gnatkovsky, V. (2009). Reevaluating the mechanisms of focal ictogenesis: The role of low-voltage fast activity. In *Epilepsia* (Vol. 50, Issue 12, pp. 2514–2525). https://doi.org/10.1111/j.1528-1167.2009.02249.x

Depannemaecker, D., Destexhe, A., Jirsa, V., & Bernard, C. (2021). Modeling seizures: From single neurons to networks. In *Seizure* (Vol. 90). https://doi.org/10.1016/j.seizure.2021.06.015

Despouy, E., Curot, J., Denuelle, M., Deudon, M., Sol, J. C., Lotterie, J. A., Reddy, L., Nowak, L. G., Pariente, J., Thorpe, S. J., Valton, L., & Barbeau, E. J. (2019). Neuronal spiking activity highlights a gradient of epileptogenicity in human tuberous sclerosis lesions. *Clinical Neurophysiology*, *130*(4), 537–547. https://doi.org/10.1016/j.clinph.2018.12.013

Di Giacomo, R., Uribe-San-Martin, R., Mai, R., Francione, S., Nobili, L., Sartori, I., Gozzo, F., Pelliccia, V., Onofrj, M., Lo Russo, G., de Curtis, M., & Tassi, L. (2019). Stereo-EEG ictal/interictal patterns and underlying pathologies. *Seizure*, *72*, 54–60. https://doi.org/10.1016/J.SEIZURE.2019.10.001

Diamond, J. M., Diamond, B. E., Trotta, M. S., Dembny, K., Inati, S. K., & Zaghloul, K. A. (2021). Travelling waves reveal a dynamic seizure source in human focal epilepsy. *Brain*, *144*(6), 1751–1763. https://doi.org/10.1093/brain/awab089

Diamond, J. M., Withers, C. P., Chapeton, J. I., Rahman, S., Inati, S. K., & Zaghloul, K. A. (2023). Interictal discharges in the human brain are travelling waves arising from an epileptogenic source. *Brain : A Journal of Neurology*, *146*(5), 1903–1915. https://doi.org/10.1093/brain/awad015

Dichter, M., & Spencer, W. A. (1969). Penicillin-induced interictal discharges from the cat hippocampus. II. Mechanisms underlying origin and restriction. *Journal of Neurophysiology*, *32*(5). https://doi.org/10.1152/jn.1969.32.5.663

Doležalová, I., Brázdil, M., Hermanová, M., Horáková, I., Rektor, I., & Kuba, R. (2013). Intracranial EEG seizure onset patterns in unilateral temporal lobe epilepsy and their relationship to other variables. *Clinical Neurophysiology*, *124*(6). https://doi.org/10.1016/j.clinph.2012.12.046

Elahian, B., Lado, N. E., Mankin, E., Vangala, S., Misra, A., Moxon, K., Fried, I., Sharan, A., Yeasin, M., Staba, R., Bragin, A., Avoli, M., Sperling, M. R., Engel, J., & Weiss, S. A. (2018). Low-voltage fast seizures in humans begin with increased interneuron firing. *Annals of Neurology*, *84*(4), 588–600. https://doi.org/10.1002/ana.25325

Ellender, T. J., Raimondo, J. V., Irkle, A., Lamsa, K. P., & Akerman, C. J. (2014). Excitatory effects of parvalbumin-expressing interneurons maintain hippocampal epileptiform activity via synchronous afterdischarges. *Journal of Neuroscience*, *34*(46). https://doi.org/10.1523/JNEUROSCI.1747-14.2014

English, D. F., McKenzie, S., Evans, T., Kim, K., Yoon, E., & Buzsáki, G. (2017). Pyramidal Cell-Interneuron Circuit Architecture and Dynamics in Hippocampal Networks. *Neuron*, *96*(2). https://doi.org/10.1016/j.neuron.2017.09.033

Evangelista, E., Bénar, C., Bonini, F., Carron, R., Colombet, B., Régis, J., & Bartolomei, F. (2015). Does the thalamo-cortical synchrony play a role in seizure termination? *Frontiers in Neurology*, *6*(SEP). https://doi.org/10.3389/fneur.2015.00192

Faught, E., Kuzniecky, R. I., & Hurst, D. C. (1992). Ictal EEG wave forms from epidural electrodes predictive of seizure control after temporal lobectomy. *Electroencephalography and Clinical Neurophysiology*, *83*(4). https://doi.org/10.1016/0013-4694(92)90116-Y

Fisher, R. S., Van Emde Boas, W., Blume, W., Elger, C., Genton, P., Lee, P., & Engel, J. (2005). Epileptic seizures and epilepsy: Definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). In *Epilepsia* (Vol. 46, Issue 4). https://doi.org/10.1111/j.0013-9580.2005.66104.x

Frazzini, V., Whitmarsh, S., Lehongre, K., Yger, P., Lemarechal, J.-D., Mathon, B., Adam, C., Hasboun, D., Lambrecq, V., & Navarro, V. (2022). *Human periventricular nodular heterotopia shows several interictal epileptic patterns and hyperexcitability of neuronal firing*.

Fried, I., Wilson, C. L., Maidment, N. T., Engel, J., Behnke, E., Fields, T. A., Macdonald, K. A., Morrow, J. W., & Ackerson, L. (1999). Cerebral microdialysis combined with single-neuron and electroencephalographic recording in neurosurgical patients: Technical note. *Journal of Neurosurgery*, *91*(4). https://doi.org/10.3171/jns.1999.91.4.0697

Fujisawa, S., Amarasingham, A., Harrison, M. T., & Buzsáki, G. (2008). Behavior-dependent short-term assembly dynamics in the medial prefrontal cortex. *Nature Neuroscience*, *11*(7). https://doi.org/10.1038/nn.2134

Gnatkovsky, V., De Curtis, M., Pastori, C., Cardinale, F., Lo Russo, G., Mai, R., Nobili, L., Sartori, I., Tassi, L., & Francione, S. (2014). Biomarkers of epileptogenic zone defined by quantified stereo-EEG analysis. *Epilepsia*, *55*(2), 296–305. https://doi.org/10.1111/epi.12507

Gnatkovsky, V., Librizzi, L., Trombin, F., & De Curtis, M. (2008). Fast activity at seizure onset is mediated by inhibitory circuits in the entorhinal cortex in vitro. *Annals of Neurology*, *64*(6), 674–686. https://doi.org/10.1002/ana.21519

Gnatkovsky, V., Pelliccia, V., de Curtis, M., & Tassi, L. (2019). Two main focal seizure patterns revealed by intracerebral electroencephalographic biomarker analysis. *Epilepsia*, *60*(1), 96–106. https://doi.org/10.1111/epi.14610

Gotman, J., & Levtova, V. (1996). Amygdala-hippocampus relationships in temporal lobe seizures: A phase-coherence study. *Epilepsy Research*, *25*(1). https://doi.org/10.1016/0920-1211(96)00021-6

Gray, C. M., Maldonado, P. E., Wilson, M., & McNaughton, B. (1995). Tetrodes markedly improve the reliability and yield of multiple single-unit isolation from multi-unit recordings in cat striate cortex. *Journal of Neuroscience Methods*, *63*(1–2). https://doi.org/10.1016/0165-0270(95)00085-2

Grinenko, O., Li, J., Mosher, J. C., Wang, I. Z., Bulacio, J. C., Gonzalez-Martinez, J., Nair, D., Najm, I., Leahy, R. M., & Chauvel, P. (2018). A fingerprint of the epileptogenic zone in human epilepsies. *Brain*, *141*(1), 117–131. https://doi.org/10.1093/brain/awx306

Gumnit, R. J., & Takahashi, T. (1965). Changes in direct current activity during experimental focal seizures. *Electroencephalography and Clinical Neurophysiology*, *19*(1). https://doi.org/10.1016/0013-4694(65)90007-6

Guye, M., Régis, J., Tamura, M., Wendling, F., Gonigal, A. M., Chauvel, P., & Bartolomei, F. (2006). The role of corticothalamic coupling in human temporal lobe epilepsy. *Brain*, *129*(7). https://doi.org/10.1093/brain/awl151

Hashemi, M., Vattikonda, A. N., Sip, V., Guye, M., Bartolomei, F., Woodman, M. M., & Jirsa, V. K. (2020). The Bayesian Virtual Epileptic Patient: A probabilistic framework designed to infer the spatial map of epileptogenicity in a personalized large-scale brain model of epilepsy spread. *NeuroImage*, *217*. https://doi.org/10.1016/j.neuroimage.2020.116839

Holtkamp, M., Sharan, A., & Sperling, M. R. (2012). Intracranial EEG in predicting surgical outcome in frontal lobe epilepsy. *Epilepsia*, *53*(10). https://doi.org/10.1111/j.1528-1167.2012.03600.x

Huberfeld, G., Blauwblomme, T., & Miles, R. (2015). Hippocampus and epilepsy: Findings from human tissues. *Revue Neurologique*, *171*(3). https://doi.org/10.1016/j.neurol.2015.01.563

Ikeda, A. (2008). DC recordings to localize the ictal onset zone. In H. O. Lüders (Ed.), *Textbook of Epilepsy Surgery* (pp. 659–666). Informa UK Ltd.

Jacobs, J., LeVan, P., Chander, R., Hall, J., Dubeau, F., & Gotman, J. (2008). Interictal high-frequency oscillations (80-500 Hz) are an indicator of seizure onset areas independent of spikes in the human epileptic brain. *Epilepsia*, *49*(11). https://doi.org/10.1111/j.1528-1167.2008.01656.x

Jacobs, J., Levan, P., Chtillon, C. D., Olivier, A., Dubeau, F., & Gotman, J. (2009). High frequency oscillations in intracranial EEGs mark epileptogenicity rather than lesion type. *Brain*, *132*(4). https://doi.org/10.1093/brain/awn351

Jiménez-Jiménez, D., Nekkare, R., Flores, L., Chatzidimou, K., Bodi, I., Honavar, M., Mullatti, N., Elwes, R. D. C., Selway, R. P., Valentín, A., & Alarcón, G. (2015). Prognostic value of intracranial seizure onset patterns for surgical outcome of the treatment of epilepsy. *Clinical Neurophysiology*, *126*(2). https://doi.org/10.1016/j.clinph.2014.06.005

Jirsa, V. K., Proix, T., Perdikis, D., Woodman, M. M., Wang, H., Bernard, C., Bénar, C., Chauvel, P., Bartolomei, F., Bartolomei, F., Guye, M., Gonzalez-Martinez, J., & Chauvel, P. (2017). The Virtual Epileptic Patient: Individualized whole-brain models of epilepsy spread. *NeuroImage*, *145*. https://doi.org/10.1016/j.neuroimage.2016.04.049

Jiruska, P., Csicsvari, J., Powell, A. D., Fox, J. E., Chang, W. C., Vreugdenhil, M., Li, X., Palus, M., Bujan, A. F., Dearden, R. W., & Jefferys, J. G. R. (2010). High-frequency network activity, global increase in neuronal activity, and synchrony expansion precede epileptic seizures in vitro. *Journal of Neuroscience*, *30*(16), 5690–5701. https://doi.org/10.1523/JNEUROSCI.0535-10.2010

Jiruska, P., de Curtis, M., Jefferys, J. G. R., Schevon, C. A., Schiff, S. J., & Schindler, K. (2013). Synchronization and desynchronization in epilepsy: Controversies and hypotheses. In *Journal of Physiology* (Vol. 591, Issue 4, pp. 787–797). https://doi.org/10.1113/jphysiol.2012.239590

Jung, W. Y., Pacia, S. V., & Devinsky, O. (1999). Neocortical temporal lobe epilepsy: Intracranial EEG features and surgical outcome. *Journal of Clinical Neurophysiology*, *16*(5). https://doi.org/10.1097/00004691-199909000-00003

Kanazawa, K., Matsumoto, R., Imamura, H., Matsuhashi, M., Kikuchi, T., Kunieda, T., Mikuni, N., Miyamoto, S., Takahashi, R., & Ikeda, A. (2015). Intracranially recorded ictal direct current shifts may precede high frequency oscillations in human epilepsy. *Clinical Neurophysiology*, *126*(1). https://doi.org/10.1016/j.clinph.2014.05.028

Kandel, E. R. (1991). Cellular mechanisms of learning and the biological basis of individuality. In E. R. Kandel, J. H. Schwartz, & T. M. Jessell (Eds.), *Principles of Neural Science* (3rd ed., pp. 1009–1031). Appleton & Lange.

Kandel, E. R., & Spencer, W. A. (1961). Excitation and inhibition of single pyramidal cells during hippocampal seizure. *Experimental Neurology*, *4*(2). https://doi.org/10.1016/0014-4886(61)90038-3

Keller, C. J., Truccolo, W., Gale, J. T., Eskandar, E., Thesen, T., Carlson, C., Devinsky, O., Kuzniecky, R., Doyle, W. K., Madsen, J. R., Schomer, D. L., Mehta, A. D., Brown, E. N., Hochberg, L. R., Ulbert, I., Halgren, E., & Cash, S. S. (2010). Heterogeneous neuronal firing patterns during interictal epileptiform discharges in the human cortex. *Brain*, *133*(6), 1668–1681. https://doi.org/10.1093/brain/awq112

Kondylis, E. D., Wozny, T. A., Lipski, W. J., Popescu, A., DeStefino, V. J., Esmaeili, B., Raghu, V. K., Bagic, A., & Richardson, R. M. (2014). Detection of high-frequency oscillations by hybrid depth electrodes in standard clinical intracranial EEG recordings. *Frontiers in Neurology*, *5 AUG*. https://doi.org/10.3389/fneur.2014.00149

Kramer, M. A., Eden, U. T., Kolaczyk, E. D., Zepeda, R., Eskandar, E. N., & Cash, S. S. (2010). Coalescence and fragmentation of cortical networks during focal seizures. *Journal of Neuroscience*, *30*(30). https://doi.org/10.1523/JNEUROSCI.6309-09.2010

Kuhlmann, L., Grayden, D. B., Wendling, F., & Schiff, S. J. (2015). Role of multiple-scale modeling of epilepsy in seizure forecasting. In *Journal of Clinical Neurophysiology* (Vol. 32, Issue 3). https://doi.org/10.1097/WNP.0000000000000149

Kutsy, R. L., Farrell, D. F., & Ojemann, G. A. (1999). Ictal patterns of neocortical seizures monitored with intracranial electrodes: Correlation with surgical outcome. *Epilepsia*, *40*(3). https://doi.org/10.1111/j.1528-1157.1999.tb00702.x

Lado, F. A., & Moshé, S. L. (2008). How do seizures stop? In *Epilepsia* (Vol. 49, Issue 10). https://doi.org/10.1111/j.1528-1167.2008.01669.x

Lagarde, S., Bonini, F., McGonigal, A., Chauvel, P., Gavaret, M., Scavarda, D., Carron, R., Régis, J., Aubert, S., Villeneuve, N., Giusiano, B., Figarella-Branger, D., Trebuchon, A., & Bartolomei, F. (2016). Seizure-onset patterns in focal cortical dysplasia and neurodevelopmental tumors: Relationship with surgical prognosis and neuropathologic subtypes. *Epilepsia*, *57*(9), 1426–1435. https://doi.org/10.1111/epi.13464

Lagarde, S., Buzori, S., Trebuchon, A., Carron, R., Scavarda, D., Milh, M., McGonigal, A., & Bartolomei, F. (2019). The repertoire of seizure onset patterns in human focal epilepsies: Determinants and prognostic values. *Epilepsia*, *60*(1), 85–95. https://doi.org/10.1111/epi.14604

Lambrecq, V., Lehongre, K., Adam, C., Erio Frazzini, V., Mathon, B., Ephane Clemenceau, S., Hasboun, D., Ephane Charpier, S., Baulac, M., Navarro, V., & Le Van Quyen, M. (2017). *Single-Unit Activities During the Transition to Seizures in Deep Mesial Structures*. https://doi.org/10.1002/ana

Lee, S. A., Spencer, D. D., & Spencer, S. S. (2000). Intracranial EEG seizure-onset patterns in neocortical epilepsy. *Epilepsia*, *41*(3). https://doi.org/10.1111/j.1528-1157.2000.tb00159.x

Lee, S., Issa, N. P., Rose, S., Tao, J. X., Warnke, P. C., Towle, V. L., van Drongelen, W., & Wu, S. (2020). DC shifts, high frequency oscillations, ripples and fast ripples in relation to the seizure onset zone. *Seizure*, *77*, 52–58. https://doi.org/10.1016/j.seizure.2019.05.001

Lévesque, M., Chen, L. Y., Hamidi, S., & Avoli, M. (2018). Dynamic interneuron-principal cell interplay leads to a specific pattern of in vitro ictogenesis. *Neurobiology of Disease*, *115*. https://doi.org/10.1016/j.nbd.2018.04.004

Lévesque, M., Salami, P., Gotman, J., & Avoli, M. (2012). Two seizure-onset types reveal specific patterns of high-frequency oscillations in a model of temporal lobe epilepsy. *Journal of Neuroscience*, *32*(38), 13264–13272. https://doi.org/10.1523/JNEUROSCI.5086-11.2012

Liou, J. Y., Smith, E. H., Bateman, L. M., Bruce, S. L., McKhann, G. M., Goodman, R. R., Emerson, R. G., Schevon, C. A., & Abbott, L. F. (2020). A model for focal seizure onset, propagation, evolution, and progression. *ELife*, *9*. https://doi.org/10.7554/eLife.50927

Lopantsev, V., & Avoli, M. (1998). Laminar organization of epileptiform discharges in the rat entorhinal cortex in vitro. *Journal of Physiology*, *509*(3). https://doi.org/10.1111/j.1469-7793.1998.785bm.x

Lüders, H. O., Najm, I., Nair, D., Widdess-Walsh, P., & Bingman, W. (2006). The epileptogenic zone: General principles. *Epileptic Disorders*, *8*(SUPPL. 2). https://doi.org/10.3109/9780203091708-107

Mader, E. C., Fisch, B. J., Carey, M. E., & Villemarette-Pittman, N. R. (2005). Ictal onset slow potential shifts recorded with hippocampal depth electrodes. *Neurology & Clinical Neurophysiology : NCN*, *2005*.

Margineanu, D. G. (2010). Epileptic hypersynchrony revisited. In *NeuroReport* (Vol. 21, Issue 15). https://doi.org/10.1097/WNR.0b013e32833ed111

Martinet, L. E., Fiddyment, G., Madsen, J. R., Eskandar, E. N., Truccolo, W., Eden, U. T., Cash, S. S., & Kramer, M. A. (2017). Human seizures couple across spatial scales through travelling wave dynamics. *Nature Communications*, *8*. https://doi.org/10.1038/ncomms14896

Matsumoto, H., & Ajmone, C. (1964). *Cortical Cellular Phenomena in Experimental Epilepsy: Ictal Manifestations*.

McCormick, D. A., & Contreras, D. (2001). On the cellular and network bases of epileptic seizures. In *Annual Review of Physiology* (Vol. 63). https://doi.org/10.1146/annurev.physiol.63.1.815

McNaughton, B. L., Barnes, C. A., & O'Keefe, J. (1983). The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Experimental Brain Research*, *52*(1). https://doi.org/10.1007/BF00237147

Merricks, E. M., Smith, E. H., Emerson, R. G., Bateman, L. M., McKhann, G. M., Goodman, R. R., Sheth, S. A., Greger, B., House, P. A., Trevelyan, A. J., & Schevon, C. A. (2021). Neuronal firing and waveform alterations through Ictal recruitment in humans. *Journal of Neuroscience*, *41*(4), 766–779. https://doi.org/10.1523/JNEUROSCI.0417-20.2020

Merricks, E. M., Smith, E. H., Mckhann, G. M., Goodman, R. R., Bateman, L. M., Emerson, R. G., Schevon, C. A., & Trevelyan, A. J. (2015). Single unit action potentials in humans and the effect of seizure activity. *Brain*. https://doi.org/10.1093/awv264

Misra, A., Long, X., Sperling, M. R., Sharan, A. D., & Moxon, K. A. (2018). Increased neuronal synchrony prepares mesial temporal networks for seizures of neocortical origin. *Epilepsia*, *59*(3), 636–649. https://doi.org/10.1111/epi.14007

Mormann, F., & Jefferys John G R. (2013). Neuronal Firing in Human Epileptic Cortex: The Ins and Outs of Synchrony During Seizures. *Epilepsy Currents*. https://doi.org/10.1038/ncomms2056

Mormann, F., Kreuz, T., Andrzejak, R. G., David, P., Lehnertz, K., & Elger, C. E. (2003). Epileptic seizures are preceded by a decrease in synchronization. *Epilepsy Research*, *53*(3). https://doi.org/10.1016/S0920-1211(03)00002-0

Muldoon, S. F., Soltesz, I., & Cossart, R. (2013). Spatially clustered neuronal assemblies comprise the microstructure of synchrony in chronically epileptic networks. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(9). https://doi.org/10.1073/pnas.1216958110

Neumann, A. R., Raedt, R., Steenland, H. W., Sprengers, M., Bzymek, K., Navratilova, Z., Mesina, L., Xie, J., Lapointe, V., Kloosterman, F., Vonck, K., Boon, P. A. J. M., Soltesz, I., Mcnaughton, B. L., & Luczak, A. (2017). Involvement of fast-spiking cells in ictal sequences during spontaneous seizures in rats with chronic temporal lobe epilepsy. *Brain*. https://doi.org/10.1093/awx205

Ogren, J. A., Wilson, C. L., Bragin, A., Lin, J. J., Salamon, N., Dutton, R. A., Luders, E., Fields, T. A., Fried, I., Toga, A. W., Thompson, P. M., Engel, J., & Staba, R. J. (2009). Three-dimensional surface maps link local atrophy and fast ripples in human epileptic hippocampus. *Annals of Neurology*, *66*(6). https://doi.org/10.1002/ana.21703

O'Keefe, J., & Recce, M. L. (1993). Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus*, *3*(3). https://doi.org/10.1002/hipo.450030307

Ostojic, S., Brunel, N., & Hakim, V. (2009). How connectivity, background activity, and synaptic properties shape the cross-correlation between spike trains. *Journal of Neuroscience*, *29*(33). https://doi.org/10.1523/JNEUROSCI.1275-09.2009

Pallud, J., Le Van Quyen, M., Bielle, F., Pellegrino, C., Varlet, P., Labussiere, M., Cresto, N., Dieme, M.-J., Baulac, M., Duyckaerts, C., Kourdougli, N., Chazal, G., Devaux, B., Rivera, C., Miles, R., Capelle, L., & Huberfeld, G. (2014). Cortical GABAergic excitation contributes to epileptic activities around human glioma. *Science Translational Medicine*. www.ScienceTranslationalMedicine.org

Pedreira, C., Martinez, J., Ison, M. J., & Quian Quiroga, R. (2012). How many neurons can we see with current spike sorting algorithms? *Journal of Neuroscience Methods*, *211*(1). https://doi.org/10.1016/j.jneumeth.2012.07.010

Penfield, & Jasper, H. (1954). Epilepsy and the Functional Anatomy of the Human Brain. In *Calif. Representative to Scientific Exhibit\p=m* (Vol. 8, Issue 9). http://archneurpsyc.jamanetwork.com/

Perucca, P., Dubeau, F., & Gotman, J. (2014). Intracranial electroencephalographic seizure-onset patterns: Effect of underlying pathology. *Brain*, *137*(1), 183–196. https://doi.org/10.1093/brain/awt299

Peyrache, A., & Destexhe, A. (2019). Electrophysiological monitoring of inhibition in mammalian species, from rodents to humans. In *Neurobiology of Disease* (Vol. 130). Academic Press Inc. https://doi.org/10.1016/j.nbd.2019.104500

Pizzo, F., Roehri, N., Giusiano, B., Lagarde, S., Carron, R., Scavarda, D., McGonigal, A., Filipescu, C., Lambert, I., Bonini, F., Trebuchon, A., Bénar, C. G., & Bartolomei, F. (2021). The Ictal Signature of Thalamus and Basal Ganglia in Focal Epilepsy: A SEEG Study. *Neurology*, *96*(2), e280–e293. https://doi.org/10.1212/WNL.0000000000011003

Ponten, S. C., Bartolomei, F., & Stam, C. J. (2007). Small-world networks and epilepsy: Graph theoretical analysis of intracerebrally recorded mesial temporal lobe seizures. *Clinical Neurophysiology*, *118*(4). https://doi.org/10.1016/j.clinph.2006.12.002

Prince, D. A., & Wilder, B. J. (1967). Control Mechanisms in Cortical Epileptogenic Foci*: 'Surround' Inhibition. *Archives of Neurology*, *16*(2). https://doi.org/10.1001/archneur.1967.00470200082007

Rampp, S., & Stefan, H. (2012). Ictal onset baseline shifts and infraslow activity. *Journal of Clinical Neurophysiology*, *29*(4). https://doi.org/10.1097/WNP.0b013e31826242b3

Ranck, J. B. (1973). Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. Part I. Behavioral correlates and firing repertoires. *Experimental Neurology*, *41*(2). https://doi.org/10.1016/0014-4886(73)90290-2

Ray, S., & Maunsell, J. H. R. (2011). Different origins of gamma rhythm and high-gamma activity in macaque visual cortex. *PLoS Biology*, *9*(4). https://doi.org/10.1371/journal.pbio.1000610

Rayport, M., & Waller, H. J. (1967). Technique and results of micro-electrode recording in human epileptogenic foci. *Electroencephalography and Clinical Neurophysiology*.

Rich, S., Chameh, H. M., Rafiee, M., Ferguson, K., Skinner, F. K., & Valiante, T. A. (2020). Inhibitory Network Bistability Explains Increased Interneuronal Activity Prior to Seizure Onset. *Frontiers in Neural Circuits*, *13*. https://doi.org/10.3389/fncir.2019.00081

Rodin, E., & Modur, P. (2008). Ictal intracranial infraslow EEG activity. *Clinical Neurophysiology*, *119*(10). https://doi.org/10.1016/j.clinph.2008.07.222

Rosenow, F., & Lüders, H. (2001). Presurgical evaluation of epilepsy. In *Brain* (Vol. 124).

Salami, P., Borzello, M., Kramer, M. A., Westover, M. B., & Cash, S. S. (2022). Quantifying seizure termination patterns reveals limited pathways to seizure end. *Neurobiology of Disease*, *165*. https://doi.org/10.1016/j.nbd.2022.105645

Scalmani, P., Paterra, R., Mantegazza, M., Avoli, M., & de Curtis, M. (2023). Involvement of GABAergic Interneuron Subtypes in 4-Aminopyridine-Induced Seizure-Like Events in Mouse Entorhinal Cortex in Vitro. *Journal of Neuroscience*, *43*(11). https://doi.org/10.1523/JNEUROSCI.1190-22.2023

Schevon, C. A., Goodman, R. R., McKhann, G., & Emerson, R. G. (2010). Propagation of epileptiform activity on a submillimeter scale. In *Journal of Clinical Neurophysiology* (Vol. 27, Issue 6, pp. 406–411). https://doi.org/10.1097/WNP.0b013e3181fdf8a1

Schevon, C. A., Ng, S. K., Cappell, J., Goodman, R. R., Mckhann, G., Waziri, A., Branner, A., Sosunov, A., Schroeder, C. E., & Emerson, R. G. (2008). Microphysiology of Epileptiform Activity in Human Neocortex. In *J Clin Neurophysiol* (Vol. 25).

Schevon, C. A., Tobochnik, S., Eissa, T., Merricks, E., Gill, B., Parrish, R. R., Bateman, L. M., McKhann, G. M., Emerson, R. G., & Trevelyan, A. J. (2019). Multiscale recordings reveal the dynamic spatial structure of human seizures. In *Neurobiology of Disease* (Vol. 127, pp. 303–311). Academic Press Inc. https://doi.org/10.1016/j.nbd.2019.03.015

Schevon, C. A., Weiss, S. A., McKhann, G., Goodman, R. R., Yuste, R., Emerson, R. G., & Trevelyan, A. J. (2012). Evidence of an inhibitory restraint of seizure activity in humans. *Nature Communications*, *3*. https://doi.org/10.1038/ncomms2056

Schiff, S. J., Colella, D., Jacyna, G. M., Hughes, E., Creekmore, J. W., Marshall, A., Bozek-Kuzmicki, M., Benke, G., Gaillard, W. D., Conry, J., & Weinstein, S. R. (2000). Brain chirps: spectrographic signatures of epileptic seizures. *Clinical Neurophysiology*. www.elsevier.com/locate/clinph

Schindler, K., Elger, C. E., & Lehnertz, K. (2007). Changes of EEG synchronization during low-frequency electric stimulation of the seizure onset zone. *Epilepsy Research*, *77*(2–3). https://doi.org/10.1016/j.eplepsyres.2007.09.011

Schlafly, E. D., Marshall, F. A., Merricks, E. M., Eden, U. T., Cash, S. S., Schevon, C. A., & Kramer, M. A. (2022). Multiple Sources of Fast TravelingWaves during Human Seizures: Resolving a Controversy. *Journal of Neuroscience*, *42*(36), 6966–6982. https://doi.org/10.1523/JNEUROSCI.0338-22.2022

Schwartz, T. H., & Bonhoeffer, T. (2001). In vivo optical mapping of epileptic foci and surround inhibition in ferret cerebral cortex. *Nature Medicine*, *7*(9). https://doi.org/10.1038/nm0901-1063

Sedley, W., & Cunningham, M. O. (2013). Do cortical gamma oscillations promote or suppress perception? An under-asked question with an over-assumed answer. In *Frontiers in Human Neuroscience* (Issue SEP). https://doi.org/10.3389/fnhum.2013.00595

Sessolo, M., Marcon, I., Bovetti, S., Losi, G., Cammarota, M., Ratto, G. M., Fellin, T., & Carmignoto, G. (2015). Parvalbumin-positive inhibitory interneurons oppose propagation but favor generation of focal epileptiform activity. *Journal of Neuroscience*, *35*(26). https://doi.org/10.1523/JNEUROSCI.5117-14.2015

Shiri, Z., Manseau, F., Lévesque, M., Williams, S., & Avoli, M. (2015). Interneuron activity leads to initiation of low-voltage fast-onset seizures. *Annals of Neurology*, *77*(3). https://doi.org/10.1002/ana.24342

Singh, S., Sandy, S., & Wiebe, S. (2015). Ictal onset on intracranial EEG: Do we know it when we see it? State of the evidence. In *Epilepsia* (Vol. 56, Issue 10, pp. 1629–1638). Blackwell Publishing Inc. https://doi.org/10.1111/epi.13120

Smith, E. H., Liou, J. Y., Davis, T. S., Merricks, E. M., Kellis, S. S., Weiss, S. A., Greger, B., House, P. A., McKhann, G. M., Goodman, R. R., Emerson, R. G., Bateman, L. M., Trevelyan, A. J., & Schevon, C. A. (2016). The ictal wavefront is the spatiotemporal source of discharges during spontaneous human seizures. *Nature Communications*, *7*. https://doi.org/10.1038/ncomms11098

Spanedda, F., Cendes, F., & Gotman, J. (1997). Relations between EEG seizure morphology, interhemispheric spread, and mesial temporal atrophy in bitemporal epilepsy. *Epilepsia*, *38*(12). https://doi.org/10.1111/j.1528-1157.1997.tb00068.x

Staba, R. J., Stead, M., & Worrell, G. A. (2014). Electrophysiological Biomarkers of Epilepsy. In *Neurotherapeutics* (Vol. 11, Issue 2). https://doi.org/10.1007/s13311-014-0259-0

Staba, R. J., Wilson, C. L., Bragin, A., Fried, I., & Engel, J. (2002). Sleep states differentiate single neuron activity recorded from human epileptic hippocampus, entorhinal cortex, and subiculum. *Journal of Neuroscience*, *22*(13). https://doi.org/10.1523/jneurosci.22-13-05694.2002

Staba, R. J., Wilson, C. L., Bragin, A., Jhung, D., Fried, I., & Engel, J. (2004). High-frequency oscillations recorded in human medial temporal lobe during sleep. *Annals of Neurology*, *56*(1). https://doi.org/10.1002/ana.20164

Stacey, W. C., Kellis, S., Greger, B., Butson, C. R., Patel, P. R., Assaf, T., Mihaylova, T., & Glynn, S. (2013). Potential for unreliable interpretation of EEG recorded with microelectrodes. *Epilepsia*, *54*(8). https://doi.org/10.1111/epi.12202

Stead, M., Bower, M., Brinkmann, B. H., Lee, K., Marsh, W. R., Meyer, F. B., Litt, B., Van Gompel, J., & Worrell, G. A. (2010). Microseizures and the spatiotemporal scales of human partial epilepsy. *Brain : A Journal of Neurology*, *133*(9), 2789–2797. https://doi.org/10.1093/BRAIN/AWQ190

Steriade, M., Amzica, F., Neckelmann, D., & Timofeev, I. (1998). Spike-wave complexes and fast components of cortically generated seizures. II. Extra- and intracellular patterns. *Journal of Neurophysiology*, *80*(3). https://doi.org/10.1152/jn.1998.80.3.1456

Steriade, M., & Contreras, D. (1998). Spike-wave complexes and fast components of cortically generated seizures. I. Role of neocortex and thalamus. *Journal of Neurophysiology*, *80*(3). https://doi.org/10.1152/jn.1998.80.3.1439

Steriade, M., Contreras, D., & Amzica, F. (1994). Synchronized sleep oscillations and their paroxysmal developments. *Trends in Neurosciences*, *17*(5). https://doi.org/10.1016/0166-2236(94)90105-8

Tanaka, H., Khoo, H. M., Dubeau, F., & Gotman, J. (2018). Association between scalp and intracerebral electroencephalographic seizure-onset patterns: A study in different lesional pathological substrates. *Epilepsia*, *59*(2), 420–430. https://doi.org/10.1111/epi.13979

Thompson, S. A., Krishnan, B., Gonzalez-Martinez, J., Bulacio, J., Jehi, L., Mosher, J., Alexopoulos, A., & Burgess, R. C. (2016). Interictal Infraslow Activity in Stereoelectroencephalography: From Focus to Network. *Journal of Clinical Neurophysiology*, *33*.

Timofeev, I., & Steriade, M. (2004). Neocortical seizures: Initiation, development and cessation. In *Neuroscience* (Vol. 123, Issue 2). https://doi.org/10.1016/j.neuroscience.2003.08.051

Trevelyan, A. J. (2009). The direct relationship between inhibitory currents and local field potentials. *Journal of Neuroscience*, *29*(48). https://doi.org/10.1523/JNEUROSCI.2019-09.2009

Trevelyan, A. J., Baldeweg, T., Van Drongelen, W., Yuste, R., & Whittington, M. (2007). The source of afterdischarge activity in neocortical tonic-clonic epilepsy. *Journal of Neuroscience*, *27*(49). https://doi.org/10.1523/JNEUROSCI.3005-07.2007

Trevelyan, A. J., Sussillo, D., Watson, B. O., & Yuste, R. (2006). Modular propagation of epileptiform activity: Evidence for an inhibitory veto in neocortex. *Journal of Neuroscience*, *26*(48). https://doi.org/10.1523/JNEUROSCI.2787-06.2006

Truccolo, W., Ahmed, O. J., Harrison, M. T., Eskandar, E. N., Rees Cosgrove, G., Madsen, J. R., Blum, A. S., Stevenson Potter, N., Hochberg, L. R., & Cash, S. S. (2014). Neuronal ensemble synchrony during human focal seizures. *Journal of Neuroscience*, *34*(30), 9927–9944. https://doi.org/10.1523/JNEUROSCI.4567-13.2014

Truccolo, W., Donoghue, J. A., Hochberg, L. R., Eskandar, E. N., Madsen, J. R., Anderson, W. S., Brown, E. N., Halgren, E., & Cash, S. S. (2011). Single-neuron dynamics in human focal epilepsy. *Nature Neuroscience*, *14*(5), 635–643. https://doi.org/10.1038/nn.2782

Velasco, A. L., Wilson, C. L., Babb, T. L., & Engel, J. (2000). Functional and Anatomic Correlates of two Frequently Observed Temporal Lobe Seizure-Onset Patterns. In *NEURAL PLASTICITY* (Vol. 7).

Verzeano, M., Crandall, P. H., & Dymond, A. (1971). Neuronal activity if the amygdala in patients with psychomotor epilepsy. *Neuropsychologia*, *9*, 331–344.

Wagner, F. B., Eskandar, E. N., Cosgrove, G. R., Madsen, J. R., Blum, A. S., Potter, N. S., Hochberg, L. R., Cash, S. S., & Truccolo, W. (2015). Microscale spatiotemporal dynamics during neocortical propagation of human focal seizures. *NeuroImage*, *122*, 114–130. https://doi.org/10.1016/j.neuroimage.2015.08.019

Ward, A. A., & Thomas, L. B. (1955). The electrical activity of single units in the cerebral cortex of man. *Electroencephalography and Clinical Neurophysiology*, *7*(1). https://doi.org/10.1016/0013-4694(55)90067-5

Weiss, S. A., Alvarado-Rojas, C., Bragin, A., Behnke, E., Fields, T., Fried, I., Engel, J., & Staba, R. (2016). Ictal onset patterns of local field potentials, high frequency oscillations, and unit activity in human mesial temporal lobe epilepsy. *Epilepsia*, *57*(1), 111–121. https://doi.org/10.1111/epi.13251

Weiss, S. A., Banks, G. P., McKhann, G. M., Goodman, R. R., Emerson, R. G., Trevelyan, A. J., & Schevon, C. A. (2013). Ictal high frequency oscillations distinguish two types of seizure territories in humans. *Brain : A Journal of Neurology*, *136*(Pt 12), 3796–3808. https://doi.org/10.1093/brain/awt276

Weiss, S. A., Fried, I., Engel, J., Sperling, M. R., Wong, R. K. S., Nir, Y., & Staba, R. J. (n.d.). Fast ripples reflect increased excitability that primes epileptiform spikes. *MedRxiV*. https://doi.org/10.1101/2023.03.26.23287702

Weiss, S. A., Song, I., Leng, M., Pastore, T., Slezak, D., Waldman, Z., Orosz, I., Gorniak, R., Donmez, M., Sharan, A., Wu, C., Fried, I., Sperling, M. R., Bragin, A., Engel, J., Nir, Y., & Staba, R. (2020). Ripples Have Distinct Spectral Properties and Phase-Amplitude Coupling With Slow Waves, but Indistinct Unit Firing, in Human Epileptogenic Hippocampus. *Frontiers in Neurology*, *11*. https://doi.org/10.3389/fneur.2020.00174

Wendling, F., Bartolomei, F., Bellanger, J. J., Bourien, J., & Chauvel, P. (2003). Epileptic fast intracerebral EEG activity: Evidence for spatial decorrelation at seizure onset. *Brain*, *126*(6). https://doi.org/10.1093/brain/awg144

Wendling, F., Bartolomei, F., Bellanger, J. J., & Chauvel, P. (2002). Epileptic fast activity can be explained by a model of impaired GABAergic dendritic inhibition. *European Journal of Neuroscience*, *15*(9). https://doi.org/10.1046/j.1460-9568.2002.01985.x

Wennberg, R., Arruda, F., Quesney, L. F., & Olivier, A. (2002). Preeminence of extrahippocampal structures in the generation of mesial temporal seizures: Evidence from human depth electrode recordings. *Epilepsia*, *43*(7). https://doi.org/10.1046/j.1528-1157.2002.31101.x

Wenzel, M., Hamm, J. P., Peterka, D. S., & Yuste, R. (2019). Acute focal seizures start as local synchronizations of neuronal ensembles. *Journal of Neuroscience*, *39*(43), 8562–8575. https://doi.org/10.1523/JNEUROSCI.3176-18.2019

Westbrook, G. L. (1991). Seizures and epilepsy. In E. R. Kandel, T. M. Jessel, & J. H. Schwartz (Eds.), *Principles of Neural Science*.

Wetjen, N. M., Marsh, W. R., Meyer, F. B., Cascino, G. D., So, E., Britton, J. W., Stead, S. M., & Worrell, G. A. (2009). Intracranial electroencephalography seizure onset patterns and surgical outcomes in nonlesional extratemporal epilepsy: Clinical article. *Journal of Neurosurgery*, *110*(6). https://doi.org/10.3171/2008.8.JNS17643

Wickham, J., Ledri, M., Andersson, M., & Kokaia, M. (2023). Cell-specific switch for epileptiform activity: critical role of interneurons in the mouse subicular network. *Cerebral Cortex*, *33*(10). https://doi.org/10.1093/cercor/bhac493

Wilson, M. A., & McNaughton, B. L. (1993). Dynamics of the hippocampal ensemble code for space. *Science*, *261*(5124). https://doi.org/10.1126/science.8351520

Worrell, G. A., Gardner, A. B., Stead, S. M., Hu, S., Goerss, S., Cascino, G. J., Meyer, F. B., Marsh, R., & Litt, B. (2008). High-frequency oscillations in human temporal lobe: Simultaneous microwire and clinical macroelectrode recordings. *Brain*, *131*(4), 928–937. https://doi.org/10.1093/brain/awn006

Worrell, G. A., Jerbi, K., Kobayashi, K., Lina, J. M., Zelmann, R., & Le Van Quyen, M. (2012). Recording and analysis techniques for high-frequency oscillations. In *Progress in Neurobiology* (Vol. 98, Issue 3). https://doi.org/10.1016/j.pneurobio.2012.02.006

Wu, S., Kunhi Veedu, H. P., Lhatoo, S. D., Koubeissi, M. Z., Miller, J. P., & Lüders, H. O. (2014). Role of ictal baseline shifts and ictal high-frequency oscillations in stereo-electroencephalography analysis of mesial temporal lobe seizures. *Epilepsia*, *55*(5). https://doi.org/10.1111/epi.12608

Wyler, A. R., Ojemann, G. A., & Ward, A. A. (1982). Neurons in human epileptic cortex: correlation between unit and EEG activity. *Ann Neurol*.

Wyler, A. R., & Ward, A. A. (1986). Neuronal firing patterns from epileptogenic foci of monkey and human. *Advances in Neurology*, *44*.

Yekhlef, L., Breschi, G. L., Lagostena, L., Russo, G., & Taverna, S. (2015). Selective activation of parvalbumin-or somatostatin-expressing interneurons triggers epileptic seizurelike activity in mouse medial entorhinal cortex. *J Neurophysiol*, *113*, 1616–1630. https://doi.org/10.1152/jn.00841.2014.-GABAergic

ARTICLE

« Recording epileptic seizures at multiple scales with intracranial tetrodes in humans »

Nous nous sommes intéressés à l'analyse des crises d'épilepsies spontanées chez les patients implantés avec des électrodes hybrides comprenant des tétrodes, dans les CHU de Toulouse et de Lyon. Nous avons comparé le signal recueilli sur les tétrodes avec celui des macroélectrodes correspondantes. Les méthodes d'analyse et les résultats ont été consignés sous la forme d'un article, préparé selon le modèle de « *Brief Communication* » en prévision d'une soumission au journal *Epilepsia*.

Received: Added at production | Revised: Added at production | Accepted: Added at production

DOI: xxx/xxxx

BRIEF COMMUNICATION

Recording epileptic seizures at multiple scales with intracranial tetrodes in humans

Pauline Calvat[1,2,3] | Emmanuel Barbeau[1,2] | Sylvain Rheims[4,5] | Marc Guénot[5,6] | Benoît Chatard[5] | Amaury De Barros[7,8] | Jean Christophe Sol[7,8] | Ludovic Gardy[1,2] | Marie Denuelle[1,2,3] | Luc Valton[1,2,3] | Jonathan Curot[1,2,3]

[1]Centre de Recherche Cerveau et Cognition, Université Toulouse III - Paul Sabatier, Toulouse, France

[2]CerCo (UMR5549), Centre National de la Recherche Scientifique, Toulouse, France

[3]Electrophysiologie cérébrale, épilepsie, sommeil, Hôpital Purpan et Université de Toulouse, Toulouse, France

[4]Neurologie fonctionnelle et Épileptologie, Hospices Civils de Lyon et Université Lyon 1, Lyon, France

[5]Centre de Recherche en Neurosciences de Lyon, INSERM U1028/ CNRS UMR5292, Université de Lyon, Lyon, France

[6]Service de neurochirurgie fonctionnelle, Hospices Civils de Lyon et Université Lyon 1, Lyon, France

[7]INSERM, U1214, TONIC, Toulouse Mind and Brain Institute, Toulouse, France

[8]Service de neurochirurgie, Hôpital Purpan et Université de Toulouse, Toulouse, France

Correspondence
Jonathan Curot, MD, PhD.
Email: calvat.p@chu-toulouse.fr - jonathan.curot@cnrs.fr

Present address
CerCo CNRS UMR 5549, Université Toulouse III
CHU Purpan, Pavillon Baudot, 31052 Toulouse Cedex, France.

Abstract

Seizure onset patterns (SOPs) recorded with intracranial macroelectrodes are related to postoperative prognosis, although their pathophysiological correlates remain widely unknown. Exploring SOP simultaneously at the scales of millimetric and micrometric local field potentials (respectively macroLFP and microLFP) with a high spatial and temporal correspondence has never been done in human.

Macro-microelectrodes (MMEs) combining the classical macrocontacts with 2-3 tetrodes (containing 4 microelectrodes, 20 µm diameter) were implanted at the Toulouse and Lyon University Hospitals (2015-2023) in pharmacoresistant epileptic (PRE) patients having stereoelectroencephalography (SEEG). We compared SOP recorded simultaneously by macrocontacts (macroLFP) and tetrodes (microLFP). We analyzed the dynamics of interictal epileptic discharges and fast-ripples in the macroLFP and microLFP just before the SOP.

Among 61 PRE patients (16-63 years old) implanted with MME (2 to 4 per patients), we recorded 26 spontaneous epileptic seizures (11 patients), including 7 seizures concurrently recorded on tetrodes. We observed several SOPs specific to microLFP, while other SOPs were highly similar at macroLFP and microLFP scales. Amplitude and frequency differences were also observed in several SOPs respectively between tetrodes, and between microLP and macroLFP.

Our results suggest that MMEs hold promise as a tool for discerning microLFP-specific characteristics of SOP, and for targeting neuronal populations within limited areas (local generators).

KEYWORDS
epilepsy, stereoelectroencephalography, seizure onset pattern, microelectrode, tetrode, time-frequency

1 | INTRODUCTION

Various seizure onset patterns (SOPs) have been identified on intracranial EEG with conventional macroelectrodes[1,2]. SOPs are associated with different histological lesions and different prognoses[3,2] and thus may correspond to heterogeneous ictogenic processes. Analyzing SOP at different electrophysiological scales should lead to a better understanding of ictogenesis[4]. However,

Abbreviations: EZ, epileptogenic zone; FR, fast ripples; HFOs, high frequency oscillations; IEDs, interictal epileptiform discharges; LFP, local field potential; macroLFP, LFP on macroelectrode; microLFP, LFP on the microelectrode; LVFA, low voltage fast activity; MME, macro-microelectrode; SEEG, stereoelectroencephalography; SOP, seizure onset pattern; TLE, temporal lobe epilepsy.

multiscale recordings must be carried out with a high degree of spatial correspondence to enable a proper synthesis between the neuronal scale and the large-scale networks. Unfortunately, scientific reports often propose multiscale analyses that involve spatial shifts (microelectrodes not being perfectly colocalized with macroelectrodes).

We introduce a new method to visualize seizures through the use of a specific design of hybrid intracerebral electrodes, with microcontacts arranged in tetrodes[5]. This stereoelectroencephalographic (SEEG) technique enables the exploration of local field potentials (LFP) at the millimeter (macroLFP) and micrometer (microLFP) scales as well as single unit activity, thanks to the tetrode design[6]). The other major asset of these MMEs is to perform these recordings with a high spatial correspondence and no spatial shift at different scales: single-units being nested in microLFP and microLFP being nested in macroLFP in the same regions.

We demonstrated that tetrodes reveal new information about the onset of epileptic seizures, already at the LFP scale, including their patterns, frequencies, and amplitudes. Our results tend to complete the current classification of SOP, through a multiscale integration approach.

TABLE 1 Patients' clinical characteristics and location of tetrodes.

patient (sex/age)	tetrodes location	ZE	MRI lesion	Surgery (outcome)
T3 (M/39)	right: amygdala, basal temporal lobe; left: ant. hippocampus	right post. lat. temporal	none	no
T21 (M/33)	right: sup. medial frontal gyrus; left: ant. cingulate gyrus, sup. medial frontal gyrus; left and right: sup. medial frontal gyrus	bifrontal mainly left	none	no
T37 (F/18)	right: polar sup. temporal gyrus, hippocampal body, parahippocampal gyrus; left: polar superior temporal gyrus	right temporal pole	grade I gangliogioma	yes (Engel 1B, ILAE class 2)
T44 (F/30)	right: hippocampal body, parietal operculum, inferior pre-cuneus; left : sup. precuneus	complex and extensive network around the right temporo-parietal junction	none	no
T50 (M/33)	left: polar medial sup. temporal gyrus, hippocampal head; right : amygdala, entorhinal cortex	left hippocampus	slight shrinkening of the left temporal pole	surgery to come
L208 (F/50)	presumably right ant. temporal lobe[a]	presumably right ant. temporal lobe[a]	scar of right ant. temporal lobectomy	no

Abreviations: F, female; M, male; ant., anterior; lat.,lateral; post., posterior; sup., superior

[a]Subject to verification with the relevant team.

2 | MATERIALS AND METHODS

2.1 | Population and surgery

All patients were pharmacoresistant epileptic (PRE) patients requiring SEEG, who were implanted by conventional macro-electrodes and macro-microelectrodes with tetrodes (MME)[5] in Toulouse and Lyon University hospitals, between 2015 and 2023. Patients gave informed consent to participate in the study (ClinicalTrials Identifier: NCT02491476). Implantation of the hybrid electrodes and the use of the data were approved by the local ethics committee and the French Drug and Health Product Safety Agency (CPP Sud-Ouest et Outre-Mer I, no.1-14-23 and ANSM 2014-A00747-40). They all had a noninvasive pre-surgical assessment (at least neurological and neuropsychological testings, brain MRI, scalp video-EEG, PET-scanner). Noninvasive workup failed to accurately localize the EZ. The electrode implantation scheme was determined according to the clinical hypotheses concerning the location of the EZ. We collected intracranial EEG, clinical data (with postoperative prognosis[7,8]) and histology when surgery could be performed.

2.2 | SEEG and electrodes

Two to four MMEs were implanted stereotactically in each patient among 8 to 15 semi-rigid multi-contact standard clinical depth macroelectrodes. The Microdeep (DIXI Medical, France) macroelectrodes (diameter = 0.8mm) contained 5 to 18 platinum/iridium contacts (contact length= 2mm, contact spacing = 1.5mm). The MMEs (DIXI Medical, France) consisted of a standard macroelectrode (0.8 mm diameter) with nine two-millimiter-long macrocontacts arranged regularly along its shaft, and 2 or 3 tetrodes extending at an angle of 30° (tetrode length = 2 mm), positioned between the two most distal macrocontacts[5]. Each tetrode was composed of four tungsten wires (20 µm diameter) and each tetrode had a diameter of 70-80 µm. The tetrodes could be extended after implantation using a micrometer screw.

2.3 | Recording system

From 2015 to 2017, macrocontact signals were recorded using two SystemPLUS EVOLUTION 64-channel acquisition units (Micromed, France) at a sampling rate of 2048 Hz (anti-aliasing filter: 926.7 Hz; high-pass filter: 0.15 Hz; low-pass filter: 1000 Hz). Tetrode signals were recorded using a 64-channel Cerebus System (Blackrock Microsystems, Salt Lake City, Utah, USA) with a sampling rate of 30 kHz (0.3–7.5 kHz bandwidth). Powerline noise elimination of 50 Hz was applied. Since 2018, a 256-channel Atlas System (Neuralynx, Bozeman, Montana, USA) has been used to record both macroelectrode and tetrode signals. Both systems were generally referenced to a macrocontact located in the white matter. Macrocontacts were recorded 24 hours a day. Tetrodes were recorded while patients were at rest or mind-wandering during daytime.

2.4 | Signal analysis

Macrocontacts were analysed by bipolar montage of pairs of adjacent contacts, while microcontacts were analysed by unipolar montage, using Brainstorm software (MatLAB software R2021a). Seizure onset was defined on macroLFP as the first change in intracranial EEG signal accompanied with sustained rhythmic activity and subsequent clinical symptoms. Seizures were selected if they had an early onset within the tetrodes. We also looked at seizures who had a propagation in tetrodes. Seizure onset patterns were described by visual analysis, on local field potential of macroecletrodes (macroLFP) and on microelectrodes (microLFP), based on previous classifications of SOP in macroelectrodes[3,2]. A 40-second window of SEEG data was extracted for each identified seizure: 20 seconds before and 20 seconds after seizure onset. Brainstorm software was used to perform time-frequency analysis on each data channel by Morlet wavelet transform and evaluated at 50 logarithmic frequencies from 1 to 200 Hz. Morlet time-frequency index was set to five. To avoid artefacts, the spectrum was normalized by 1/f compensation. Interictal epileptic discharges (IEDs) were manually tagged in the Brainstorm software for macroLFP and microLFP, and then visually compared.

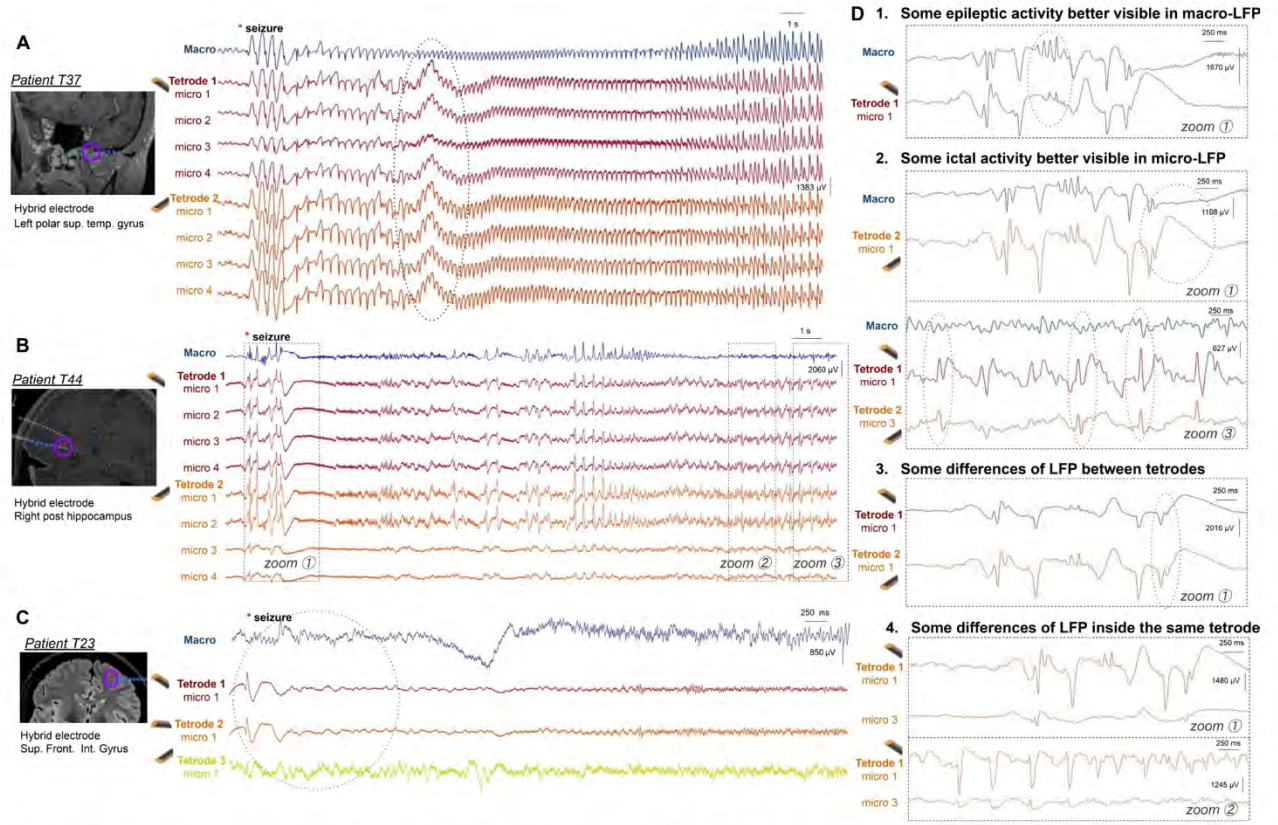


FIGURE 1 The tetrodes offers a different visualization of seizures with similarities and differences between the macro-LFP and the micro-LFP.

A. *In dark and light blue, raw signal of bipolar mounting of the two more distal macrocontact located in the left polar superior temporal gyrus. In red (tetrode 1) and orange (tetrode 2), the monopolar mounting (raw signal) of the corresponding microcontact between the two most distal macrocontacts. We note the same seizure onset pattern, characterized by a spike-and-wave activity, that appears similar in the macroLFP and the microLFP. The seizure onset is tagged with a red star. Curiously, we observe a baseline shift or slow wave, after the seizure onset, only visible in the tetrodes (circled by a dotted line).*

B. *An example of a seizure in another patient with the same setup. We observe a similar pattern in macroLFP and microLFP with burst of polyspikes, followed by a LVFA in the posterior hippocampus. For this seizure, we have detailed the analysis of 3 zoom in* ***(D)****.We can see some discharges better visible in macroLFP* ***(D.1.)****. We observe also, some ictal discharges and a baseline shift only visible in microLFP after the seizure onset* ***(D.2.)****. There is differences between the different tetrode* ***(D.3.)****, and more surprising, a same tetrode can record different activity* ***(D.4.)****.*

C. *For another patient with the same setup, a seizure was observed with the hybrid electrode placed in the superior frontal gyrus. For this seizure, the propagation can be observed in the microelectrodes since it originated on the lateral cortex of the hybrid electrode, adjacent to a tuber, that is located opposite to the microelectrodes. This resulted in a different pattern of seizure onset, starting with macroLFP with LVF activity, and with a spike-wave preceding LVF in microLFP.*

3 | RESULTS

3.1 | Patient features

We collected 26 recordings of spontaneous seizures (lasting 10.8 to 102.1 seconds) during simultaneous macroLFP and microLFP recordings among the 61 patients implanted with MME. Seven seizures originated from the most distal macrocontacts of the 20 MME (just around the tetrodes) in 6 different patients (two seizures in patient 3 and one seizure in patients 21, 37, 44, 50, and 208). Clinical and EEG data for these patients are shown in Table 1. (Table 1).

3.2 | Similarities and differences in the seizure onset patterns in macroLFP and microLFP

We identified various SOP by macroLFP and microLFP analysis (see Figure 1) :

- For patient T3, the SOP in macroLFP for both seizures (duration 37.5 seconds and 38.9 seconds) was spike-and-wave activity followed by low-voltage fast activity (LVFA)[3] and was initiated in amygdala and rhinal MME. The same pattern was observed in microLFP.
- The seizure in patient T21 started diffusely in macroLFP with a burst of polyspikes followed by LVFA during 29.5 s before spikes-and-waves and pseudo-rhythmic activity and spikes lasting more than four minutes. The same pattern was observed in microLFP.
- The onset of the seizure in patient T37 originated from the left polar temporal gyrus and was characterized by rhythmic spiking that spread over a limited area and persisted for 102 seconds. A similar pattern was observed in microLFP.
- In patient T44, the seizure appears as a burst of polyspikes in posterior hippocampus, followed by LVFA with the same pattern in microLFP.
- For patient T50, the seizure appears as a beta sharp activity in the left hippocampal head and body. We observe the same pattern in microLFP.
- For patient L208, we observed the same seizure onset patterns with a beta sharp activity, seen in the microelectrode located in the right temporal lobe. Due to technical reasons, it was not possible to analyze the macroLFP signal in this patient.

In another patient not shown in the table, we also recorded seizure propagation in the microcontacts. originating in the cortex surrounding the lateral part of the hybrid electrode, i.e. at a distance from the microcontacts. (Figure 1C). For this patient, suffering from tuberous sclerosis complex, the seizure began in the superior frontal gyrus near a tuber, with rapid low-voltage activity in macroLFP, occuring later in the microLFP. An isolated spike is only visible in microLFP at the time of seizure initiation in macroLFP.

Most SOPs were similar between macroLFP and microLFP in our patients. Nevertheless, some variations should be noted. Variations in amplitude between the tetrodes providing spatial stereo or three-dimensional information, with tetrodes emerging between two macrocontacts and at varying distances from the neuronal generators (Fig.1A and 1B). Ictal activities can be exclusively detectable with tetrodes (Fig. 1D). The presence of slow waves or ictal baseline shifts (Fig. 1B and 1C) are also revealed by the tetrodes within the first seconds of the seizure.

Time-frequency analysis revealed an ictal pattern that partially resembles the previously described signature of the EZ in macroLFP[9] (Figure 2A and B). The microLFP time-frequency analysis showed a single narrow band of activity around 10 Hz during the seizure onset with greater power than in the correspondant macroLFP. We also observed a narrower frequency distribution in microLFP.

3.3 | Some differences also with interictal epileptiform discharges

IED amplitudes appear different between microLFP and macroLFP: a smaller amplitude was generally observed in microLFP (Figure 2C and D). An overall fewer rate of IEDs was detected by tetrodes compared to macroelectrodes. Non-visible IEDs in microLFP often correspond to slow spikes in the macroLFP. For instance in patient T3, the channel located in the left anterior hippocampus, i.e. contralaterally to the EZ, recorded slow sharp activity in macroLFP that disappears in the micro-LFP. On the contrary in rare cases, IEDs are exclusively recorded in the microLFP (especially in amygdala in our database).

4 | DISCUSSION AND CONCLUSION

Our study represents an innovative illustration of epileptic seizures through the prism of tetrodes in human subjects. Notable variations in the recordings obtained from tetrodes in microLFP in comparison to macroLFP highlight the value of multiscale recordings with MME equipped with tetrodes: seizure-specific properties can be detected in the microLFP. Different amplitudes across tetrodes of the same SOP and a narrower spectral distribution in microLFP can be interpreted as a refined signal captured by the tetrode in the vicinity of very local generators (<1 mm). Very local differences in activity can even be observed within tetrodes, with differences between microwires close to each other. By enabling seizures to be viewed in stereo, MME also makes

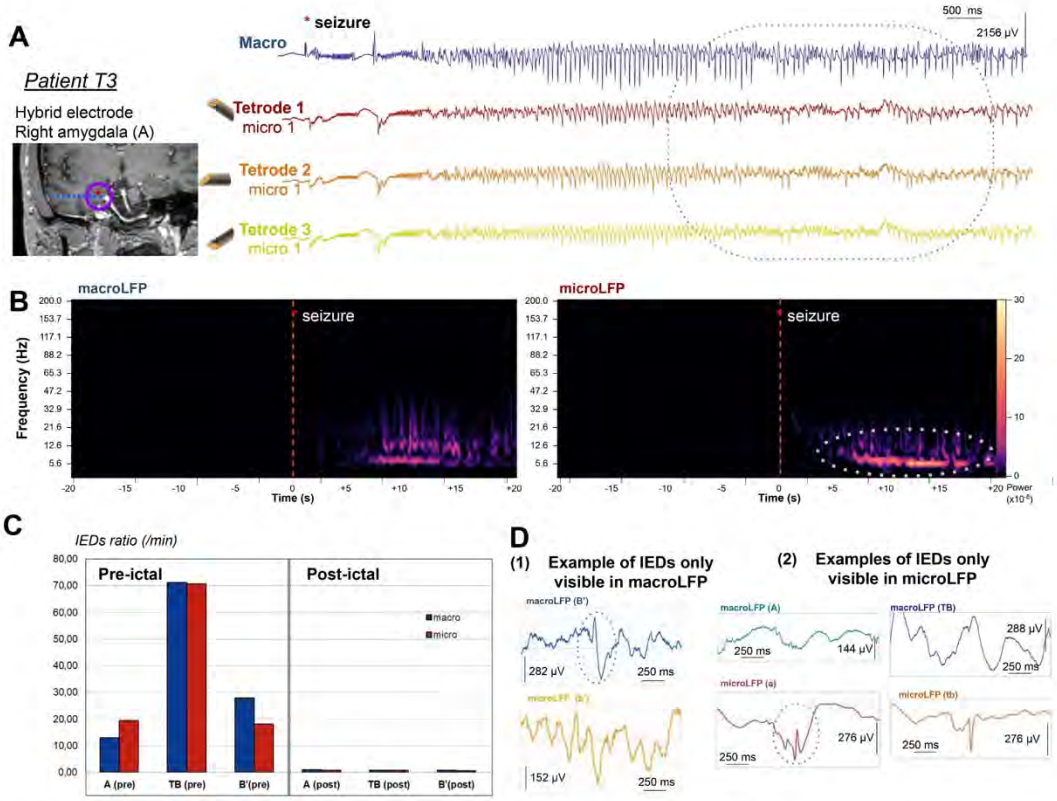


FIGURE 2 Time-frequency map and IEDs analyses demonstrate differences between these two scales.

A. *In patient T3, this seizure appears similar in visual analysis comparing macroLFP and microLFP, characterized by a spike-and-wave followed by LVFA occurring in the right mesial temporal lobe.*

B. *The time-frequency analysis of the seizure onset shows a difference in tetrode, with more power in the frequencies around 10 Hz, and a less wide frequency distribution. The two time-frequency maps appears with the same scale. The seizure onset is tagged with the red star and the red dotted line.*

C. *For the same patient, we have quantified the IEDs before and after the two seizures recorded. We analyzed 604 sec in pre-ictal period and 377 sec in post-ictal period, for the three channels in macro-LFP and micro-LFP in (A), (TB), (B'), respectively the right amygdala, the right basal temporal pole and the left hippocampus. The result is displayed with a ratio per minute.*

D. *We show examples of IEDs only visible in macroLFP or in microLFP.*

it possible to correlate neuronal dynamics with pathological oscillations recorded at a very local scale, as already demonstrated with the study of fast-ripples[10].

Until recently, tetrodes have been used in animals to go beyond multiunit activities by detecting single-unit activities[6,11]. Implantation with MME containing tetrodes have been performed since 2015 in humans, and would quickly spread across epilepsy centers, with the ultimate goal of studying neural circuits at the cellular level during epileptic activities. Although the next step is to study neuronal activities, our preliminary results show that information relevant to understanding the epilepsy network is already available at the microLFP scale.

In 2017, we demonstrated differences in macroLFP and microLFP recordings of IEDs in an epileptic patient: some IEDs but also fast-ripples can be detected by tetrodes better than macrocontacts.[10]. Here, preliminary analysis of IEDs suggested that some IEDs appeared only in microelectrodes. Moreover, we show examples of ictal baseline shift, or DC shift, detected only by the tetrodes. These observations suggest MME with tetrodes could prove important for clinical reflection, since fast-ripples and baseline shift have been associated with the epileptogenic zone in the macroelectrodes.

Multiscale analyses with other microelectrodes devices have so far been patchy: comparing either macroLFP with multi-units, or microLFP with multi-units, but rarely all three scales at once. The description of patterns specific to microLFPs suggests that it is not possible to simply transpose reasoning and classifications developed in macroLFP to microelectrodes recordings. A specific classification of microLFP SOP and also a nomenclature of microLFP IEDs should be proposed. A systematic consideration of the the simultaneous macroLFP, microLFP, multi-unit and single-unit recording scales is now necessary in multiscale approaches to synthesize ictogenesis processes.

AUTHOR CONTRIBUTIONS

Pauline Calvat: Validation, Data curation, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. Emmanuel Barbeau: Conceptualization, Project administration, Funding acquisition, Methodology, Writing - original draft. Sylvain Rheims: Resources. Marc Guénot: Resources. Benoît Chatard: Resources. Amaury De Barros: Resources. Jean-Christophe Sol: Resources. Ludovic Gardy : Data curation, Formal analysis, Software. Marie Denuelle: Resources.Luc Valton: Resources, Conceptualization, Funding acquisition. Jonathan Curot: Conceptualization, Validation, Data curation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing.

ACKNOWLEDGMENTS

We would like to thank Simona Celebrini for her management of the electrodes and assistance in the data acquisition process. We thank Benoît Marcy, Aube Darves-Bornoz, Leila Reddy for their contributions to the data acquisition phase. We also want to acknowledge Alexis Robin and Fleur Gérard for their participation on the data analysis pipeline.

FINANCIAL DISCLOSURE

This work received funding from the European Research Council, (under the European Union's Seventh Framework Programme (FP/2007-2013) / ERC Grant Agreement no. 323711, M4 project), the Fondation Française pour la Recherche sur l'Epilepsie (Prix Marion Clignet), the Fédération Française sur le Cerveau/Rotary Club, and a call for technological and organisation innovation research projects (Toulouse University Hospital). This work was also supported by a grant with a with a poster presentation at the European Congress of Neurophysiology 2023, in Marseille.

CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

REFERENCES

1. Lagarde S, Bonini F, McGonigal A, et al. Seizure-onset patterns in focal cortical dysplasia and neurodevelopmental tumors: Relationship with surgical prognosis and neuropathologic subtypes. *Epilepsia.* 2016;57:1426-1435. doi: 10.1111/epi.13464
2. Perucca P, Dubeau F, Gotman J. Intracranial electroencephalographic seizure-onset patterns: Effect of underlying pathology. *Brain.* 2014;137:183-196. doi: 10.1093/brain/awt299
3. Lagarde S, Buzori S, Trebuchon A, et al. The repertoire of seizure onset patterns in human focal epilepsies: Determinants and prognostic values. *Epilepsia.* 2019;60:85-95. doi: 10.1111/epi.14604
4. Schevon CA, Tobochnik S, Eissa T, et al. Multiscale recordings reveal the dynamic spatial structure of human seizures. *Neurobiology of Disease.* 2019;127:303-311. doi: 10.1016/j.nbd.2019.03.015
5. Despouy E, Curot J, Reddy L, et al. Recording local field potential and neuronal activity with tetrodes in epileptic patients. *Journal of Neuroscience Methods.* 2020;341. doi: 10.1016/j.jneumeth.2020.108759
6. Buzsáki G. Large-scale recording of neuronal ensembles. *Nature Neuroscience.* 2004;7:446-451. doi: 10.1038/nn1233
7. Engel J. Update on surgical treatment of the epilepsies: Summary of the second international palm desert conference on the surgical treatment of the epilepsies (1992). *Neurology.* 1993;43:1612-1617. doi: 10.1212/wnl.43.8.1612
8. Wieser HG, Blume WT, Fish D, et al. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia.* 2001;42. doi: 10.1046/j.1528-1157.2001.35100.x
9. Grinenko O, Li J, Mosher JC, et al. A fingerprint of the epileptogenic zone in human epilepsies. *Brain.* 2018;141:117-131. doi: 10.1093/brain/awx306
10. Curot J, Barbeau E, Despouy E, et al. Local neuronal excitation and global inhibition during epileptic fast ripples in humans. *Brain : a journal of neurology.* 2023;146:561-575. LU 04/23doi: 10.1093/brain/awac319
11. Lévesque M, Avoli M. High-frequency oscillations and focal seizures in epileptic rodents. *Neurobiology of Disease.* 2019;124:396-407. doi: 10.1016/j.nbd.2018.12.016

SUPPORTING INFORMATION

This document is in preparation for an upcoming submission to the journal Epilepsia, on a brief communication.

CONCLUSION

À la lumière de ces deux études, nous avons mis en évidence l'intérêt manifeste des enregistrements intracrâniens grâce aux tétrodes, dans le contexte du bilan pré-chirurgical des patients souffrant d'épilepsie pharmacorésistante. Les tétrodes ont déjà prouvé leur utilité dans l'enregistrement des oscillations rapides pathologiques (fast-ripples) en interictal, pour en approcher les corrélats neuronaux. Elles pourraient aussi, par la détection des fast-ripples, être un outil performant pour la détermination de la zone épileptogène.

Nos enregistrements EEG intracrâniens au cours des crises épileptiques à l'aide de macroélectrodes et de microélectrodes, simultanément aux différentes échelles, ont permis d'étudier spécifiquement le début et la propagation de ces crises, avec une haute correspondance spatiale et temporelle à l'échelle des potentiels de champs locaux. Nous avons démontré que beaucoup de crises épileptiques présentent un pattern de départ qui semble similaire entre ces deux échelles. Néanmoins, plusieurs caractéristiques spécifiques sont aussi détectées uniquement à l'échelle des microélectrodes : un DC shift (décalage de la ligne de base en début de crise qui a été précédemment mise en relation avec la zone épileptogène dans les macroélectrodes), des décharges de pointes ou des pointes intercritiques isolées, ainsi qu'une moindre dispersion de la composition spectrale fréquentielle. Ces activités uniquement démasquées par les microélectrodes pourraient élargir leur potentiel à déterminer la zone épileptogène.

En perspective, pour obtenir une vision plus complète de l'initiation des crises épileptiques à différentes échelles et en comprendre les substrats neuronaux, nous poursuivons ces travaux en incluant la détection des activités neuronales à la fois multi-unitaires et unitaires, ainsi qu'une classification par type cellulaire. Il est désormais primordial de combiner les signaux de chacune des différentes échelles (potentiels de champ provenant des macroélectrodes et des microélectrodes, activités neuronales multi-unitaires et unitaires) afin d'aboutir à une réelle synthèse des mécanismes neuronaux de l'ictogenèse.

le 25/08/23
Vu et permis d'imprimer
Le Président de l'Université Toulouse III – Paul Sabatier
Faculté de Santé
Par délégation,
La Doyenne-Directrice
Du Département de Médecine, Maïeutique, Paramédical
Professeure Odile RAUZY

le 14/08/23
Professeur Jérémie PARIENTE
Service de Neurologie
CHU Hôpital Purpan
TSA 40031
31059 TOULOUSE Cedex 9

RÉFÉRENCES BIBLIOGRAPHIQUES

Babb, T. L., E. Carr, and P. H. Crandall. 1973. “Analysis of Extracellular Firing Patterns of Deep Temporal Lobe Structures in Man.” *Electroencephalography and Clinical Neurophysiology* 34:247–57.

Barba, Carmen, Sabrina Giometto, Ersilia Lucenteforte, Simona Pellacani, Giulia Matta, Alessandra Bettiol, Sara Minghetti, Lavinia Falorni, Federico Melani, Gianpiero Di Giacomo, Flavio Giordano, Salvatore De Masi, and Renzo Guerrini. 2022. “Seizure Outcome of Temporal Lobe Epilepsy Surgery in Adults and Children: A Systematic Review and Meta-Analysis.” *Neurosurgery* 91(5). doi: 10.1227/neu.0000000000002094.

Bartolomei, Fabrice, Patrick Chauvel, and Fabrice Wendling. 2008. “Epileptogenicity of Brain Structures in Human Temporal Lobe Epilepsy: A Quantified Study from Intracerebral EEG.” *Brain* 131(7):1818–30. doi: 10.1093/brain/awn111.

Bartolomei, Fabrice, Stanislas Lagarde, Fabrice Wendling, Aileen McGonigal, Viktor Jirsa, Maxime Guye, and Christian Bénar. 2017. “Defining Epileptogenic Networks: Contribution of SEEG and Signal Analysis.” *Epilepsia* 58(7):1131–47.

Baud, Maxime O., Thomas Perneger, Attila Rácz, Max C. Pensel, Christian Elger, Bertil Rydenhag, Kristina Malmgren, J. Helen Cross, Grainne McKenna, Martin Tisdall, Herm J. Lamberink, Sylvain Rheims, Philippe Ryvlin, Jean Isnard, François Mauguière, Alexis Arzimanoglou, Serdar Akkol, Kaancan Deniz, Cigdem Ozkara, Morten Lossius, Ivan Rektor, Reetta Kälviäinen, Lotta Maria Vanhatalo, Petia Dimova, Krassimir Minkin, Anke Maren Staack, Bernhard J. Steinhoff, Adam Kalina, Pavel Krsek, Petr Marusic, Zsofia Jordan, Daniel Fabo, Evelien Carrette, Paul Boon, Saulius Rocka, Rūta Mameniškienė, Serge Vulliemoz, Francesca Pittau, Kees P. J. Braun, and Margitta Seeck. 2018. “European Trends in Epilepsy Surgery.” *Neurology* 91(2). doi: 10.1212/WNL.0000000000005776.

Beghi, Ettore, Giorgia Giussani, Foad Abd-Allah, Jemal Abdela, Ahmed Abdelalim, Haftom Niguse Abraha, Mina G. Adib, Sutapa Agrawal, Fares Alahdab, Ashish Awasthi, Yohanes Ayele, Miguel A. Barboza, Abate Bekele Belachew, Belete Biadgo, Ali Bijani, Helen Bitew, Félix Carvalho, Yazan Chaiah, Ahmad Daryani, Huyen Phuc Do, Manisha Dubey, Aman Yesuf Yesuf Endries, Sharareh Eskandarieh, Andre Faro, Farshad Farzadfar, Seyed Mohammad Fereshtehnejad, Eduarda Fernandes, Daniel Obadare Fijabi, Irina Filip, Florian Fischer, Abadi Kahsu Gebre, Afewerki Gebremeskel Tsadik, Teklu Gebrehiwo Gebremichael, Kebede Embaye Gezae, Maryam Ghasemi-Kasman, Kidu Gidey Weldegwergs, Meaza Girma Degefa, Elena V. Gnedovskaya, Tekleberhan B. Hagos, Arvin Haj-Mirzaian, Arya Haj-Mirzaian, Hamid Yimam Hassen, Simon I. Hay, Mihajlo Jakovljevic, Amir Kasaeian, Tesfaye Dessale Kassa, Yousef Saleh Khader, Ibrahim Khalil, Ejaz Ahmad Khan, Jagdish Khubchandani, Adnan Kisa, Kristopher J. Krohn, Chanda Kulkarni, Yirga Legesse Nirayo, Mark T. Mackay, Marek Majdan, Azeem

Majeed, Treh Manhertz, Man Mohan Mehndiratta, Tesfa Mekonen, Hagazi Gebre Meles, Getnet Mengistu, Shafiu Mohammed, Mohsen Naghavi, Ali H. Mokdad, Ghulam Mustafa, Seyed Sina Naghibi Irvani, Long Hoang Nguyen, Emma Nichols, Molly R. Nixon, Felix Akpojene Ogbo, Andrew T. Olagunju, Tinuke O. Olagunju, Mayowa Ojo Owolabi, Michael R. Phillips, Gabriel David Pinilla-Monsalve, Mostafa Qorbani, Amir Radfar, Anwar Rafay, Vafa Rahimi-Movaghar, Nickolas Reinig, Perminder S. Sachdev, Hosein Safari, Saeed Safari, Saeid Safiri, Mohammad Ali Sahraian, Abdallah M. Samy, Shahabeddin Sarvi, Monika Sawhney, Masood A. Shaikh, Mehdi Sharif, Gagandeep Singh, Mari Smith, Cassandra E. I. Szoeke, Rafael Tabarés-Seisdedos, Mohamad Hani Temsah, Omar Temsah, Miguel Tortajada-Girbés, Bach Xuan Tran, Amanuel Amanuel Tesfay Tsegay, Irfan Ullah, Narayanaswamy Venketasubramanian, Ronny Westerman, Andrea Sylvia Winkler, Ebrahim M. Yimer, Naohiro Yonemoto, Valery L. Feigin, Theo Vos, and Christopher J. L. Murray. 2019. “Global, Regional, and National Burden of Epilepsy, 1990–2016: A Systematic Analysis for the Global Burden of Disease Study 2016.” *The Lancet Neurology* 18(4). doi: 10.1016/S1474-4422(18)30454-X.

Bragin, Anatol, Istvan Mody, Charles L. Wilson, and Jerome Engel. 2002. “Local Generation of Fast Ripples in Epileptic Brain.” *Journal of Neuroscience* 22(5). doi: 10.1523/jneurosci.22-05-02012.2002.

Buzsáki, György. 2004. “Large-Scale Recording of Neuronal Ensembles.” *Nature Neuroscience* 7(5):446–51.

Callaghan, Brian C., Kishlay Anand, Dale Hesdorffer, W. Allen Hauser, and Jacqueline A. French. 2007. “Likelihood of Seizure Remission in an Adult Population with Refractory Epilepsy.” *Annals of Neurology* 62(4). doi: 10.1002/ana.21166.

Chaudhary, Umair J., David W. Carmichael, Roman Rodionov, Rachel C. Thornton, Phillipa Bartlett, Serge Vulliemoz, Caroline Micallef, Andrew W. McEvoy, Beate Diehl, Matthew C. Walker, John S. Duncan, and Louis Lemieux. 2012. “Mapping Preictal and Ictal Haemodynamic Networks Using Video- Electroencephalography and Functional Imaging.” *Brain* 135(12). doi: 10.1093/brain/aws302.

Cohen-Gadol, Aaron A., Brian G. Wilhelmi, Frederic Collignon, J. Bradley White, Jeffrey W. Britton, Denise M. Cambier, Teresa J. H. Christianson, W. Richard Marsh, Fredric B. Meyer, and Gregory D. Cascino. 2006. “Long-Term Outcome of Epilepsy Surgery among 399 Patients with Nonlesional Seizure Foci Including Mesial Temporal Lobe Sclerosis.” *Journal of Neurosurgery* 104(4). doi: 10.3171/jns.2006.104.4.513.

Cross, J. Helen, Prasanna Jayakar, Doug Nordli, Olivier Delalande, Michael Duchowny, Heinz G. Wieser, Renzo Guerrini, and Gary W. Mathern. 2006. “Proposed Criteria for Referral and Evaluation of Children for Epilepsy Surgery: Recommendations of the Subcommission for Pediatric Epilepsy Surgery.” *Epilepsia* 47(6). doi: 10.1111/j.1528-1167.2006.00569.x.

Curot, Jonathan, Emmanuel Barbeau, Elodie Despouy, Marie Denuelle, Jean Christophe Sol, Jean Albert Lotterie, Luc Valton, and Adrien Peyrache. 2023. “Local Neuronal

Excitation and Global Inhibition during Epileptic Fast Ripples in Humans." *Brain : A Journal of Neurology* 146(2):561–75. doi: 10.1093/brain/awac319.

Despouy,E (2019). Validation d'une nouvelle électrode hybride intracérébrale comportant des tétrodes dans l'épilepsie pharmaco-résistante. PhD thesis, Université de Toulouse, Université Toulouse III – Paul Sabatier.

Despouy, Elodie, Jonathan Curot, Marie Denuelle, Martin Deudon, Jean Christophe Sol, Jean Albert Lotterie, Leila Reddy, Lionel G. Nowak, Jérémie Pariente, Simon J. Thorpe, Luc Valton, and Emmanuel J. Barbeau. 2019. "Neuronal Spiking Activity Highlights a Gradient of Epileptogenicity in Human Tuberous Sclerosis Lesions." *Clinical Neurophysiology* 130(4):537–47. doi: 10.1016/j.clinph.2018.12.013.

Despouy, Elodie, Jonathan Curot, Leila Reddy, Lionel G. Nowak, Martin Deudon, Jean Christophe Sol, Jean Albert Lotterie, Marie Denuelle, Ali Maziz, Christian Bergaud, Simon J. Thorpe, Luc Valton, and Emmanuel J. Barbeau. 2020. "Recording Local Field Potential and Neuronal Activity with Tetrodes in Epileptic Patients." *Journal of Neuroscience Methods* 341. doi: 10.1016/j.jneumeth.2020.108759.

Devaux, B., F. Chassoux, E. Landré, B. Turak, P. Varlet, C. Miquel, C. Mellerio, and J. F. Meder. 2014. "Chirurgie Des Épilepsies Partielles Pharmaco-Résistantes de l'adulte." *Pratique Neurologique - FMC* 5(4). doi: 10.1016/j.praneu.2014.10.005.

Van Diessen, Eric, Sander J. H. Diederen, Kees P. J. Braun, Floor E. Jansen, and Cornelis J. Stam. 2013. "Functional and Structural Brain Networks in Epilepsy: What Have We Learned?" *Epilepsia* 54(11).

Donoghue, John P. 2002. "Connecting Cortex to Machines: Recent Advances in Brain Interfaces." *Nature Neuroscience* 5(11s).

Engel, Jerome. 1993. "Update on Surgical Treatment of the Epilepsies: Summary of the Second International Palm Desert Conference on the Surgical Treatment of the Epilepsies (1992)." *Neurology* 43(8):1612–17. doi: 10.1212/wnl.43.8.1612.

Engel, Jerome, Michael P. McDermott, Samuel Wiebe, John T. Langfitt, John M. Stern, Sandra Dewar, Michael R. Sperling, Irenita Gardiner, Giuseppe Erba, Itzhak Fried, Margaret Jacobs, Harry V. Vinters, Scott Mintzer, and Karl Kieburtz. 2012. "Early Surgical Therapy for Drug-Resistant Temporal Lobe Epilepsy: A Randomized Trial." *JAMA* 307(9). doi: 10.1001/jama.2012.220.

Engel, Jerome, Samuel Wiebe, Jacqueline French, Michael Sperling, Peter Williamson, Dennis Spencer, Robert Gumnit, Catherine Zahn, Edward Westbrook, and Bruce Enos. 2003. "Practice Parameter: Temporal Lobe and Localized Neocortical Resections for Epilepsy." *Epilepsia* 44(6).

Englot, Dario J., Leighton B. Hinkley, Naomi S. Kort, Brandon S. Imber, Danielle Mizuiri, Susanne M. Honma, Anne M. Findlay, Coleman Garrett, Paige L. Cheung, Mary Mantle, Phiroz E. Tarapore, Robert C. Knowlton, Edward F. Chang, Heidi E. Kirsch, and Srikantan

S. Nagarajan. 2015. “Global and Regional Functional Connectivity Maps of Neural Oscillations in Focal Epilepsy.” *Brain* 138(8). doi: 10.1093/brain/awv130.

Fiest, Kirsten M., Khara M. Sauro, Samuel Wiebe, Scott B. Patten, Churl Su Kwon, Jonathan Dykeman, Tamara Pringsheim, Diane L. Lorenzetti, and Nathalie Jetté. 2017. “Prevalence and Incidence of Epilepsy.” *Neurology* 88(3).

Fried, Itzhak, Charles L. Wilson, Nigel T. Maidment, Jerome Engel, Eric Behnke, Tony A. Fields, Katherine A. Macdonald, Jack W. Morrow, and Larry Ackerson. 1999. “Cerebral Microdialysis Combined with Single-Neuron and Electroencephalographic Recording in Neurosurgical Patients: Technical Note.” *Journal of Neurosurgery* 91(4). doi: 10.3171/jns.1999.91.4.0697.

Gardy, Ludovic (2021). Détection automatique multiéchelle et de grande envergure d'oscillations intracérébrales pathologiques dans l'épilepsie par réseaux de neurones artificiels. PhD thesis, Université de Toulouse, Université Toulouse III – Paul Sabatier.

Gilioli, Isabella, Aglaia Vignoli, Elisa Visani, Marina Casazza, Laura Canafoglia, Valentina Chiesa, Elena Gardella, Francesca La Briola, Ferruccio Panzica, Giuliano Avanzini, Maria Paola Canevini, Silvana Franceschetti, and Simona Binelli. 2012. “Focal Epilepsies in Adult Patients Attending Two Epilepsy Centers: Classification of Drug-Resistance, Assessment of Risk Factors, and Usefulness of ‘New’ Antiepileptic Drugs.” *Epilepsia* 53(4). doi: 10.1111/j.1528-1167.2012.03416.x.

Gray, Charles M., Pedro E. Maldonado, Mathew Wilson, and Bruce McNaughton. 1995. “Tetrodes Markedly Improve the Reliability and Yield of Multiple Single-Unit Isolation from Multi-Unit Recordings in Cat Striate Cortex.” *Journal of Neuroscience Methods* 63(1–2). doi: 10.1016/0165-0270(95)00085-2.

Guye, Maxime, Gaelle Bettus, Fabrice Bartolomei, and Patrick J. Cozzone. 2010. “Graph Theoretical Analysis of Structural and Functional Connectivity MRI in Normal and Pathological Brain Networks.” *Magnetic Resonance Materials in Physics, Biology and Medicine* 23(5–6).

Harris, Kenneth D., Darrell A. Henze, Jozsef Csicsvari, Hajime Hirase, and György Buzsáki. 2000. “Accuracy of Tetrode Spike Separation as Determined by Simultaneous Intracellular and Extracellular Measurements.” *Journal of Neurophysiology* 84(1). doi: 10.1152/jn.2000.84.1.401.

House, Paul A., Joel D. MacDonald, Patrick A. Tresco, and Richard A. Normann. 2006. “Acute Microelectrode Array Implantation into Human Neocortex: Preliminary Technique and Histological Considerations.” *Neurosurgical Focus* 20(5). doi: 10.3171/foc.2006.20.5.5.

Howard, Matthew A., Igor O. Volkov, Mark A. Granner, Hanna M. Damasio, Michael C. Ollendieck, and Hans E. Bakken. 1996. “A Hybrid Clinical-Research Depth Electrode for Acute and Chronic in Vivo Microelectrode Recording of Human Brain Neurons.” *Journal of Neurosurgery* 84(1). doi: 10.3171/jns.1996.84.1.0129.

Ioannou, Persefoni, Daniella L. Foster, Josemir W. Sander, Sophie Dupont, Antonio Gil-Nagel, Ewa Drogon O'Flaherty, Elena Alvarez-Baron, and Jasmina Medjedovic. 2022. "The Burden of Epilepsy and Unmet Need in People with Focal Seizures." *Brain and Behavior* 12(9).

Isnard, Jean, Delphine Taussig, Fabrice Bartolomei, Pierre Bourdillon, Hélène Catenoix, Francine Chassoux, Mathilde Chipaux, Stéphane Clémenceau, Sophie Colnat-Coulbois, Marie Denuelle, Stéphane Derrey, Bertrand Devaux, Georg Dorfmüller, Vianney Gilard, Marc Guenot, Anne Sophie Job-Chapron, Elisabeth Landré, Axel Lebas, Louis Maillard, Aileen McGonigal, Lorella Minotti, Alexandra Montavont, Vincent Navarro, Anca Nica, Nicolas Reyns, Julia Scholly, Jean Christophe Sol, William Szurhaj, Agnès Trebuchon, Louise Tyvaert, Maria Paola Valenti-Hirsch, Luc Valton, Jean Pierre Vignal, and Paul Sauleau. 2018. "French Guidelines on Stereoelectroencephalography (SEEG)." *Neurophysiologie Clinique* 48(1).

Jacobs, Julia, Pierre LeVan, Rahul Chander, Jeffery Hall, François Dubeau, and Jean Gotman. 2008. "Interictal High-Frequency Oscillations (80-500 Hz) Are an Indicator of Seizure Onset Areas Independent of Spikes in the Human Epileptic Brain." *Epilepsia* 49(11). doi: 10.1111/j.1528-1167.2008.01656.x.

Jeha, Lara E., Imad Najm, William Bingaman, Dudley Dinner, Peter Widdess-Walsh, and Hans Lüders. 2007. "Surgical Outcome and Prognostic Factors of Frontal Lobe Epilepsy Surgery." *Brain* 130(2). doi: 10.1093/brain/awl364.

Ko, Tae Sung, and Gregory L. Holmes. 1999. "EEG and Clinical Predictors of Medically Intractable Childhood Epilepsy." *Clinical Neurophysiology* 110(7). doi: 10.1016/S1388-2457(99)00068-1.

Kwan, Patrick, Alexis Arzimanoglou, Anne T. Berg, Martin J. Brodie, W. Allen Hauser, Gary Mathern, Solomon L. Moshé, Emilio Perucca, Samuel Wiebe, and Jacqueline French. 2010. "Definition of Drug Resistant Epilepsy: Consensus Proposal by the Ad Hoc Task Force of the ILAE Commission on Therapeutic Strategies." *Epilepsia* 51(6).

Kwan, Patrick, and Martin J. Brodie. 2000. "Early Identification of Refractory Epilepsy." *New England Journal of Medicine* 342(5). doi: 10.1056/nejm200002033420503.

Lagarde, Stanislas, Sinziana Buzori, Agnès Trebuchon, Romain Carron, Didier Scavarda, Mathieu Milh, Aileen McGonigal, and Fabrice Bartolomei. 2019. "The Repertoire of Seizure Onset Patterns in Human Focal Epilepsies: Determinants and Prognostic Values." *Epilepsia* 60(1):85–95. doi: 10.1111/epi.14604.

Laulan, R. 1954. "Un Traité Akkadien de Diagnostics et de Pronostics Médicaux." *La Presse Médicale* 62(67).

Lüders, Hans O., Imad Najm, Dileep Nair, Peter Widdess-Walsh, and William Bingman. 2006. "The Epileptogenic Zone: General Principles." in *Epileptic Disorders*. Vol. 8.

Malinowska, Urszula, Jean Michel Badier, Martine Gavaret, Fabrice Bartolomei, Patrick Chauvel, and Christian George Bénar. 2014. “Interictal Networks in Magnetoencephalography.” *Human Brain Mapping* 35(6). doi: 10.1002/hbm.22367.

Mann, M. W., and G. Pons. 2008. “La Pharmacorésistance Des Épilepsies Partielles : Épidémiologie, Mécanismes, Pharmacogénétique, Perspectives Thérapeutiques.” *Neurochirurgie* 54(3). doi: 10.1016/j.neuchi.2008.02.018.

Misra, Amrit, Xianda Long, Michael R. Sperling, Ashwini D. Sharan, and Karen A. Moxon. 2018. “Increased Neuronal Synchrony Prepares Mesial Temporal Networks for Seizures of Neocortical Origin.” *Epilepsia* 59(3):636–49. doi: 10.1111/epi.14007.

Munari Claudio, and Bancaud Jean. 1987. “The Role of Stereo-Electroencephalography (SEEG) in the Evaluation of Partial Epileptic Patients.” Pp. 267–306 in *The epilepsies*, edited by R. J. Porter and P. L. Morselli. London: Butterworth.

Nevalainen, Päivi, Nicolás Von Ellenrieder, Petr Klimeš, François Dubeau, Birgit Frauscher, and Jean Gotman. 2020. “Association of Fast Ripples on Intracranial EEG and Outcomes after Epilepsy Surgery.” *Neurology* 95(16). doi: 10.1212/WNL.0000000000010468.

Penfield, and Herbert Jasper. 1954. *Epilepsy and the Functional Anatomy of the Human Brain*. Vol. 8.

Rayport, M., and H. J. Waller. 1967. “Technique and Results of Micro-Electrode Recording in Human Epileptogenic Foci.” *Electroencephalography and Clinical Neurophysiology*.

Renshaw, B., A. Forbes, and B. R. Morison. 1940. “ACTIVITY OF ISOCORTEX AND HIPPOCAMPUS: ELECTRICAL STUDIES WITH MICRO-ELECTRODES.” *Journal of Neurophysiology* 3(1). doi: 10.1152/jn.1940.3.1.74.

Rosenow, Felix, and Hans Lüders. 2001. *Presurgical Evaluation of Epilepsy*. Vol. 124.

Ryvlin, Philippe, J. Helen Cross, and Sylvain Rheims. 2014. “Epilepsy Surgery in Children and Adults.” *The Lancet Neurology* 13(11).

Schevon, Catherine A., Steven Tobochnik, Tahra Eissa, Edward Merricks, Brian Gill, R. Ryley Parrish, Lisa M. Bateman, Guy M. McKhann, Ronald G. Emerson, and Andrew J. Trevelyan. 2019. “Multiscale Recordings Reveal the Dynamic Spatial Structure of Human Seizures.” *Neurobiology of Disease* 127:303–11.

Schlafly, Emily D., François A. Marshall, Edward M. Merricks, Uri T. Eden, Sydney S. Cash, Catherine A. Schevon, and Mark A. Kramer. 2022. “Multiple Sources of Fast TravelingWaves during Human Seizures: Resolving a Controversy.” *Journal of Neuroscience* 42(36):6966–82. doi: 10.1523/JNEUROSCI.0338-22.2022.

Schoffelen, Jan Mathijs, and Joachim Gross. 2009. “Source Connectivity Analysis with MEG and EEG.” *Human Brain Mapping* 30(6).

Scott Perry, M., and Michael Duchowny. 2013. “Surgical versus Medical Treatment for Refractory Epilepsy: Outcomes beyond Seizure Control.” *Epilepsia* 54(12).

Semah, Franck, M. C. Picot, C. Adam, D. Broglin, A. Arzimanoglou, B. Bazin, D. Cavalcanti, and M. Baulac. 1998. “Is the Underlying Cause of Epilepsy a Major Prognostic Factor for Recurrence?” *Neurology* 51(5). doi: 10.1212/WNL.51.5.1256.

Shafer, Stephen Q., W. Allen Hauser, John F. Annegers, and Donald W. Klass. 1988. “EEG and Other Early Predictors of Epilepsy Remission: A Community Study.” *Epilepsia* 29(5). doi: 10.1111/j.1528-1157.1988.tb03767.x.

Smith, Elliot H., Jyun You Liou, Tyler S. Davis, Edward M. Merricks, Spencer S. Kellis, Shennan A. Weiss, Bradley Greger, Paul A. House, Guy M. McKhann, Robert R. Goodman, Ronald G. Emerson, Lisa M. Bateman, Andrew J. Trevelyan, and Catherine A. Schevon. 2016. “The Ictal Wavefront Is the Spatiotemporal Source of Discharges during Spontaneous Human Seizures.” *Nature Communications* 7. doi: 10.1038/ncomms11098.

Stam, C. J., E. C. W. van Straaten, E. Van Dellen, P. Tewarie, G. Gong, A. Hillebrand, J. Meier, and P. Van Mieghem. 2016. “The Relation between Structural and Functional Connectivity Patterns in Complex Brain Networks.” *International Journal of Psychophysiology* 103. doi: 10.1016/j.ijpsycho.2015.02.011.

Talairach, J., and J. Bancaud. 1966. “Lesion, ‘Irritative’ Zone and Epileptogenic Focus.” *Confinia Neurologica* 27(1). doi: 10.1159/000103937.

Thornton, Rachel, Serge Vulliemoz, Roman Rodionov, David W. Carmichael, Umair J. Chaudhary, Beate Diehl, Helmut Laufs, Christian Vollmar, Andrew W. McEvoy, Matthew C. Walker, Fabrice Bartolomei, Maxime Guye, Patrick Chauvel, John S. Duncan, and Louis Lemieux. 2011. “Epileptic Networks in Focal Cortical Dysplasia Revealed Using Electroencephalography-Functional Magnetic Resonance Imaging.” *Annals of Neurology* 70(5). doi: 10.1002/ana.22535.

Thorsteinsdottir, Jun, Christian Vollmar, Jörg Christian Tonn, Friedrich Wilhelm Kreth, Soheyl Noachtar, and Aurelia Peraud. 2019. “Outcome after Individualized Stereoelectroencephalography (SEEG) Implantation and Navigated Resection in Patients with Lesional and Non-Lesional Focal Epilepsy.” *Journal of Neurology* 266(4). doi: 10.1007/s00415-019-09213-3.

Verzeano, Marcel, Paul H. Crandall, and Anthony Dymond. 1971. “Neuronal Activity If the Amygdala in Patients with Psychomotor Epilepsy.” *Neuropsychologia* 9:331–44.

Wetjen, Nicholas M., W. Richard Marsh, Fredric B. Meyer, Gregory D. Cascino, Elson So, Jeffrey W. Britton, S. Matthew Stead, and Gregory A. Worrell. 2009. “Intracranial Electroencephalography Seizure Onset Patterns and Surgical Outcomes in Nonlesional Extratemporal Epilepsy: Clinical Article.” *Journal of Neurosurgery* 110(6). doi: 10.3171/2008.8.JNS17643.

Wiebe, Samuel, Warren T. Blume, John P. Girvin, and Michael Eliasziw. 2001. “A Randomized, Controlled Trial of Surgery for Temporal-Lobe Epilepsy.” *The New England Journal of Medicine* 345(5).

Wieser, H. G., W. T. Blume, D. Fish, E. Goldensohn, A. Hufnagel, D. King, M. R. Sperling, H. Lüders, and Timothy A. Pedley. 2001. “Proposal for a New Classification of Outcome with Respect to Epileptic Seizures Following Epilepsy Surgery.” *Epilepsia* 42(2). doi: 10.1046/j.1528-1157.2001.35100.x.

Wyler, A. R., and A. A. Ward. 1986. “Neuronal Firing Patterns from Epileptogenic Foci of Monkey and Human.” *Advances in Neurology* 44.

Wyler, Allen R., Eberhard E. Fetz, and Arthur A. Ward. 1973. “Spontaneous Firing Patterns of Epileptic Neurons in the Monkey Motor Cortex.” *EXPERIMENTAL NEUROLOGY* 40:567–85.

Wyler, Allen R., George A. Ojemann, and Arthur A. Ward. 1982. “Neurons in Human Epileptic Cortex: Correlation between Unit and EEG Activity.” *Ann Neurol*.

ANNEXES

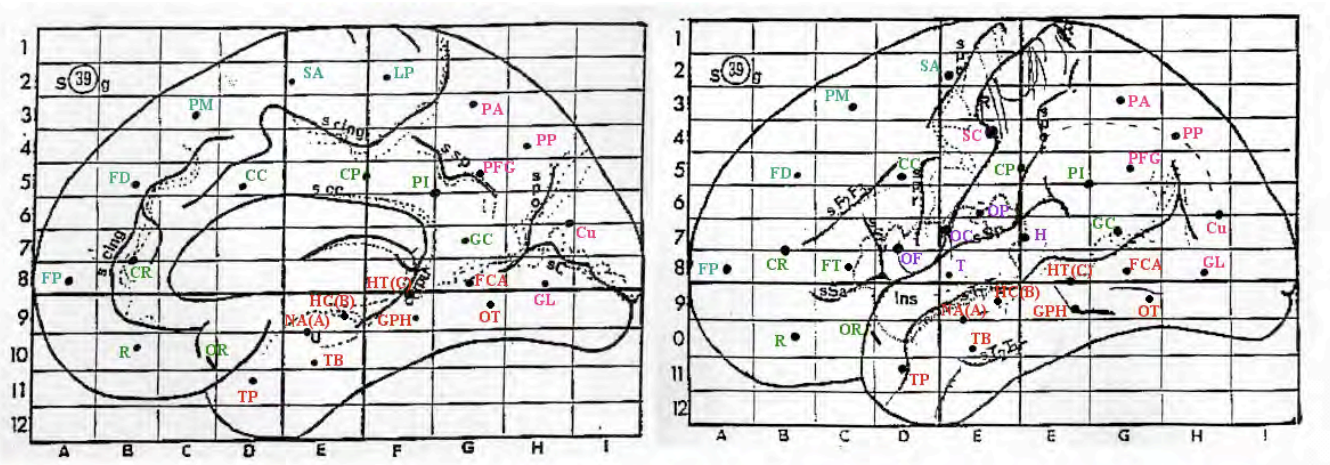
1. Évaluation du pronostic post-opératoire par les classifications d'Engel et classification de l'ILAE (Devaux et al. 2014)

Tableau I. Principales classifications utilisées pour exprimer le devenir des crises d'épilepsie après chirurgie : classification d'Engel (d'après Engel J. Jr et al., 1993) et classification de l'ILAE (International League Against Epilepsy ; d'après Wieser HG. et al., 2001).

Classification d'Engel
Classe I : sans crise invalidante
IA sans aucune crise depuis l'intervention
IB crises partielles simples non invalidantes depuis l'intervention
IC quelques crises postopératoires, mais pas de crise pendant au moins 2 ans
ID crises généralisées de sevrage
Classe II : crises rares (presque sans crise)
IIA initialement sans crise mais rares crises actuellement
IIB crises rares depuis l'intervention
IIC crises postopératoires, mais rares crises depuis au moins 2 ans
IID crises nocturnes seulement
Classe III : amélioration significative
IIIA réduction appréciable des crises
IIIB périodes sans crise prolongées, totalisant plus de la moitié du suivi, et pas moins de 2 ans
Classe IV : pas d'amélioration significative
IVA réduction des crises
IVB pas de changement appréciable
IVC aggravation des crises
Classification de l'ILAE (International League Against Epilepsy)
Classe 1 : sans aucune crise ni aura
Class 1a : sans aucune crise ni aura depuis l'intervention
Class 2 : auras seulement ; pas d'autre crise
Class 3 : 1 à 3 jours avec crises par an ± auras
Class 4 : de 4 jours avec crises par an à 50 % de réduction du nombre initial de jours avec crises par an ± auras
Class 5 : < 50 % de réduction du nombre initial de jours avec crises par an à 100 % d'augmentation du nombre initial de jours avec crises par an ± auras
Class 6 : > 100 % d'augmentation du nombre initial de jours avec crises par an ± auras

Annexe 1

2. Plan d'implantation des électrodes profondes en SEEG



Annexe 2

CALVAT Pauline 2023 TOU3 1577

Recording seizures at multiple scale with tetrodes in pharmaco-resistant epileptic patients, from large-scale networks to inframillimetric neuronal populations

Introduction: In some pharmacoresistant epileptic (PRE) patients, surgical resection of the epileptogenic zone (EZ) may require the implantation of intracranial electrodes (stereoelectroencephalography) to record seizures and determine the EZ. Analysis of intracranial seizure onset patterns (SOPs) has suggested a relation with postoperative prognosis, although their pathophysiological correlates remain widely unknown.

Objective: We aimed to explore the initial spatial dynamics of SOP at multiple scales by using new hybrid electrodes: these hybrids explore in vivo simultaneously millimetric and micrometric local field potentials (LFP) but also single unit activities, with a high spatio-temporal correspondence.

Method: Four hybrids per patient were implanted at the Toulouse and Lyon University Hospitals (2015-2023). Hybrids combine the classical macrocontacts with 2-3 tetrodes (4 microelectrodes, 20µm diameter). We compared SOP visually and by spectral decomposition of intracranial EEG recorded simultaneously by macrocontacts and tetrodes. We analyzed the dynamics of interictal/pre-ictal epileptic discharges and fast-ripples at different levels just before the SOP.

Results: Among the 61 PRE patients (16-63 years old) implanted with hybrids, we recorded 26 spontaneous epileptic seizures (11 patients), including 7 seizures concurrently recorded on tetrodes. We observed several SOPs specific to tetrodes LFP, while other SOPs were highly similar at different scales. Amplitude and frequency differences were also observed in several SOPs respectively between tetrodes, and between micro- and macroscales.

Discussion: While analyses are underway to understand the inconsistent variability at different scales, these hybrid electrodes are a promising device to identify SOP specific to microelectrodes, and to approach limited neuronal populations (local generators).

DISCIPLINE ADMINISTRATIVE : Médecine spécialisée clinique

KEYWORDS: pharmacoresistant focal epilepsy, stereoelectroencephalography, tetrode, microelectrode, seizure onset pattern, fast-ripples

Université Toulouse III-Paul Sabatier
Faculté de Santé de Toulouse
37 Allées Jules Guesde 31000 Toulouse

Centre de Recherche Cerveau et Cognition,
CNRS, Pavillon Baudot, Place du Dr Baylac
31052 Toulouse Cedex

THESIS DIRECTOR: Dr Jonathan CUROT

CALVAT Pauline 2023 TOU3 1577

Les crises épileptiques vues à des échelles multiples – des réseaux larges aux populations neuronales inframillimétriques – grâce à des tétrodes chez des patients épileptiques pharmacorésistants

Introduction : Dans l'épilepsie focale pharmacorésistante (EFPR), l'identification des zones cérébrales responsables de la génération des crises peut nécessiter un enregistrement invasif intracrânien tel que la stéréo-électroencéphalographie (SEEG), qui permet de déterminer la zone épileptogène (ZE) avec une valeur pronostique.

Objectif : Cette étude explore les schémas d'émergence des crises à différentes échelles grâce à des électrodes intracérébrales hybrides avec des tétrodes, permettant d'enregistrer l'activité neuronale unitaire, offrant une haute correspondance spatiale entre ces échelles.

Méthodes : Quatre électrodes hybrides par patient porteur d'une EFPR ont été implantées, associées à des macroélectrodes classiques, aux CHU de Toulouse et de Lyon de 2015 à 2023. Les électrodes hybrides intègrent des microcontacts de 20µm de diamètre, agencés en tétrodes, émergeant entre les deux derniers macrocontacts. Les schémas d'apparition des crises sont analysés visuellement, suivi d'une décomposition temps-fréquence du signal et comparés entre échelles millimétrique et micrométrique.

Résultats : Parmi les 61 patients (16-63 ans) implantés, 26 crises ont été enregistrées simultanément en macro et microélectrodes, dont 7 ont débuté dans les électrodes hybrides, chez 6 patients différents. Les schémas de début de crises sont comparés entre ces deux échelles avec des similitudes et des différences constatées. Des activités épileptiques intercritiques ont été retrouvées uniquement en microélectrode.

Discussion : Cette étude présente la première comparaison des schémas d'apparition des crises via tétrodes chez l'humain. Ces résultats soulignent le potentiel des électrodes hybrides pour la visualisation multi-échelle des crises, révélant des populations neuronales visibles seulement à l'échelle micrométrique, au-delà du champ d'application classique avec les macroélectrodes.

Recording seizures at multiple scale with tetrodes in pharmaco-resistant epileptic patients, from large-scale networks to inframillimetric neuronal populations

DISCIPLINE ADMINISTRATIVE : Médecine spécialisée clinique

MOTS-CLÉS : épilepsie focale pharmaco-résistante, stéréo-électroencéphalographie, microélectrode, tétrode, pattern de début de crise

Université Toulouse III-Paul Sabatier
Faculté de Santé de Toulouse
37 Allées Jules Guesde 31000 Toulouse

Centre de Recherche Cerveau et Cognition,
CNRS, Pavillon Baudot, Place du Dr Baylac
31052 Toulouse Cedex

DIRECTEUR DE THESE : Dr Jonathan CUROT