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Understanding memory deficits in patients with drug-resistant epilepsy: key factors and impact on quality of life

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ÍNDICE

PREFACIO

La epilepsia es una enfermedad neurológica caracterizada por una predisposición a presentar crisis epilépticas y por las consecuencias neurobiológicas, cognitivas, psicológicas y sociales asociadas, y puede suponer una condición potencialmente estresante. Esta enfermedad es tratada principalmente con fármacos antiepilépticos (FAEs). Sin embargo, aproximadamente un 30% de los pacientes presentan epilepsia farmacorresistente y pueden ser candidatos a procedimientos quirúrgicos, con demostrada eficacia en el control de las crisis. Tanto la exposición repetida a crisis epilépticas como su tratamiento suelen conllevar déficits cognitivos relativamente variables, siendo el deterioro de la memoria una queja referida por más del 70% de pacientes. Estos déficits de memoria pueden comprometer el principal objetivo terapéutico de los pacientes consistente en mejorar, en último término, su calidad de vida.

Se han propuesto diferentes factores, en su mayoría directamente relacionados con las crisis epilépticas, que podrían modular el rendimiento en memoria en pacientes con epilepsia farmacorresistente. Entre ellos, destacan: la localización y la lateralización del área epileptógena, la frecuencia y el tipo de crisis, la edad de inicio y la duración de la epilepsia, la presencia de esclerosis hipocampal, y las características de los diferentes tratamientos. Sin embargo, apenas se han explorado otros factores relacionados con el sustrato neural de la memoria (i.e., la morfología del hipocampo a lo largo de su eje anterior-posterior, el patrón de activación funcional durante el procesamiento cognitivo y la edad en el momento de la cirugía del lóbulo temporal) u otros que podrían considerarse indicadores del estado de salud (i.e., los niveles de cortisol y la afectividad negativa). Por ello, la presente Tesis doctoral pretende clarificar los factores intervinientes en el funcionamiento mnésico de las personas con epilepsia farmacorresistente y el impacto de dicho funcionamiento en la calidad de vida de esta población.

El primer capítulo contiene una introducción general, presentando en su primera sección el cuerpo de datos con el que se cuenta en la actualidad acerca de los factores intervinientes en la memoria en personas con epilepsia, haciendo hincapié en las cuestiones que permanecen sin resolver. La segunda sección del capítulo define qué es la calidad de vida, presenta un modelo de calidad de vida en personas con epilepsia, y aborda lo que se sabe en la actualidad acerca de las repercusiones del funcionamiento mnésico en la calidad de vida de esta población.

Uno de los factores incluidos en el primer capítulo cuyo papel sobre la memoria apenas se ha estudiado es el cortisol, que es uno de los productos finales de la respuesta de estrés. Dado

que la epilepsia puede ser considerada como un modelo de estrés crónico en seres humanos y que el cortisol se ha propuesto como un indicador del estado de salud implicado en el funcionamiento de la memoria en otras poblaciones, el estudio de los niveles de cortisol es especialmente interesante. Para analizar su impacto sobre la memoria de pacientes con epilepsia, se considera relevante conocer qué se sabe sobre los niveles de esta hormona en esta población y cómo interactúa con otros factores relacionados con la epilepsia. Con este fin, el segundo capítulo incluye una revisión sistemática sobre el cortisol y las crisis epilépticas en personas con epilepsia, describiendo los datos existentes sobre los niveles de esta hormona en condiciones basales y en situaciones estresantes como las crisis o las manipulaciones experimentales.

El tercer capítulo presenta los principales objetivos e hipótesis de la Tesis doctoral, que serán desarrollados posteriormente en los estudios recogidos en los siguientes capítulos.

Los capítulos cuarto, quinto, sexto y séptimo incluyen cuatro estudios empíricos diseñados para investigar los factores intervinientes en el funcionamiento mnésico de personas con epilepsia farmacorresistente, tales como los sustratos neurales subyacentes al procesamiento cognitivo de esta población (estudios 1 y 2), la intervención quirúrgica sobre este sustrato (estudio 3) y otros factores endocrinos y psicológicos (estudio 4). Así, el primer estudio examina la influencia de la morfología del hipocampo a lo largo de su eje anterior-posterior y sus relaciones con la activación cerebral funcional durante la codificación mnésica y el rendimiento en memoria. El segundo estudio pretende clarificar el papel del patrón de asimetría hemisférica durante el procesamiento del lenguaje en el rendimiento en memoria, considerando posibles factores mediadores. El tercer estudio se focaliza en determinar si la edad en el momento de la cirugía es un predictor fiable de la evolución mnésica en pacientes sometidos a cirugía del lóbulo temporal desde una perspectiva multivariada. El cuarto estudio se centra en determinar la influencia de los niveles de cortisol y de la afectividad negativa en el funcionamiento de la memoria de esta población, considerando el papel de otros posibles factores influyentes.

El capítulo octavo presenta el quinto estudio empírico de la Tesis doctoral, centrado en clarificar el papel del funcionamiento de la memoria sobre la calidad de vida de pacientes con epilepsia farmacorresistente, considerando la influencia de variables relacionadas con las crisis epilépticas y de otros factores psicobiológicos y sociales no directamente relacionados con las crisis.

Cada estudio descrito en los capítulos de la presente Tesis contiene una breve introducción, método, resultados y discusión de los principales resultados.

El capítulo noveno incluye una discusión general de los principales resultados de la Tesis doctoral, así como sus implicaciones clínicas y limitaciones, sugiriendo algunas direcciones futuras.

Por último, el décimo capítulo incluye las principales conclusiones de la Tesis doctoral.

Finalmente, los capítulos undécimo y duodécimo incluyen un resumen extenso de la Tesis en inglés y en castellano, respectivamente, en el que se presentan los objetivos e hipótesis, los estudios realizados, los principales hallazgos y las conclusiones extraídas.

ABREVIATURAS / ABBREVIATIONS

ACTH = adrenocorticotropic hormone

AED = antiepileptic drug

AH = amygdalohippocampectomy

AUC = area under curve

AUC_g = area under the curve with respect to ground

AUC_i = area under the curve with respect to increase

BA = Brodmann's area

BCN-R = Test de Barcelona Revisado

BDI-II = Beck Depression Inventory-II

BMIPB = British Memory and Information Processing Battery

BNT = Boston Naming Test

BOLD = blood-oxygen level-dependent

C = cortisol

CA = *cornus ammonis*

CBG = cortisol-binding globulin

CBZ = carbamazepine

CDIC = Centro de Diagnóstico por la Imagen Clínic

CG = control group

CI = cociente intelectual

CLZ = clonazepam

CPS = complex partial seizures

CRF = corticotropin-releasing factor

CSF = cerebrospinal fluid

CVLT = California Verbal Learning Test

DDD = defined daily dose

DZP = diazepam

E = epilepsy

EEG = electroencephalography

EHI = Edinburgh Handedness Inventory

EIAED = enzyme inducer AEDs

ELF = epilepsia del lóbulo frontal

ELT = epilepsia del lóbulo temporal

EpiCARE = European Reference Network for Epilepsy

ESS-R = Escala de Síntomas Somáticos Revisada

ETLE: extratemporal lobe epilepsy

FAE = fármaco antiepiléptico

FCD = focal cortical dysplasia

FDG = fluorodeoxyglucose

FDR = False Discovery Rate

FIML = full information maximum likelihood

FLE = frontal lobe epilepsy

fMRI = functional magnetic resonance imaging

FR = faces remembered

FWE = family-wise error

G = group

GE = generalized epilepsy

GR = glucocorticoid

GTCS = generalized tonic-clonic seizures

HPA = hypothalamus-pituitary-adrenal

HS = hippocampal sclerosis

IE = idiopathic epilepsy

ILAE = International League Against Epilepsy

ILE = insular epilepsy

IQ = intelligence quotient

LEV = levetiracetam

LH = left-hemisphere

LIs = laterality indexes

LTG = lamotrigine

LTLE = left TLE

LTLE+sz = LTLE with seizures

LTLE-sz = LTLE seizure-free

MOS = Medical Outcomes Study Social Support Survey

MR = mineralocorticoid

MRI = magnetic resonance imaging

n.s.d.= no significant differences

ne = not specified

NEIAED = non-enzyme inducer AEDs

OLE = occipital lobe epilepsy

OXC = oxcarbazepine

PB = phenobarbital

PE = partial epilepsy

PET = positron emission tomography

PGE = primary generalized epilepsy

PGS = primary generalized seizures

PHT = phenytoin

PLE = parietal lobe epilepsy

PMD = primidone

PNES = psychogenic non-epileptic seizures

PSSG = partial seizures with secondary generalization

QOL = quality of life

QOLIE-31 = Quality-of-Life in Epilepsy Inventory

RCI = reliable change index

RH = right-hemisphere

RMf = resonancia magnética funcional

ROI = region-of-interest

RTLE = right TLE

SE = secondary epilepsy

SGS = secondary generalized seizures

Side = side of seizure focus

SPECT = single photon emission computed tomography

SPHARM-PDM = spherical harmonics point distribution model

SPS = simple partial seizures

STAI = State-Trait Anxiety Inventory

STAI-S = state anxiety scale of the STAI

STAI-T = trait anxiety scale of the STAI

TAVEC = Test de Aprendizaje Verbal España-Complutense

TCS = tonic-clonic seizures

TIV = total intracranial volume

TL = temporal lobectomy

TLE = temporal lobe epilepsy

TMT = Trail Making Test

TPM = topiramate

VNS = vagus nerve stimulation

VPA = valproic acid

WFU = Wake Forest University

WMS-III = Wechsler Memory Scale-Third Edition

WR = words remembered

CAPÍTULO 1

Introducción general

1. Epilepsia y memoria: factores intervinientes

La epilepsia es una afectación neurológica que afecta a más de 70 millones de personas en el mundo (Thijs, Surges, O'Brien y Sander, 2019). La concepción actual de epilepsia requiere de alguna de las siguientes condiciones: a) un mínimo de dos crisis epilépticas no provocadas que ocurran con más de 24 horas de diferencia; b) una crisis epiléptica no provocada y una probabilidad de presentar nuevas crisis similar al riesgo de recurrencia tras experimentar dos crisis no provocadas (al menos del 60% en los próximos 10 años); y c) el diagnóstico de un síndrome epiléptico (Fisher et al., 2014). Se trata de una condición heterogénea caracterizada por diferentes tipos de crisis epilépticas. Así, diferenciamos tres tipos de crisis: crisis de inicio focal – que se originan en redes limitadas a un hemisferio; crisis de inicio generalizado – que surgen e involucran rápidamente a redes distribuidas bilateralmente; y crisis de inicio desconocido – que son aquellas que no pueden clasificarse en las categorías anteriores debido a una evidencia insuficiente (Fisher et al., 2017).

La Liga Internacional Contra la Epilepsia (ILAE) enfatiza la incontrolabilidad e impredecibilidad de las crisis epilépticas, y define la epilepsia como una enfermedad caracterizada tanto por la predisposición a presentar crisis epilépticas, como por las consecuencias neurobiológicas, cognitivas, psicológicas y sociales asociadas (Fisher et al., 2005).

La mayoría de las personas que padecen epilepsia controlan adecuadamente sus crisis con fármacos antiepilépticos (FAEs). Sin embargo, aproximadamente un 30% de éstas presentan epilepsia farmacorresistente o refractaria a fármacos (Barr y Morrison, 2014; de Tisi et al., 2011; Kwan, Schachter y Brodie, 2011). Este tipo de epilepsia se define por el fracaso de dos fármacos antiepilépticos, adecuadamente tolerados y elegidos (en monoterapia o politerapia), en el control de las crisis de forma prolongada (Kwan et al., 2010). Los pacientes con epilepsia refractaria pueden ser candidatos a cirugía de epilepsia, que, en el caso de presentar crisis focales, habitualmente consistirá en la resección de la zona epileptógena, siendo este procedimiento frecuentemente eficaz en el control de las crisis (Helmstaedter, 2013).

Tanto la exposición repetida a crisis incontrolables como los diferentes tratamientos que se han empleado para el control de éstas suelen conllevar cuadros relativamente variables de déficits cognitivos, incluyendo alteraciones en memoria, atención, funciones ejecutivas y lenguaje (Aldenkamp, Baker y Meador, 2004; Helmstaedter, 2013). De entre estos dominios cognitivos, el deterioro de la memoria es una de las quejas más frecuentes (Helmstaedter, 2013;

Hoppe, Elger y Helmstaedter, 2007; Lee, Yip y Jones-Gotman, 2002; Thompson et al., 2016), referida por más del 70% de pacientes (Thompson y Corcoran, 1992).

La memoria se define como un proceso cognitivo que permite la codificación, el almacenamiento y la recuperación de la información aprendida. Tradicionalmente, se han diferenciado dos grandes subsistemas de memoria: la memoria declarativa o explícita y la memoria no declarativa o implícita (Squire, 1992). Dentro de la memoria declarativa, distinguimos dos tipos: la memoria de hechos y acontecimientos de una persona (memoria episódica) y la referida a la información de los objetos del medio y de su significado (memoria semántica) (Tulving, 1972). Por su parte, la memoria no declarativa o implícita incluye formas de memoria como el *priming*, las habilidades y los hábitos, el aprendizaje asociativo, la habituación y la sensibilización. En este trabajo, nos centraremos en la memoria declarativa episódica verbal o visual, atendiendo al tipo de información almacenada.

Se han propuesto diferentes factores, en su mayoría directamente relacionados con las crisis epilépticas, que podrían modular el rendimiento en memoria en pacientes con epilepsia farmacorresistente. Entre ellos, destacan: la localización y la lateralización del área epileptógena, la frecuencia y el tipo de crisis, la edad de inicio y la duración de la epilepsia, la presencia de esclerosis hipocampal, y las características de los diferentes tratamientos (FAEs y cirugía) (Figura 1). Sin embargo, apenas se ha explorado el papel de otras variables no directamente relacionadas con las crisis. Entre estas variables, por una parte, destacan las relacionadas con el sustrato neural de la memoria como la morfología del hipocampo a lo largo de su eje anterior-posterior, la activación funcional durante el procesamiento cognitivo, y la edad en la que se interviene dicho sustrato neural mediante cirugía del lóbulo temporal. Por otra parte, encontramos factores que podrían considerarse indicadores del bienestar del individuo como los niveles de cortisol y la afectividad negativa (Figura 1). A continuación, describiremos brevemente los conocimientos con los que se cuenta en la actualidad acerca de los factores nombrados anteriormente, haciendo hincapié en las cuestiones que permanecen sin resolver.

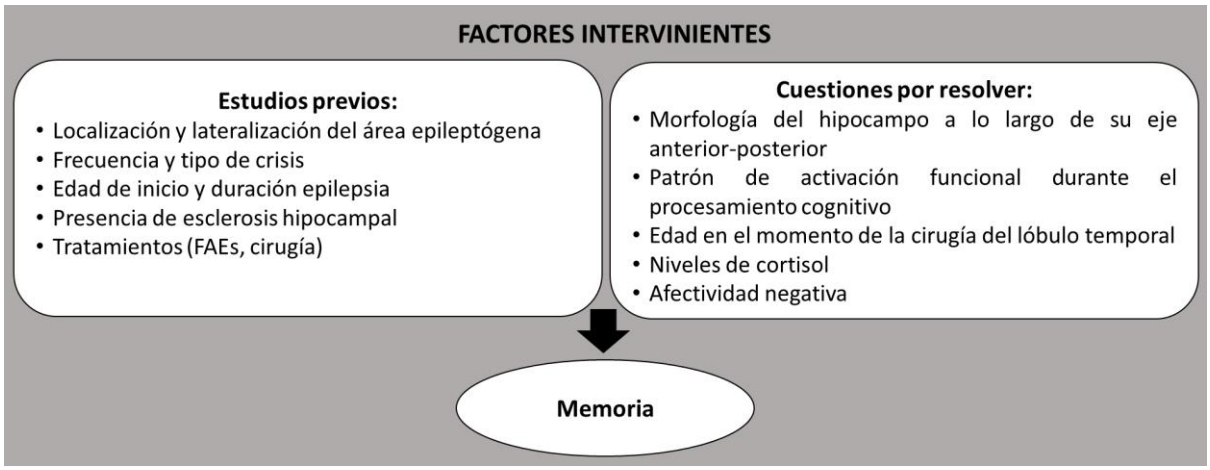

Figura 1. Factores propuestos como moduladores del funcionamiento mnésico en personas con epilepsia y cuestiones por resolver.

1.1. Factores intervinientes en estudios previos

1.1.1. Localización y lateralización del área epileptógena

El perfil de memoria ha sido estudiado, predominantemente, en pacientes con epilepsia del lóbulo temporal (ELT) y, en menor medida, en aquellos con epilepsia del lóbulo frontal (ELF), existiendo escasa información sobre otros tipos de epilepsia.

La ELT es el tipo más común de epilepsia farmacorresistente (Téllez-Zenteno y Hernández-Ronquillo, 2012), afectando al 70-90% de pacientes con epilepsia focal (Barr y Morrison, 2014). Además, se trata del tipo de epilepsia más frecuentemente asociado a déficits en memoria (Tramoni-Negre, Lambert, Bartolomei y Felician, 2017), estimándose que el 70% de los pacientes con ELT presentan alteraciones mnésicas (Helmstaedter y Kockelmann, 2006). Además, algunos estudios han mostrado que los pacientes con ELT no son un grupo homogéneo en lo que respecta al perfil cognitivo, diferenciando tres fenotipos: deterioro cognitivo mínimo o funcionamiento cognitivo preservado, deterioro exclusivo de la memoria, y deterioro cognitivo generalizado en memoria, funciones ejecutivas y velocidad de procesamiento de la información (Hermann, Seidenberg, Lee, Chan y Rutecki, 2007).

El segundo tipo de epilepsia focal más prevalente es la ELF, que afecta al 10-20% de pacientes con epilepsia farmacorresistente (Jokeit y Schacher, 2004). Aunque en la ELF son habituales las alteraciones en las habilidades motoras, la atención, la respuesta de inhibición, la memoria de trabajo, la planificación y la velocidad psicomotora (revisado por Elger,

Helmstaedter y Kurthen, 2004), los estudios son más inconsistentes en cuanto a las alteraciones en memoria. Así, en algunos casos no se han encontrado diferencias en el rendimiento en memoria entre pacientes con ELF y personas sanas (Delaney, Rosen, Mattson y Novelly, 1980). En cambio, en otros estudios se ha sugerido que los pacientes con ELF presentan mayores dificultades que aquellos con ELT en ciertos procesos intervinientes en el aprendizaje y la memoria, como la susceptibilidad a la interferencia proactiva (McDonald, Bauer, Grande, Gilmore y Roper, 2001) o el uso de estrategias de memoria (Lee, 2010). También se ha propuesto que los pacientes con ELF muestran alteraciones en los procesos mnésicos de recuperación, posiblemente como consecuencia de un uso asistemático de estrategias de memoria (Lee, 2010). De hecho, su perfil mnésico suele caracterizarse por la preservación de los procesos de codificación y consolidación de la información, que se manifiesta con un rendimiento ajustado a la media en paradigmas que evalúan memoria de reconocimiento (Lee, 2010).

En cuanto a la lateralización del área epileptógena, tradicionalmente se ha defendido la especificidad hemisférica para el material verbal y visoespacial. En este contexto, se ha asociado la afectación del hemisferio dominante para el lenguaje (típicamente izquierdo) con déficits en memoria verbal (Frisk y Milner, 1990), y la afectación del hemisferio no dominante (típicamente derecho) con un deterioro de la memoria visoespacial (Smith y Milner, 1981). Aunque con posterioridad la primera relación se ha encontrado de manera consistente (Aikia, Salmenpera, Partanen y Kalvianen, 2001; Gleissner, Helmstaedter, Schramm y Elger, 2004; Golby et al., 2001; Rausch et al., 2003), los resultados son menos consistentes con respecto a la asociación entre la disfunción del hemisferio derecho y los déficits en memoria visoespacial. Así, en algunos estudios se ha corroborado dicha asociación (Giovagnoli, Casazza y Avanzini, 1995), pero no así en otros (Alessio et al., 2004). Se ha especulado que una posible explicación para esta falta de consistencia podría ser la dificultad para encontrar un test "puro" de memoria visoespacial, ya que frecuentemente las personas utilizan estrategias verbales para realizar tareas no verbales (Baxendale, Thompson y Duncan, 2008; Helmstaedter, Pohl y Elger, 1995; Vaz, 2004).

Como consecuencia de los resultados anteriores, se ha ido modificando progresivamente la comprensión del funcionamiento de la memoria, desde este modelo que defendía la especificidad del tipo de material hacia un planteamiento más complejo. Así, actualmente se asume que, aunque el patrón de disfunción de memoria específico del material puede ser observado en candidatos a cirugía de la epilepsia y puede ser útil para confirmar la localización

y lateralización del área epileptógena, existen otros factores moduladores que pueden dificultar encontrar esta asociación, dando lugar a resultados discordantes (Barr y Morrison, 2014).

1.1.2. Frecuencia y tipo de crisis

La frecuencia y el tipo de crisis también pueden influir en el rendimiento mnésico. Así, una mayor frecuencia de crisis podría implicar un aumento del daño cerebral esperado y de la probabilidad de desarrollar déficits de memoria (revisado por Dodrill, 2004). No obstante, existen dificultades metodológicas para poner de manifiesto esta lógica asunción, entre las que se incluyen la dificultad para controlar la influencia del deterioro cognitivo asociado a la edad y la subjetividad de los autoinformes sobre la frecuencia de crisis (Dodrill, 2004). Estas dificultades metodológicas podrían explicar, al menos en parte, la inconsistencia entre los resultados de algunos estudios que examinan esta cuestión. A pesar de estas consideraciones, se ha encontrado una asociación significativa entre mayor frecuencia de crisis y mayor deterioro mnésico en algunos estudios (Helmstaedter, Kurthen, Lux, Reuber y Elger, 2003; Hermann et al., 2006; Thompson y Duncan, 2005).

Respecto al tipo de crisis, los resultados son contradictorios. En general, se ha hallado mayor deterioro cognitivo general en personas con crisis generalizadas tónico-clónicas respecto a aquellas con crisis focales (simples o complejas) (Dodrill, 1986; Rausch y Victoroff, 1991). No obstante, parece que la principal diferencia radica en que las crisis focales se relacionan con alteraciones cognitivas más específicas, principalmente en memoria (Thompson y Duncan, 2005). Además, los pacientes que presentan diferentes tipos de crisis suelen tener mayor deterioro cognitivo que aquellos que sufren un solo tipo (Seidenberg, Pulsipher y Hermann, 2007).

1.1.3. Edad de inicio y duración de la epilepsia

La edad de inicio y la duración de la epilepsia también se han asociado al perfil de memoria en personas con epilepsia. Habitualmente, resulta difícil separar los efectos de la duración de la enfermedad y de la edad de inicio de ésta. La mayoría de los estudios centrados en estos factores sugieren que un inicio temprano y una mayor duración de la epilepsia se asocian con mayor deterioro cognitivo. En este sentido, aunque una edad temprana de inicio de la epilepsia puede favorecer la redistribución de las funciones cognitivas como consecuencia de una mayor

plasticidad cerebral (Loring, Barr, Hamberger y Helmstaedter, 2008), se ha evidenciado que las personas que sufren crisis epilépticas desde la infancia son más vulnerables a experimentar un compromiso neurológico durante etapas críticas del desarrollo (Dennis, 2000; Vingerhoets, 2006). Así, la edad de inicio temprana podría comprometer el desarrollo cognitivo y favorecer una mayor vulnerabilidad a los efectos de las crisis y del tratamiento farmacológico (Dennis, 2000; Elger et al., 2004; Hermann et al., 2006). No obstante, cabe destacar que algunos estudios han encontrado déficits de memoria en pacientes con un diagnóstico reciente de epilepsia no tratados con FAEs, sugiriendo que el deterioro de memoria en pacientes con epilepsia de larga duración no puede ser atribuido exclusivamente a la recurrencia de crisis y a los efectos de los FAEs, siendo necesario explorar otros factores (Aikia et al., 2001).

1.1.4. Presencia de esclerosis hipocampal

El hipocampo está implicado en la formación de la memoria. Una de las alteraciones estructurales más frecuentes en pacientes con epilepsia es la esclerosis hipocampal o esclerosis mesial temporal, que afecta al 80% de pacientes con ELT (Tatum, 2012). Se caracteriza por la gliosis y la pérdida neuronal en el hipocampo, que puede estar causada por mecanismos congénitos que impiden la maduración, migración o densidad normal de las neuronas (Luders y Comair, 2001).

La pérdida de volumen hipocampal se ha asociado con un funcionamiento mnésico pobre. Dado que el funcionamiento en memoria verbal está fuertemente ligado al hemisferio dominante para el lenguaje, la atrofia hipocampal izquierda se ha asociado con déficits en memoria verbal (Alessio et al., 2004; Kilpatrick et al., 1997). También se ha sugerido una asociación análoga entre la atrofia hipocampal derecha y los déficits en memoria visual (Baxendale et al., 1998a), aunque estos resultados son menos consistentes (Alessio et al., 2004).

A su vez, la integridad hipocampal modula el declive de memoria tras la cirugía. En este sentido, se ha evidenciado que los pacientes con mayor densidad neuronal en el hipocampo izquierdo son más proclives a experimentar un declive significativo en memoria verbal tras la resección de dicho hipocampo (Witt et al., 2015).

1.1.5. Características de los diferentes tratamientos: FAEs y cirugía

Como se ha indicado anteriormente, el tratamiento más habitual para el control de las crisis epilépticas es el farmacológico. Los FAEs suelen conllevar efectos cognitivos colaterales, siendo los más comunes la disminución de la velocidad de procesamiento de la información y la inatención (revisado por Hermann, Meador, Gaillard y Cramer, 2010). Aunque con menor frecuencia, los FAEs también pueden implicar un deterioro en el aprendizaje y la memoria (Lee, 2010) que, además, puede verse acrecentado de manera secundaria a las dificultades anteriores. La severidad de estos efectos adversos depende del tipo de FAE y es mayor cuando se toman altas dosis y cuando se emplean en politerapia (Javed et al., 2015; Kwan y Brodie, 2001). A este respecto, podemos diferenciar entre los FAEs de primera generación o clásicos (e.g., fenobarbital, fenitoína, carbamazepina, primidona y ácido valproico) y los "nuevos" FAEs, de segunda o tercera generación (e.g., lamotrigina, gabapentina, tiagabina, topiramato, oxcarbazepina, levetiracetam, pregabalina, zonisamida, lacosamida, acetato de eslicarbazepina, perampanel y brivaracetam), con menores efectos cognitivos colaterales (revisado por Aldenkamp, De Krom y Reijs, 2003). Una notable excepción entre los "nuevos" FAEs es, sin embargo, el topiramato, que se ha asociado con alteraciones en la atención y las funciones verbales (Aldenkamp et al., 2003).

La cirugía de la epilepsia se ha convertido en un tratamiento cada vez más seguro y efectivo para la epilepsia farmacorresistente, debido a los avances en los procedimientos diagnósticos y quirúrgicos que han permitido la realización de resecciones específicas del área epileptógena (Clusmann, Schramm, Kral, Helmstaedter y Ostertun, 2002). Así, aproximadamente el 70% de pacientes sometidos a cirugía quedan libres de crisis a largo plazo (Baud et al., 2018), siendo este porcentaje variable en función de las bases de datos consultadas. A pesar de la eficacia de la cirugía en el control de las crisis, también puede conllevar efectos cognitivos colaterales, especialmente en el funcionamiento mnésico. Factores como el perfil cognitivo prequirúrgico, el tipo de cirugía, el hemisferio intervenido, la extensión de la cirugía y el control postquirúrgico de las crisis pueden modular dichos efectos colaterales.

En cuanto al perfil cognitivo prequirúrgico, presentar un funcionamiento preservado de la memoria antes de la cirugía implica mayor riesgo de deterioro mnésico postquirúrgico, especialmente cuando se interviene el hemisferio dominante para el lenguaje. Las relaciones que se producen entre el funcionamiento de la memoria antes de la cirugía y la evolución postquirúrgica de esta función cognitiva son complejas. Para explicarlas se han propuesto dos modelos: el modelo de reserva funcional (Chelune, 1995) y el modelo de adecuación funcional

(Kneebone, Chelune, Naugle, Dinner, y Awad, 1995). El modelo de reserva funcional se basa en que la integridad funcional del hemisferio contralateral al área epileptógena permite predecir los cambios que se producen en el funcionamiento mnésico tras la lobectomía temporal, siendo más favorable el pronóstico a mayor integridad funcional de este hemisferio (Chelune, 1995). Por su parte, el modelo de adecuación funcional defiende que los déficits de memoria postquirúrgicos se relacionan con la adecuación funcional del lóbulo temporal ipsilateral al área epileptógena, de manera que, cuanto más funcional es este lóbulo, mayor es el riesgo de deterioro postquirúrgico de la memoria (Kneebone et al., 1995).

Respecto al tipo de cirugía, los procedimientos quirúrgicos más habituales en la ELT mesial son la amigdalohipocampectomía selectiva y la amigdalohipocampectomía acompañada de una lobectomía temporal anterior (Fabinyi, 2002; Helmstaedter et al., 2008). En casos de ELT neocortical, es habitual realizar una resección temporal neocortical que, en algunos pacientes, incluye los dos tercios anteriores del lóbulo temporal (Helmstaedter, Reuber y Elger, 2002). En epilepsias neocorticales con lesión única circunscrita, la intervención indicada es la lesionectomía (Clusmann, 2009). Los estudios que han examinado la evolución mnésica postquirúrgica en función del tipo de cirugía realizada han encontrado resultados inconsistentes. Por una parte, se ha encontrado una mejor evolución mnésica tras la amigdalohipocampectomía selectiva que tras la amigdalohipocampectomía acompañada de lobectomía temporal anterior (Morino et al., 2006), pero también una ausencia de diferencias significativas (Helmstaedter et al., 2002), o incluso peor evolución en memoria verbal tras la amigdalohipocampectomía selectiva (Helmstaedter et al., 2008). Por otra parte, se han encontrado resultados superiores en la evolución mnésica postquirúrgica con la lesionectomía que con los procedimientos anteriores (Helmstaedter, Elger, Hufnagel, Zentner y Schramm, 1996).

Algunos estudios sugieren que el hemisferio intervenido y la extensión de la cirugía son variables más relevantes que el tipo de cirugía en lo que respecta a la evolución mnésica postquirúrgica (Clusmann et al., 2002; Elger et al., 2004; Helmstaedter et al., 2003). En cuanto al hemisferio intervenido, se ha estimado que el riesgo de declive de memoria verbal tras la cirugía del lóbulo temporal izquierdo es del 44%, el doble que para la cirugía del lóbulo temporal derecho que es del orden del 20% (Sherman et al., 2011). Sin embargo, se ha encontrado un riesgo de declive de memoria visual similar en ambos casos, situado entre el 21-23%, independientemente del hemisferio intervenido (Sherman et al., 2011). Respecto a la extensión de la cirugía, se ha encontrado una mejor evolución cognitiva con resecciones limitadas respecto a otras más extensas en pacientes con ELT (Clusmann et al., 2002). En

relación a la cantidad de tejido resecado a nivel mesial, se ha hallado que, cuanto más limitada es la resección, mejor es la evolución mnésica, sugiriendo que la resección de tejidos funcionales no patológicos podría explicar el declive postquirúrgico de memoria (Helmstaedter, Roeske, Kaaden, Elger y Schramm, 2011).

Además, cabe destacar que el declive mnésico tras la cirugía es más frecuente cuando no se logra el control postquirúrgico de las crisis (Helmstaedter et al., 2003). De hecho, Baxendale y Thompson (2018) emplearon el concepto de "doble pérdida" para referirse a aquellos pacientes que continúan experimentando crisis tras la cirugía y, además, sufren un declive significativo en memoria, ya sea verbal, no verbal o de ambos tipos.

1.2. Cuestiones por resolver

1.2.1. Influencia de la morfología del hipocampo a lo largo de su eje anterior-posterior

El rendimiento mnésico en pacientes con epilepsia farmacorresistente, especialmente en aquellos con ELT, se ha asociado con alteraciones estructurales y funcionales en el hipocampo y en otras estructuras del lóbulo temporal medial.

A nivel estructural, se han identificado regiones específicas del hipocampo en las que la pérdida de volumen es más frecuente en personas con ELT (Bronen et al., 1995; Cook, Fish, Shorvon, Straughan y Stevens, 1992; Hogan et al., 2000; Hogan, Bucholz y Joshi, 2003; Oppenheim et al., 1998), sugiriendo la existencia de patrones específicos de atrofia. En general, se ha demostrado que la pérdida celular en la región del *cornus ammonis* (CA) 1 es la más característica de la ELT mesial, existiendo grandes variaciones en la pérdida neuronal en CA2, y estando la integridad estructural del giro dentado y de la región CA3 menos afectada (Pauli, Hildebrandt, Romstöck, Stefan y Blümcke, 2006). Sin embargo, el papel de estas regiones del hipocampo en la codificación mnésica apenas ha sido estudiado, permaneciendo sin esclarecer si determinados subtipos de esclerosis hipocampal se asocian con mayor riesgo de deterioro mnésico.

La mayoría de los estudios focalizados en este tema se basan en recuentos de células mediante técnicas histológicas, un procedimiento invasivo que requiere la resección quirúrgica de tejido cerebral para su análisis, no permitiendo la evaluación de pacientes no sometidos a cirugía. Estos estudios han hallado resultados inconsistentes, posiblemente debido a la

existencia de dificultades en la diferenciación de subregiones del hipocampo con tinciones histológicas de rutina (Coras y Blümcke, 2015). De hecho, se ha encontrado una asociación positiva entre el recuento de células neuronales en la región CA1 y el rendimiento en memoria (Baxendale et al., 1998b; Pauli et al., 2006; Sass et al., 1995; Zentner et al., 1999), pero también la ausencia de una relación significativa (Coras et al., 2014). Otros estudios han encontrado una asociación positiva entre el rendimiento mnésico y el recuento de células neuronales en otras regiones como CA3 (Sass et al., 1990, 1991, 1992), CA4 (Sass et al., 1992; O'Rourke et al., 1993; Shing et al., 2011; Witt et al., 2014) y el subiculum (Zentner et al., 1999). Típicamente, en estos estudios histológicos únicamente se analiza un número limitado de porciones de la mitad anterior del hipocampo, limitando la posibilidad de establecer conclusiones sobre las alteraciones estructurales del hipocampo a lo largo de su eje anterior-posterior.

A nivel funcional, la reorganización del funcionamiento mnésico al lóbulo temporal medial contralesional en pacientes con ELT ha sido consistentemente descrita en estudios de neuroimagen. Aunque las implicaciones de esta reorganización se han asociado al rendimiento en memoria, los resultados no son homogéneos en este aspecto. En algunos casos, se ha encontrado que la activación en el lóbulo temporal medial derecho es un proceso eficiente para la codificación verbal en pacientes con esclerosis hipocampal izquierda (Sidhu et al., 2013; Richardson, Strange, Duncan y Dolan, 2003). En otros estudios, únicamente la activación temporal medial izquierda se ha asociado a un mejor rendimiento en memoria verbal en estos pacientes (Powell et al., 2007). Respecto a la memoria visual, algunos estudios han mostrado que únicamente la activación temporal medial derecha se asocia a un mejor rendimiento (Bonelli et al., 2010; Powell et al., 2007), mientras que otros han hallado que la activación temporal medial bilateral supone una red eficiente de memoria (Guedj et al., 2011; Sidhu et al., 2013). Cabe destacar que la reorganización funcional es un proceso de larga duración, por lo que la posible variabilidad en la duración del período comprendido entre el inicio de la lesión y la evaluación podría explicar, al menos parcialmente, la discrepancia en los resultados.

La reorganización funcional de la memoria podría ser un mecanismo compensatorio que se produce como consecuencia de alteraciones estructurales. Sin embargo, apenas se ha estudiado la relación entre las alteraciones estructurales y la activación funcional durante la codificación mnésica. Algunos estudios han hallado que una mayor severidad de la esclerosis mesial se asocia a una menor activación funcional en el hipocampo afectado y más activación en el hipocampo contralateral (Richardson, Strange y Dolan, 2004; Powell et al., 2007). Estas relaciones se han examinado considerando el hipocampo como un todo. Sin embargo, como se

ha expuesto anteriormente, la esclerosis hipocampal no afecta al hipocampo uniformemente, existiendo diferentes subtipos (Blümcke et al., 2013). Se desconoce si el daño selectivo en regiones anteriores o posteriores del hipocampo se relaciona con un patrón diferente de activación funcional de la memoria y con un rendimiento mnésico diferente. Una comprensión más detallada de las interacciones estructurales y funcionales del hipocampo podría ayudar a clasificar los fenotipos de la ELT (Coras y Blümcke, 2015) y a comprender por qué algunas personas con ELT son más propensas a presentar déficits de memoria respecto a otras.

1.2.2. Papel del patrón de activación funcional durante el procesamiento cognitivo

La exposición repetida a crisis incontrolables en personas con epilepsia farmacorresistente puede producir daño cerebral alrededor de áreas elocuentes para el lenguaje, dando lugar a una reorganización inter-hemisférica del lenguaje (Tzourio-Mazoyer, Perrone-Bertolotti, Jobard, Mazoyer y Baciu, 2017). Por ello, las personas con epilepsia presentan con mayor frecuencia que la población general una lateralización derecha o bilateral del lenguaje (Hamberger y Cole, 2011). Este patrón de lateralización del lenguaje fue definido como lateralización atípica, considerando la lateralización izquierda como el patrón típico (Mateer y Dodrill, 1983).

Aunque existe cierto consenso sobre la reorganización del lenguaje en pacientes con foco epileptógeno izquierdo, sus implicaciones cognitivas permanecen sin esclarecer. En algunos casos, la lateralización atípica del lenguaje se ha asociado con un deterioro en dominios no verbales y una preservación de los dominios verbales (Berl et al., 2005; Loring et al., 1999; Strauss, Satz y Wada, 1990) o incluso con mejor rendimiento en dominios verbales respecto a pacientes con asimetría típica (Thivard et al., 2005), entendiéndola como un mecanismo compensatorio. No obstante, también se ha definido un fenómeno denominado "*crowding*" (podría traducirse como "*apiñamiento*"), según el cual sería esperable que una mayor activación del hemisferio derecho durante el procesamiento del lenguaje favoreciera una competición de recursos cognitivos de ambos hemisferios implicados en la realización de una misma tarea, desestabilizando el rendimiento cognitivo (Jokeit y Ebner, 2002). Este fenómeno sería congruente con el hecho de que la epilepsia crónica puede implicar un deterioro cognitivo general y progresivo (Helmstaedter et al., 2003). Sin embargo, se requieren más estudios que permitan contrastar si este fenómeno puede explicar las relaciones entre la asimetría hemisférica durante el procesamiento del lenguaje y la ejecución cognitiva.

La resonancia magnética funcional (RMf) nos permite abordar esta cuestión de manera no invasiva (Benjamin et al., 2017), aunque la inconsistencia de los resultados encontrados puede deberse a la gran variabilidad de paradigmas utilizados. Entre ellos, uno de los más frecuentes ha sido el de fluidez verbal fonémica (Sanjuán et al., 2013). Aunque este paradigma favorece una prominente activación del lóbulo frontal izquierdo correspondiente al área de Broca, tiende a producir una menor activación de los lóbulos temporales superiores o mediales (Bonelli et al., 2012). La utilización de paradigmas de comprensión verbal que activen de forma fiable áreas implicadas en el lenguaje receptivo podría ser de gran utilidad en el análisis de las relaciones entre la asimetría en la activación hemisférica durante el procesamiento del lenguaje y el rendimiento mnésico. A su vez, sería necesario analizar el papel de otras variables que podrían estar implicadas en esta asociación como el sexo, la dominancia manual o el hemisferio afectado, y considerar la asociación entre la memoria y otros procesos cognitivos, que dependen de la conectividad funcional entre diferentes regiones cerebrales que funcionan como una red (Bota, Sporns y Swanson, 2015; Dinkelacker et al., 2015; Garcia-Ramos et al., 2016), a fin de desarrollar una visión más integradora de esta temática.

1.2.3. Relevancia de la edad en el momento de la cirugía del lóbulo temporal

Es habitual que los pacientes con epilepsia farmacorresistente sean referidos a una unidad de cirugía de la epilepsia a edades tardías, tras haber sufrido crisis epilépticas durante un largo período de tiempo (Haneef, Stern, Dewar y Engel, 2010). Por ello, es especialmente relevante analizar cuál es el momento vital más apropiado para someterse a una cirugía de la epilepsia que permita lograr el control de las crisis epilépticas, minimizando los efectos cognitivos colaterales.

Diversos estudios han mostrado que la plasticidad cerebral varía a lo largo de la vida, existiendo etapas críticas de plasticidad cerebral en la infancia hasta los 6 años de edad y en la adolescencia hasta los 15 años, y produciéndose un declive del nivel de plasticidad alrededor de los 30 años en personas con epilepsia (Gleissner, Sassen, Schramm, Elger y Helmstaedter, 2005; Helmstaedter, 1999). Resulta razonable hipotetizar que la cirugía a edades más tempranas favorecerá una mejor evolución cognitiva postquirúrgica, sobre todo teniendo en cuenta que la edad en el momento de la cirugía se ha propuesto como un factor modulador de la reserva cognitiva del paciente (Helmstaedter, 2004, 2013). A pesar de ello, son escasos los estudios que han abordado el papel de este factor en la evolución mnésica postquirúrgica, encontrando,

además, resultados inconsistentes (Chapin et al., 2013; Gleissner et al., 2005; Grivas et al., 2006; Jambaqué et al., 2007; Thompson, Baxendale, McEvoy y Duncan, 2015; Stewart y Smith, 2019). En estudios longitudinales realizados con niños con ELT, se han encontrado mejorías significativas en el rendimiento en memoria verbal (Jambaqué et al., 2007) y ausencia de cambios en memoria visual un año después de la cirugía (Jambaqué et al., 2007; Stewart y Smith, 2019). Cuando se ha comparado la evolución cognitiva de niños y adultos un año después de la cirugía, se ha evidenciado una mejor evolución del funcionamiento de la memoria verbal y visual en niños (Gleissner et al., 2005). En adultos, se ha hallado mayor declive postquirúrgico de memoria en pacientes mayores respecto a los más jóvenes (Thompson et al., 2015), pero también ausencia de diferencias significativas (Grivas et al., 2006), o incluso el resultado contrario (Chapin et al., 2013). Factores no considerados en algunos de estos estudios como la frecuencia de crisis, la inclusión de pacientes con dominancia atípica del lenguaje, o el posible efecto de aprendizaje que puede conllevar el uso de un mismo test neuropsicológico en varias ocasiones, podrían explicar, al menos parcialmente, la heterogeneidad de los resultados.

Aunque se ha analizado la influencia de la edad en el momento de la cirugía, junto con la frecuencia de las crisis y la dominancia del lenguaje, sobre la evolución cognitiva tras la cirugía, ha resultado particularmente difícil desentrañar el impacto relativo de la edad desde una perspectiva multivariada (Ji et al., 2015). Además, en la mayoría de los casos, se ha estudiado su papel predictivo sobre la memoria y otros dominios cognitivos, considerándolos como procesos independientes, sin examinar la posible asociación entre ellos. La identificación de diferentes patrones de evolución cognitiva tras la cirugía, considerando la posible asociación entre diferentes procesos cognitivos, podría proveer de mayor validez ecológica a la evaluación neuropsicológica y contribuir al proceso de toma de decisiones clínicas con pacientes con epilepsia farmacorresistente.

1.2.4. Papel del cortisol

Siguiendo la definición de la ILAE (Fisher et al., 2014), la epilepsia puede entenderse como una enfermedad que implica una sobrecarga a largo plazo. Así, las personas con epilepsia farmacorresistente sufren crisis epilépticas repetidas, impredecibles e incontrolables, siendo esta condición potencialmente estresante. Otros factores como el propio proceso clínico – incluyendo el tratamiento farmacológico o quirúrgico, la pérdida de funcionalidad en las actividades diarias, las restricciones de participación social (i.e., las dificultades en la obtención

del permiso de conducción, que pueden limitar la elección del empleo) y los aspectos sociales asociados (i.e., estigma social y discriminación) pueden conllevar una sobrecarga importante (De Boer, Mula y Sander, 2008).

En la última década, la investigación sobre los procesos cognitivos y afectivos en relación con el estrés ha recibido especial atención, debido a su capacidad para modificar la excitabilidad neuronal, la neurogénesis y la migración neuronal. Así, el cortisol, uno de los productos finales de la respuesta de estrés, se ha propuesto como un indicador del estado de salud (Hellhammer et al., 2007) implicado en el procesamiento cognitivo (Adam y Kumari, 2009). De hecho, los niveles altos de cortisol se han asociado a un pobre rendimiento en memoria en personas sanas (Fonda, Bertrand, O'Donnell, Longcope y McKinlay, 2005; Lee et al., 2007) y en personas con trastornos emocionales (Hinkelmann et al., 2009; Rubinow, Post, Savard y Gold, 1984). Sin embargo, apenas existen estudios sobre su influencia en personas con epilepsia (Busch et al., 2012).

El estudio de los niveles de cortisol en esta población implica un reto en la medida en que diferentes factores como el tipo de tratamiento y la dosis de FAEs, el control de las crisis y el tipo de crisis, pueden interactuar con los niveles de esta hormona, generando efectos de confusión. A fin de conocer su impacto sobre la memoria, se considera de especial relevancia conocer qué se sabe acerca de los niveles de cortisol en personas con epilepsia, clarificando la influencia de dichos factores. El capítulo 2, en el que se incluye una revisión sistemática, pretende responder esta cuestión.

1.2.5. Influencia de la afectividad negativa

La afectividad negativa es un constructo referido a la tendencia estable a experimentar emociones negativas (Denollet y Pedersen, 2009; Watson y Clark, 1984). Así, las personas con alta afectividad negativa son más propensas a informar de disforia, ansiedad, irritabilidad y percepción de amenazas y castigos, y presentan una elevada predisposición a desarrollar un amplio espectro de patologías (Steptoe, Wardle y Marmot, 2005).

En contextos en los que la homeostasis del individuo se ve amenazada por estresores crónicos es frecuente encontrar aumentos en la afectividad negativa (Lazarus, 2006). En este sentido, cuando los acontecimientos son evaluados como amenazantes y se considera que superan la capacidad de afrontamiento del individuo, el sufrimiento emocional y el *arousal* fisiológico facilitan el desarrollo de una amplia variedad de emociones negativas (Lazarus,

2006). A su vez, la afectividad negativa puede tener repercusiones en la activación fisiológica, dando lugar a una relación bidireccional que favorece estados desadaptativos de salud. De hecho, en estudios recientes llevados a cabo por nosotros en otras poblaciones sometidas a estrés crónico, hemos encontrado que la afectividad negativa favorece el empeoramiento de la salud percibida, el aumento de la sintomatología somática y una respuesta amortiguada de estrés atendiendo a los niveles de cortisol (De Andrés-García, Cano-López, Moya-Albiol y González-Bono, 2016). En su conjunto, estos resultados son interpretados como una merma en el mecanismo adaptativo de estrés (De Andrés-García et al., 2016).

Las personas con epilepsia farmacorresistente podrían considerarse expuestas a una condición de estrés crónico, debido a la repetibilidad, incontrolabilidad e impredictibilidad de las crisis y a sus consecuencias en su procesamiento cognitivo y su la calidad de vida. La incontrolabilidad, la impredictibilidad y la generalización de las consecuencias de la enfermedad a diferentes ámbitos (familiar, laboral y afectivo) pueden situar a las personas con epilepsia en un contexto de indefensión aprendida. De hecho, más del 60% de personas con epilepsia presentan trastornos emocionales comórbidos (Gur-Ozmen, Leibetseder, Cock, Agrawala y von Oertzen, 2017; Kanner, 2016), con una alta prevalencia de ansiedad y depresión (Kwon y Park, 2014; Mensah, Beavis, Thapar y Kerr, 2007; Park, 2016). Estas alteraciones afectivas podrían ser el resultado de la epilepsia o de su tratamiento, compartiendo la misma fisiopatología subyacente a la epilepsia (Helmstaedter et al., 2014), por lo que el estudio de la afectividad negativa en esta población es especialmente relevante.

A pesar de ello, son escasos los estudios que evalúan el impacto de la depresión y de la ansiedad sobre la memoria en pacientes con epilepsia y, en general, muestran resultados inconsistentes. Algunos de ellos, han comparado el rendimiento mnésico de pacientes con alta o baja sintomatología depresiva. Siguiendo esta estrategia, Paradiso, Hermann, Blumer, Davies y Robinson (2001), en una muestra de 70 pacientes con ELT unilateral, hallaron que aquellos que tenían un diagnóstico de depresión mostraban peor rendimiento en memoria respecto a los que no padecían depresión. Aunque la incidencia de la depresión fue similar independientemente del hemisferio afectado, los efectos cognitivos adversos de la depresión fueron mayores en los pacientes con ELT izquierda (Paradiso et al., 2001). Sin embargo, siguiendo la misma estrategia de trabajo, Tracy et al. (2007a) no hallaron un efecto significativo del nivel de depresión sobre la memoria en 59 pacientes con ELT.

Otros estudios han analizado la asociación entre los niveles de ansiedad o depresión, como una variable continua, sobre la memoria. Helmstaedter, Sonntag-Dillender, Hoppe y Elger

(2004) hallaron una asociación negativa y significativa entre las puntuaciones en depresión y el rendimiento en tareas de memoria verbal y visual, pero únicamente en los pacientes con ELT lateral izquierda. Sin embargo, Miller et al. (2016b) no encontraron que el nivel de depresión fuera un predictor significativo del rendimiento mnésico en 38 pacientes con epilepsia, en su mayoría ELT. No obstante, sí que hallaron que mayores niveles de ansiedad-rasgo predecían significativamente un peor rendimiento en memoria visual (Miller et al., 2016b).

En la mayoría de los casos, se ha evaluado el impacto de la ansiedad o de la depresión sobre la memoria separadamente, lo que puede conducir a una pérdida de información relevante. El análisis de las relaciones de ambos factores con el rendimiento mnésico podría ofrecer una explicación más integrada de los aspectos afectivos y cognitivos en personas con epilepsia farmacorresistente. Además, sería de especial relevancia examinar si los niveles subclínicos de estas variables se relacionan con la ejecución mnésica, a fin de contrastar si estos factores pueden servir para detectar potenciales comorbilidades o diferencias individuales en la vulnerabilidad al estrés antes de adquirir la relevancia de síntomas clínicos.

2. Deterioro de la memoria y calidad de vida

La Organización Mundial de la Salud define la calidad de vida de un individuo como la percepción que una persona tiene de su posición en la vida, en el contexto de la cultura y del sistema de valores en los que vive y en relación con sus objetivos, expectativas, normas y preocupaciones (World Health Organisation Quality of Life Group, 1996). Siguiendo esta definición, la calidad de vida se entiende como un constructo amplio, que se ve afectado de manera compleja por la salud física, el estado psicológico, el nivel de independencia, las relaciones sociales, las creencias personales y su relación con las características más destacadas de su entorno.

En personas con epilepsia farmacorresistente, la exposición crónica a crisis epilépticas puede suponer un desafío, implicando ciertas demandas de adaptación que pueden comprometer su calidad de vida (Poochikian-Sarkissian, Wennberg, Sidani y Devins, 2007). Así, los pacientes con epilepsia farmacorresistente experimentan la mayor parte de la carga de la enfermedad (World Health Organization, 2014), ya que son más propensos a experimentar discapacidades asociadas, discriminación social, efectos secundarios de los FAEs y efectos colaterales de la cirugía (Jacoby y Baker, 2008).

Baker, Smith, Dewey, Jacoby y Chadwick (1993) propusieron un modelo de calidad de vida y salud en personas con epilepsia, que parte de una definición global de salud que incluye los dominios físico, social y psicológico (ver Figura 2). El dominio físico incluye aspectos como el estado de salud general, la frecuencia y la severidad de las crisis epilépticas (Baker et al., 1993). El dominio social incluye aspectos relacionados con las relaciones sociales, el trabajo y las finanzas personales (Baker et al., 1993). Finalmente, el dominio psicológico incluye una dimensión cognitiva (i.e., funcionamiento cognitivo general) y una dimensión emocional (i.e., afectividad negativa) (Baker et al., 1993). Este modelo proporciona un marco teórico para investigar las complejas interacciones entre las manifestaciones físicas, sociales y psicológicas de la epilepsia.

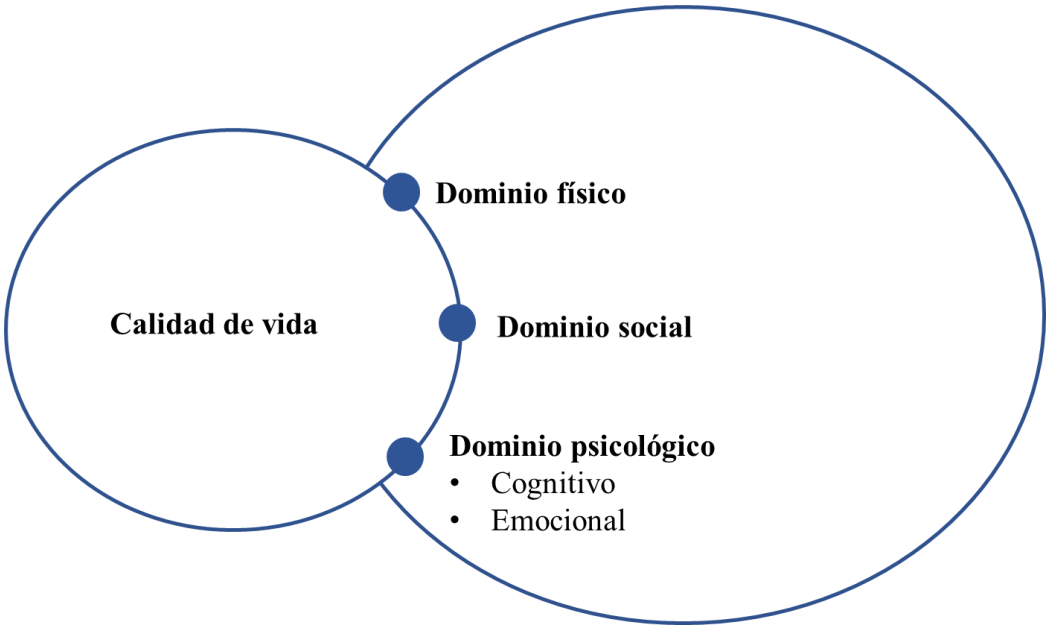

Figura 2. Modelo de calidad de vida en personas con epilepsia basado en la salud (Baker et al., 1993).

Cabe destacar que, hasta la fecha, la mayoría de los estudios sobre calidad de vida en personas con epilepsia se han centrado en factores específicos, principalmente relacionados con las crisis (Piperidou et al., 2008; Şenol, Soyuer, Arman y Öztürk, 2007; Akdemir, Sut y Guldiken, 2016), sin analizar de forma global la contribución relativa de otros factores físicos, sociales y psicológicos contemplados en el modelo propuesto por Baker et al. (1993).

Siguiendo dicho modelo (Baker et al., 1993), la memoria formaría parte de la dimensión cognitiva del dominio psicológico de la calidad de vida de personas con epilepsia. Las

alteraciones de memoria, al ser una de las quejas más frecuentes de pacientes con epilepsia (Helmstaedter, 2004; Thompson et al., 2016; Vingerhoets, 2006), podrían ser uno de los principales factores que contribuyen a la carga de esta enfermedad, perturbando su calidad de vida. El análisis del impacto del rendimiento en memoria sobre la calidad de vida facilitaría la toma de decisiones clínicas con estos pacientes, justificando, en su caso, la realización de programas de rehabilitación específicos. Sin embargo, son escasos los estudios centrados en el papel predictivo de la memoria sobre la calidad de vida de estos pacientes, mostrando resultados inconsistentes. Giovagnoli y Avanzini (2000) hallaron que la percepción del funcionamiento mnésico, pero no el rendimiento mnésico objetivo, tenía un impacto significativo en la calidad de vida de pacientes con ELT. Sin embargo, Perrine et al. (1995) mostraron que el rendimiento en memoria verbal era un predictor significativo de la calidad de vida en una muestra variada de pacientes con epilepsia farmacorresistente y pacientes con epilepsia controlada con fármacos. En estos estudios, además de la memoria, se analizó el papel predictivo de otro factor psicológico, la afectividad negativa, pero no el impacto de factores físicos no directamente relacionados con las crisis epilépticas (i.e., el estado de salud general) ni de factores sociales (Giovagnoli y Avanzini, 2000; Perrine et al., 1995).

Hasta donde sabemos, no se ha analizado de forma global la contribución relativa de factores psicobiológicos y sociales, incluyendo variables cognitivas como la memoria, en una misma muestra formada exclusivamente por pacientes con epilepsia farmacorresistente. Este enfoque permitiría clarificar el impacto de estos factores en la calidad de vida y detectar perfiles asociados a alto riesgo de experimentar una calidad de vida pobre. A su vez, el estudio de los factores presentados en el apartado 1.2. de esta Tesis (i.e., la morfología del hipocampo a lo largo de su eje anterior-posterior, el patrón de activación funcional durante el procesamiento cognitivo, la edad en el momento de la cirugía del lóbulo temporal, los niveles de cortisol y la afectividad negativa), cuya relación con la memoria permanece sin esclarecer, podría ser muy relevante en esta población, en la medida en que estarían potencialmente asociados con la calidad de vida, que es el objetivo terapéutico final en estos pacientes.

CHAPTER 2

Cortisol levels and seizures in adults with epilepsy: a systematic review [1]

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Como se ha expuesto anteriormente, la epilepsia podría ser considerada como un modelo de estrés crónico en seres humanos, por lo que el estudio de los niveles de cortisol en esta población es especialmente relevante. Diferentes factores pueden interactuar con los niveles de esta hormona en personas con epilepsia, produciendo efectos de confusión. En este capítulo se presenta una revisión sistemática sobre los niveles de cortisol en personas con epilepsia, describiendo los datos existentes en la literatura sobre niveles de cortisol en condiciones basales y en situaciones estresantes como crisis o manipulaciones experimentales.

1. Introduction

Epilepsy is one of the most common neurological diseases, affecting more than 70 million people worldwide (Thijs et al., 2019). According to available data from 2013, 2750 sudden unexpected deaths of patients with epilepsy were counted in the United States, and 3994 in the European Union (Beghi, 2016). Individuals with epilepsy are predisposed to spontaneous, unpredictable, and uncontrollable seizures with numerous neurobiological, cognitive, psychological, and social consequences (Fisher et al., 2014). Memory and executive function impairments and anxiety and depression are some of these consequences, which can be accompanied by social stigma (McKee & Privitera, 2017) and alterations in patients' daily functionality and quality of life (Cano-López, Hampel, Garcés, Villanueva, & González-Bono, 2018b). Although pharmacological or surgical approaches can have side effects, most patients achieve adequate seizure control with antiepileptic drugs (AEDs) or surgery (Cano-López et al., 2017).

Available data point to a relationship between stress and seizures in humans. In fact, patients commonly report in their narratives that acute stress episodes are a trigger for seizures (Lang, Taylor, & Kasper, 2018; Novakova, Harris, Ponnusamy, & Reuber, 2013). Relationships between perceived daily stress and seizure records have also been described (Allendorfer & Szaflarski, 2014; Gunn & Baram, 2017; Joëls, 2009; McKee & Privitera, 2017; van Campen, Janse, de Graan, Braun, & Joels, 2014). Neuroimaging studies show that stress induces metabolic changes in the prefrontal cortex, limbic system, and basal ganglia, among other regions that have receptors for stress hormones (Pruessner et al., 2010). In this regard, limbic network reorganization can be directly involved in the generation of seizure activity (Bonilha et al., 2013), which has been made evident by the efficacy of temporal lobectomy in controlling seizures in drug-resistant epilepsy (Cano-López et al., 2017). However, the mechanisms underlying the stress-seizures interaction are not completely clear.

Two data corpuses can help to clarify the interaction between stress and epilepsy and determine the key underlying mechanisms. First, animal studies use epilepsy models to provide useful data through different degrees of manipulation of the involved variables. Second, in order to gain ecological validity, data have been obtained from studies with epilepsy patients from the perspective of stress, considering seizures to be acute stressors in the context of epilepsy as a chronically stressful setting.

From the first perspective, animal studies strongly suggest that the facilitating effect of stressful events on seizures could be associated with increases in glucocorticoid levels (Kanner, 2017), which enhance cortical hyperexcitability, directly or through their effects on serotonin, glutamate, and GABA levels (Kovac & Walker, 2013). In fact, stress-induced increases in glucocorticoids can contribute to the severity of the epileptic phenotype in a genetic model for absence epilepsy (Tolmacheva, Oitzl, & van Luijtelaar, 2012). Moreover, corticosterone increases associated with early-life stress and amygdala kindling significantly contribute to epileptogenesis in animal models of epilepsy (Desgent et al., 2012; Taher, Salzberg, Morris, Rees, & O'Brien, 2005). The timing of stress appears to be relevant in the potential epileptogenic role of glucocorticoids. Thus, in an interesting study by Maggio, Shavit Stein, and Segal (2017), stress and pilocarpine (a status epilepticus inducer) exert differential effects on hippocampus-dependent long-term potentiation, depending on the administration time. Thus, stress before pilocarpine injection can play a protective role in cognitive performance, with transient increases in corticosterone levels, whereas stress after pilocarpine can exacerbate its effect, producing long-term increases in glucocorticoids and impairing cognitive performance (Maggio et al., 2017). This long-term role of stress in hippocampus-dependent learning points to mineralocorticoid (MR) or glucocorticoid (GR) receptors as mediators of the stress-epilepsy-learning interaction. In turn, long-term reorganization of the key neural network may result in abnormal, increased stress responses to new acute challenges (Wulsin et al., 2018), compromising its adaptive value. In mice, pilocarpine-induced epilepsy is related to profound alterations in brain circuits responsible for the control of stress reactivity, resulting in exaggerated glucocorticoid secretion in response to acute stress (Wulsin et al., 2018). This animal model of epilepsy also increases anxiety- and depression-like behavior (Wulsin et al., 2018), which is consistent with the high prevalence of anxiety and depression comorbidity in patients with epilepsy.

Although the underlying mechanisms are not completely clear, MR and GR activation in the limbic system is crucial. In the hippocampus, the increase in stress-induced corticosterone enhances neuronal excitability by means of MR receptors, which have an important inhibitory role in the stress response and are frequently compromised in temporal lobe epilepsy (TLE) (Gunn & Baram, 2017). In this regard, increases in the frequency of excitatory postsynaptic currents in the dentate gyrus granule and Cornu Ammonis (CA)1 pyramidal cells, and decreases in the frequency of spontaneous inhibitory postsynaptic currents in CA1 pyramidal cells, have been described (Gunn & Baram, 2017). In the amygdala, amygdala kindling enhances

corticosterone levels through the activation of MR and GR receptors (Szafarczyk et al., 1986; Smith et al., 1991). Thus, the interaction between these mechanisms mediates the effects of stress hormones on neural tissue.

From the second perspective, in humans, an approach that could help to clarify the possible overlapping effects of the stress-seizure interaction would be to consider a seizure as an acute stressor in itself, within the framework of epilepsy as a potentially chronic state. Thus, both stress and seizures would be capable of modifying cortisol levels. The stress process has been widely defined, with several nuances and sometimes certain ambiguity. In general, stress is defined as a process in which an individual perceives that the demands exceed the regulatory capability of the organism to adapt to a psychological or physiological challenge or stressor. From a restrictive view, Koolhaas et al. (2011) reported that the term stress should only be used when challenges are unpredictable, uncontrollable, and life-threatening. One of the final products of the acute physiological and emotional stress response are glucocorticoid levels, which are rapidly hypersecreted within 15-30 min after the onset of the challenge in animals (corticosterone) and humans (cortisol). Thus, the hypothalamus-pituitary-adrenal (HPA) axis is driven by neurons that release the corticotropin-releasing factor (CRF) into circulation upon stress activation, resulting in a release of the adrenocorticotropic hormone (ACTH), which activates the synthesis and release of cortisol by the adrenal gland cortex (Charmandari, Tsigos, & Chrousos, 2005). In turn, cortisol is able to reduce the activity of the HPA axis through a negative feedback mechanism that involves the action of glucocorticoids on several neural targets, including the hypothalamus, prefrontal cortex, hippocampus, and amygdala (Charmandari et al., 2005). Thus, among other loci, the integrity of the limbic system, which involves key regions for cognitive and emotional processing, is required for the effective termination of the stress response (Charmandari et al., 2005). For this purpose, limbic structures contain MR receptors, which respond to low concentrations of glucocorticoids, and GR receptors, which respond to both basal and stress concentrations of cortisol, and during the circadian cortisol peak (Charmandari et al., 2005).

Time is a relevant variable in stress processes. Prolonged exposure to stressors or high repeatability of the stressors throughout prolonged periods may result in states of chronic stress. Prolonged exposure to stress has been associated with hypersecretion of baseline glucocorticoids as a result of an increase in the central tone of the HPA axis and a reduction in the efficacy of glucocorticoid negative feedback in central key regions such as the limbic network (Jankord & Herman, 2008). Moreover, alterations in the diurnal cortisol profile have

been proposed as an indicator of maladaptation of the neuroendocrine processes, especially in chronic stress states (Chida & Steptoe, 2009; Clow, Thorn, Evans, & Hucklebridge, 2004; Fries, Dettenborn, & Kirschbaum, 2009; Kudielka & Wüst, 2010). Interestingly, prolonged elevations of glucocorticoids are known to remodel and potentially injure limbic networks, sculpting dendrites and synaptic connections in many brain regions, including the hippocampus, amygdala, and medial prefrontal and orbitofrontal cortex (McEwen, 2007, McEwen, Nasca, & Gray, 2016). Furthermore, this HPA hyperactivation has been related to memory impairments and anxiety-like and depression-like behaviors in general and clinical populations, predisposing individuals to stress-related psychopathologies (Drexler & Wolf, 2017; de Quervain, Schwabe, & Roozendaal, 2017; Weger & Sandi, 2018).

Epilepsy is a disease that produces a long-term burden, as redefined in the position paper of the International League Against Epilepsy (ILAE; Fisher et al., 2014). Considering that this condition is potentially stressful, it seems likely that shifts in network excitability may result in or contribute to enhanced seizure susceptibility stemming from nonlinear interactions between cortisol levels and other stress mediators (Kovac & Walker, 2013). The mechanisms, which are not yet fully understood, may stem from the temporal integration of stress-induced alterations in intrinsic neuronal properties, or influence the network as a whole or unbalance excitatory and inhibitory transmission at specific hippocampal nodes (Gunn & Baram, 2017).

Considered as a whole, the study of cortisol levels in patients with epilepsy is a challenge because factors such as the type and dose of AEDs and the frequency and type of seizures could interact with the levels of this hormone and produce confused effects. In addition, it has been suggested that different types of epilepsy require different treatments, influencing hormonal levels in different ways (Luef & Rauchenzauner, 2009). The way AEDs increase or decrease cortisol levels could help to explain, at least in part, the mechanisms underlying individual differences in people with epilepsy. The study of these factors also raises the opportunity to examine the acute and chronic stress involved in epilepsy. In this regard, it is noteworthy that methodological advances in stress research, such as the consolidation of non-invasive sampling procedures or the development of validated protocols to study the stress response in humans, have rarely been implemented in studies with people with epilepsy.

Thus, the aim of this systematic review was to discover what it is known about cortisol levels in adult patients with epilepsy, in order to clarify potential underlying mechanisms involved in seizure susceptibility. For this purpose, available data on cortisol levels are

collected, first in basal conditions, and second in stressful situations such as seizures or experimental manipulations. Clinical data and pharmacological treatments are also specified because they could contribute to explaining the variability in the results of different patients.

2. Material and methods

2.1. Data sources and searches

This review was conducted and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher, Liberati, Tetzlaff, & Altman, 2009). The present review was registered in PROSPERO on May 31, 2018 (CRD42018096066).

The search was performed in the PsycINFO, PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane Library databases on April 18, 2018. The following keywords were used for a Boolean search: (epilepsy * OR seizure * OR convulsion) AND cortisol. These keywords were examined in both the "title and abstract" sections, as well as the "Medical Subject Heading (MeSH)". The search was limited in terms of the type of document, as only peer-reviewed journal papers were included. However, the search was not limited in terms of date or age. Although this review was focused on studies of cortisol levels in adults with epilepsy, limiting age a priori could exclude articles with samples of young participants (including children and adolescents). In addition, an inverse search was carried out by examining the reference lists of the reviews and empirical studies to identify articles not indexed in these databases.

2.2. Eligibility

The inclusion criteria were the following: (1) original and empirical articles published in peer-reviewed journals; (2) studies including adult people with a diagnosis of epilepsy; (3) data from patients with epilepsy separated from other groups of patients included in the study; (4) cortisol levels as a dependent variable; (5) human participants; and (6) English language.

The exclusion criteria were the following: (1) mixed data on people with epilepsy and other groups of patients; (2) exclusively including patients with psychogenic non-epileptic seizures (PNES); (3) single-case studies, reviews, meta-analyses, editorials, or conference abstracts; (4)

pharmacological approaches that directly involve changes in endocrine levels; (5) including HPA axis hormones other than cortisol; (6) endocrine disorders without a diagnosis of epilepsy, such as primary diabetes, Cushing or Addison syndromes, congenital adrenal hyperplasia, or adrenal insufficiency; and (7) psychiatric disorders without a diagnosis of epilepsy. Studies were not excluded due to other premorbid conditions, the etiology of epilepsy, or treatment with AEDs.

2.3. Study selection

The two authors (EGB and ICL) independently assessed titles and abstracts for possible agreement with the inclusion criteria. The few discrepancies (two abstracts) were resolved through critical discussion until 100% agreement was reached. Following this, each researcher individually assessed the full text of the articles selected to determine whether they met the inclusion criteria. Studies failing to meet the inclusion criteria were excluded, with reasons for exclusion listed in Figure 1.

2.4. Data extraction

Data from eligible studies were extracted by two reviewers (EGB and ICL) independently and imputed to four custom tables. The extracted data included: (1) reference; (2) sample groups (i.e., patients with epilepsy, healthy controls, PNES); (3) sex; (4) mean age; (5) epilepsy type or semiology; (6) seizure frequency; (7) experimental treatment (if applicable); (8) AEDs; (9) cortisol fluid; (10) time after event; and (11) cortisol results.

2.5. Data synthesis

Data extracted from the included articles were divided into four categories: (1) studies examining basal cortisol levels; (2) articles focused on the effects of different AEDs on cortisol levels; (3) articles focused on seizure effects on cortisol levels; and (4) studies considering perceived stress or stress manipulation effects on cortisol levels.

3. Results

3.1. Literature search (Figure 1)

The initial search yielded a total of 1328 articles, with 571 articles remaining after eliminating the duplicates. Of the 84 articles reviewed in full, 44 were excluded for different reasons: inclusion of children and adolescents exclusively (n = 17); inclusion of people with PNES exclusively (n = 7); molecular approximation without cortisol data (n = 4); theoretical articles (n = 2); no specific epilepsy data (n = 4); single-case studies (n = 2); endocrine manipulation (n = 6); no cortisol data (n = 2); full text unavailable (n = 1). Thirty-nine articles were initially included in the review. However, the study by Upton et al. (1987) included six patients who were exposed to electrical stimulation in the anterior nuclei of the thalamus, with cortisol levels only available for two patients. As cortisol data from this study did not significantly contribute to the aim of the review, this article was deleted. Thus, thirty-eight articles were included in the review and marked with the symbol (*) in the references section.

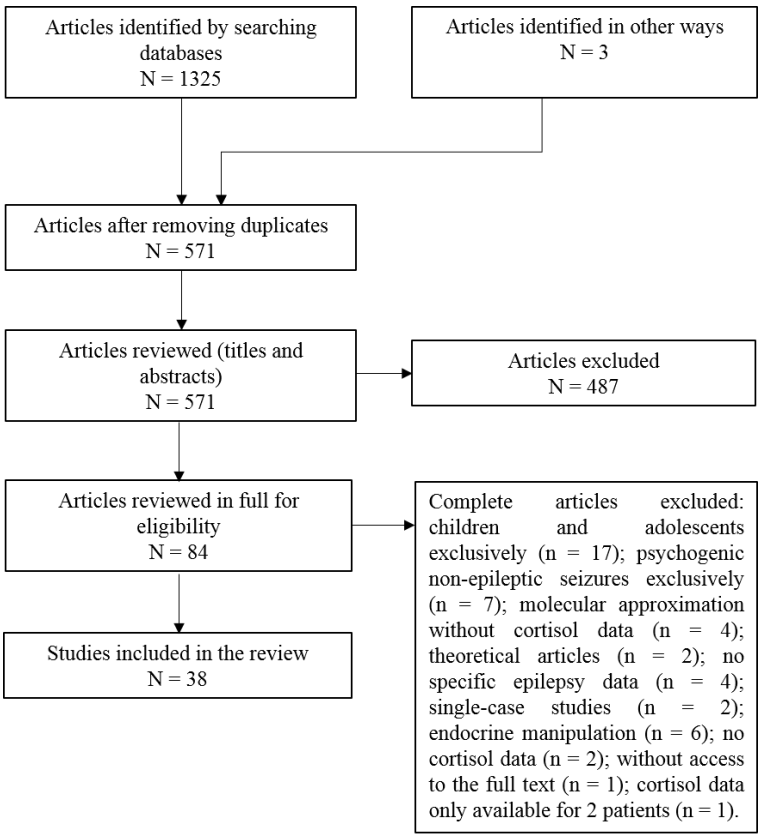

Figure 1. Flow of the identification and selection of studies.

3.2. Studies examining basal cortisol levels (Table 1)

Fourteen studies examined basal cortisol levels (37% of the total sample). To analyze differences in cortisol levels between people with epilepsy and other populations, seven of the 14 studies (50%) included a control group of healthy participants (Afifi et al., 2011; Bakvis, Spinhoven, & Roelofs, 2009; Cavallo, Moore, Nahori, Beaumanoir, & Sizonenko, 1984; Gallagher, Murvin, Flanigin, King, & Luney, 1984; Galli et al., 1996; Majoie et al., 2011; Molaie, Culebras, & Miller, 1987), and one study included a group of patients with PNES as a control group (representing 7% of the studies in this section) (Novakova, Harris, & Reuber, 2017). However, six studies (43%) did not include other populations as a control group (Bauer, Stoffel-Wagner, Flugel, Kluge, & Elger, 2000a; Bauer et al., 2000b; Busch et al., 2012; Calabrese et al., 1993; Devinsky, Emoto, Porter, Theodore, & Nadi, 1991; Laakso, Leinonen, Hätönen, Alila, & Heiskala, 1993).

Two of the 14 studies (14%) established comparisons between subgroups of patients with epilepsy based on different factors, such as their prognosis (Calabrese et al., 1993) or their quality of sleep (Laakso et al., 1993).

Three studies (making up 21% of the studies in this section) examined changes in basal cortisol levels after surgery (Bauer et al., 2000a, 2000b; Gallagher et al., 1984), and one study (7%) examined cortisol levels after a 28-week treatment with vagus nerve stimulation (VNS) (Majoie et al., 2011).

Only four studies (29% of the studies in this section) focused on the relationships between cortisol levels and cognitive-emotional factors, the relationships between cortisol levels and verbal and visual memory, as well as trait anxiety (Busch et al. al., 2012), antisocial behavior and depression (Afifi et al., 2011; Devinsky et al., 1991), or perceived stress (Novakova et al., 2017).

Table 1. Summary of the results of the studies examining basal cortisol levels in people with epilepsy.

Reference	Sample	Sex	Mean age in years (range)	Epilepsy type, semiology	Seizure frequency (monthly)	Experimental treatment	AEDs	C fluid	Time after event	C results
Afifi et al. (2011)	EG1: 20 E + depression EG2: 20 E CG: 20 healthy	60♂	X = 30.5-34 SD = 10.62-12.48	EG1: 10 TCS, 10 CPS EG2: 10 TCS, 10 CPS	ne	__	No AEDs	serum	9:00 a.m.	EG1 > EG2 > CG
Bakvis et al. (2009)	EG: 17 E CG1: 19 PNES CG2: 20 healthy	EG: 11♀, 6♂ CG1: 15♀,4♂	EG: X = 42.4; SD = 12.9 CG1: X = 27.6; SD = 7.3 CG2: X = 22.1; SD = 4.2	11 TLE, 3 FLE, 2 undefined, 1 PGE	ne	Emotional stroop	9 CBZ, 6 VPA, 1 CBZ + clobazam, 1 no AEDs	saliva	ne, basal	n.s.d.
Bauer et al. (2000a)	EG: 16 E	16♀	X = 31.6 (21–42)	TLE (10 LTLE, 6 RTLE)	50% seizure-free after surgery	Surgery	10 CBZ, 6 CBZ + 1 ne	serum	8:00 a.m. – 10:00 a.m.	n.s.d. before-after surgery
Bauer et al. (2000b)	22 focal E	22 ♂	X = 34.9 (25–48)	20 TLE (10 LTLE, 10 RTLE), 2 others Seizures: 9 CPS, 6 SPS + CPS + TCS, 3 SPS + CPS	63.6% seizure-free after surgery	Surgery	CBZ	serum	8:00 a.m. – 10:00 a.m.	n.s.d. before-after surgery n.s.d. by side of seizure focus
Busch et al. (2012)	EG: 24 E	Ne	X=39.71; SD=11.56 (20-61)	RTLE=11 LTLE=12 Bilateral TLE=1	ne	__	ne	saliva	00:00 a.m.	Corr. –: long-term verbal and visual memory Corr. +: trait anxiety
Calabrese et al. (1993)	EG: 27 E EG1: 16 good prognosis EG2: 11 poor prognosis	EG1: 7♀, 9♂ EG2: 5♀, 6♂	EG1: X=57.9 (19-80) EG2: X=62.5 (25-74)	Symptomatic or idiopathic seizures, duration greater than 30 minutes, non-convulsive	ne	__	yes, ne	serum	ne, 12 hours seizure-free	EG2 > EG1 Normal levels after seizures ↑ C in 13 of 27 patients (n.s.d.)
Cavallo et al. (1984)	EG: 19 E CG: 12 healthy	EG: 7♀, 12♂ CG: 12♂	EG: X (♀)= 13.3 (7-20) EG: X(♂)= 17.3 (9-34) CG: ne (12-21)	10 CPS, 6 TCS, 3 SPS	ne	__	yes, 10 VPA, 1 PHT, 1 PHT + PB, 1 CBZ + VPA + DZP, 6 no AEDs	serum	8:00 p.m., 12:00 p.m., 4:00 a.m., 8:00 a.m.	n.s.d. C profile n.s.d. EG vs CG n.s.d. VPA treatment
Devinsky et al. (1991)	EG: 19 E	13♂, 6♀	X = 30.7 (21-42)	Drug-resistant, CPS, 9 LH, 4 RH, 6 bilateral	ne	__	2 none, 9 CBZ, 1 PHT, 7 CBZ+PHT	CSF	7:00 a.m. – 9:00 a.m.	Corr. +: antisocial behavior and depression
Gallagher et al. (1984)	EG: 18 E (7 pre- and 11 post-surgery) CG: 9 healthy	EG: 6♂, 1♀ CG: 5♂, 4♀	EG: X= 28; SEM = 3.4 (24-34) CG: X= 32; SEM = 9.6 (23-48)	TLE, 1 FLE	ne	11 surgery	PHT, CBZ, PB, VPA, PMD, ethosuximide, CLZ, methsuximide	serum	2:00 p.m. – 4:00 p.m.	C average concentration and secretion ratio: EG > GC

Table 1. Continued.

Reference	Sample	Sex	Mean age in years (range)	Epilepsy type, semiology	Seizure frequency (monthly)	Experimental treatment	AEDs	C fluid	Time after event	C results
Galli et al. (1996)	EG: 15 E CG: 15 healthy	30 ♀	EG: X= 33.7 (18-50) CG: X= 33 (25-46)	TLE	ne	__	More than 1 AED	plasma	ne	n.s.d.
Laakso et al. (1993)	EG: 16 E	9♀, 7♂	ne (8-45)	Lennox-Gastaut	ne	sleep problems	Polytherapy 2/3 CBZ, CLZ, DZP, PB, PHT, VPA	saliva	ne, 2 h in 2 days	n.s.d. rhythm
Majoie et al. (2011)	EG: 11 E CG: 11 healthy	EG: 6♂, 5♀ CG: 6♂, 5♀	EG: X= 30 (12-58) CG: X= 28 (10-64)	Drug-resistant E. 4 SE, 1 GE	ne	VNS	5–15, ne	plasma	ne, pre- and 28 weeks after	C: EG > CG VNS: EG ≈ CG
Molaie et al. (1987)	EG: 15 E CG: 5 healthy	EG: 15♂ CG: 5♂	EG: X= 39 CG: X= 52	7 TLE (4 CPS + PSSG and 3 CPS), 2 FLE (CPS + PSSG), 1 OLE (CPS), 5 bilateral (PGE)	ne	__	11 PHT monotherapy or combined with another AED	plasma	11:30 p.m. – 6:30 a.m.	n.s.d.
Novakova et al. (2017)	EG: 22 E CG: 33 PNES	EG: 13♀, 9♂	X=39.0; SEM=16.1	14 focal, 1 generalized idiopathic, 7 unclassified	15.2 (24.2)	__	5 AEDs monotherapy, 16 AEDs polytherapy, 7 anxiolytics / antidepressives, 8 others, 1 none	saliva	ne, morning and night	No corr. C and perceived stress. n.s.d. EG vs CG

Abbreviations. AEDs = antiepileptic drugs; C = cortisol; CBZ = carbamazepine; CG = control group; CLZ = clonazepam; corr. = correlation; CPS = complex partial seizures; CSF = cerebrospinal fluid; DZP = diazepam/nitrazepam; E = epilepsy; FLE = frontal lobe epilepsy; G = group; GE = generalized epilepsy; LH = left-hemisphere; LTLE = left temporal lobe epilepsy; ne = not specified; n.s.d.= no significant differences; OLE = occipital lobe epilepsy; PB = phenobarbital; PGE = primary generalized epilepsy; PHT = phenytoin; PMD = primidone; PNES = psychogenic non-epileptic seizures; PSSG = partial seizures with secondary generalization; RH = right-hemisphere; RTLE = right temporal lobe epilepsy; SE = secondary epilepsy; SPS = simple partial seizures; TCS = tonic-clonic seizures; TLE = temporal lobe epilepsy; VNS = vagus nerve stimulation; VPA = valproic acid.

3.3. Studies related to pharmacological aspects of epilepsy (Table 2)

Eight studies focused on the effects of different AEDs on cortisol levels (21% of the total sample). Among them, four studies employed monotherapy treatments, making up 50% of the studies (Hill et al., 2011; Isojrvi, 1990; Marek et al., 2010; Ostrowska, Buntner, Rościszewska, & Guz, 1988), and the remaining four used polytherapy (50% of the studies in this section) (Beastall, Cowan, Gray, & Fogelman, 1985; Galimberti et al., 2005; Morimoto, Hashimoto, Kitaoka, & Kyotani, 2018; Rozza, Marcolla, & Ferrari, 1987). All the studies, except for those by Morimoto et al. (2018), included a control group to compare cortisol levels of people with epilepsy treated with different AED types and healthy people.

With regard to the AED type, four studies (50%) administered carbamazepine, two of them in monotherapy (Isojrvi, 1990; Marek et al., 2010), one in polytherapy (Rozza et al., 1987), and one in a mixed sample of patients treated with monotherapy or polytherapy (Galimberti et al., 2005). Four studies (50%) administered phenytoin, one in monotherapy (Ostrowska et al., 1988), one in polytherapy (Morimoto et al., 2018), and two including both types of treatment (Beastall et al., 1985; Galimberti et al., 2005). Thus, Beastall et al. (1985) studied a group of women treated with phenytoin monotherapy and a group of men treated with phenytoin and phenobarbital, whereas Galimberti et al. (2005) included 56 patients treated with phenytoin or another enzyme-inducing drug monotherapy and 44 patients who received AED polytherapy. In the case of phenobarbital, four studies used this AED (making up 50% of the studies), three of them in polytherapy (Beastall et al., 1985; Morimoto et al., 2018; Rozza et al., 1987) and one including both types of treatments (Galimberti et al., 2005). Three studies administered lamotrigine (38% of the studies in this section), one in monotherapy (Hill et al., 2011), one in polytherapy (Morimoto et al., 2018), and one with both types of treatments (Galimberti et al., 2005). Other AEDs such as oxcarbazepine, primidone, valproic acid, clonazepam, and levetiracetam were included in two studies (Galimberti et al., 2005; Morimoto et al., 2018). Galimberti et al. (2005) analyzed differences in cortisol levels between patients treated with enzyme inducing AEDs (phenobarbital, carbamazepine, oxcarbazepine, phenytoin, and primidone) and patients treated with non-enzyme inducing AEDs (valproic acid and lamotrigine). Morimoto et al. (2018) examined differences in cortisol levels, comparing patients treated with newer AEDs (clonazepam, lamotrigine, and levetiracetam) combined with conventional AEDS (valproic acid, phenobarbital, and phenytoin) and patients treated with conventional AEDs alone.

Five studies (63% of the studies in this section) were cross-sectional and did not measure cortisol prior to AED treatment (Beastall et al., 1985; Galimberti et al., 2005; Hill et al., 2011; Marek et al., 2010; Rozza et al., 1987). The remaining three studies (38%) were longitudinal. Two studies included cortisol measurements before AED treatment and compared them to a control group of healthy people (Isojrvi, 1990; Ostrowska et al., 1988). One study included cortisol measurements prior to the initiation of newer AEDs in the group receiving treatment with newer AEDs in addition to conventional AEDs, but without a control group of healthy people (Morimoto et al., 2018).

Table 2. Summary of results of studies examining AEDs effects on cortisol levels in people with epilepsy.

Reference	Sample	Sex	Mean age in years (range)	Epilepsy type, semiology	Seizure frequency	Experimental treatment	AEDs	C fluid	Time after event	C results
Beastall et al. (1985)	EG: 21 E CG: 20 healthy	EG: 10♀,11♂ CG: 10♀,10♂	♀: X = 39.3 (21-58) ♂: X = 40.3 (21-63)	ne	ne	PHT + PB	♀: PHT ♂: PHT + PB	serum	2:00 p.m. – 4:00 p.m.	♀: EG < CG ♂: n.s.d.
Galimberti et al. (2005)	EG: 113 E CG: 30 healthy	EG:113♀ CG: 30♀	EG: X = 28.1; SD = 8 (16–47) CG: X = 28.3; SD = 8.5 (19–47)	40 PGE 68 PE 5 undefined	X: one seizure monthly or less	EIAED and NEIAED	56 EIAED: PB, CBZ, OXC, PHT or PMD 13 NEIAED: VPA, LTG 44 polytherapy	serum	8:00 a.m. and 9:00 a.m.	Baseline: EG > CG n.s.d. C in severe E than in E without seizures Corr. + C and seizure frequency n.s.d. EIAED vs NEIAED
Hill et al. (2011)	EG: 11 E CG: 11 healthy	EG: 11♀ CG: 11 ♀	EG: X= 28 (24-31) CG: X= 28 (26-31)	4 focal 7 generalized	1 year seizure-free	LTG	LTG	serum	ne, morning	EG < CG in luteal phase n.s.d. in follicular phase
Isojrvi (1990)	EG1: 10 E short-term CBZ EG2: 13 E long-term CBZ CG**:** 17 healthy	EG1: 10♀ EG2: 13♀ CG: 17♀	EG1: X=25.7 (16.0-37.2) EG2: X=32.7 (23.6-45.1) CG: X=30.8 (20.8-42.8)	EG1: 6 PGE, 4 EP, 8 EI, 2 ES EG2: 5 PGE, 8 EP, 11 EI, 2 ES	> 2 GTCS or partial seizures per year	CBZ	CBZ	serum	08:00 a.m. fast	n.s.d. C after CBZ Basal C: n.s.d.
Marek et al. (2010)	EG: 17 E CG: 6 healthy	EG: 14♂, 3♀ CG: ne	EG: X = 31.8; SEM=10.8	CPS and TCS	Weekly frequency or annual frequency	CBZ	CBZ (300–1800 mg/day)	plasma	8:00 a.m., 2:00 p.m., 8:00 p.m., 02:00 a.m.	EG > GC, independently seizure frequency and duration
Morimoto et al. (2018)	EG1: 23 E new AEDs EG2: 21 E convenitonal AEDs	EG1: 16♂,7♀ EG2: 14♂,7♀	EG1: X = 26.5; SD = 7.3 EG2: X = 29.8; SD = 8.3	SE, severe intellectual and motor disability	ne	Conventional AEDs vs newer AEDs	Newer AEDs: CLZ, LTG, LEV Conventional AEDs: VPA, PHT, PB.	plasma	6:00 a.m. fast	Newer AEDs: ↓ C Newer AEDs: corr. - C and albumin
Ostrowska et al. (1988)	EG: 45 E CG: 45 healthy	EG: 45 ♂ CG: 45 ♂	EG: X = 32.4; SD = 8.6 (20-49) CG: X = 39.1; SD = 9.1 (20-49)	24 PGE, 21 SE (PGS o PSSG, TCS), 9 TLE (2 TCS)	ne, pre-treatment	PHT	PHT (200-300 mg/day)	serum	8:00 a.m. – 9:00 a.m.	Pre-treatment.: EG < CG 3 and 6 months after treatment onset: ↓ 12 months after treatment onset: C similar to baseline
Rozza et al. (1987)	EG: 15 E CG: 37 ne	EG: 15 ♂ CG: 37 ♂	EG: X= ne (21 – 35) CG: X = 24	Focal (8 PSSG, 1 SPS, 6 CPS)	ne	PB (40 mcg/ml) + CBZ (I0 mcg/ml) 1-5 years	PB (40 mcg/ml) + CBZ (I0 mcg/ml) 1-5 years	plasma	8:00 a.m. – 9:00 a.m., 5:00 p.m.	EG > CG EG > variability CG No corr. treatment duration

Abbreviations. AEDs = antiepileptic drugs; C = cortisol; CBZ = carbamazepine; CG = control group; CLZ = clonazepam; corr. = correlation; CPS = complex partial seizures; E = epilepsy; EIAED = enzyme inducer AEDs; FLE = frontal lobe epilepsy; G = group; IE = idiopathic epilepsy; LEV= levetiracetam; LTG = lamotrigine; ne = not specified; NEIAED = non-enzyme inducer AEDs; n.s.d.= no significant differences; OXC = oxcarbazepine; PB = phenobarbital; PE = partial epilepsy; PGE = primary generalized epilepsy; PGS= primary generalized seizures; PHT = phenytoin; PMD = primidone; PSSG = partial seizures with secondary generalization; SE = secondary epilepsy; SPS = simple partial seizures; TCS = tonic-clonic seizures; TLE = temporal lobe epilepsy; VPA = valproic acid.

3.4. Studies examining the effects of seizures (Table 3)

Although the classification of seizures has recently been revised by the ILAE (Fisher et al., 2017), we maintained the nomenclature of the studies in this review to more accurately reflect the authors' descriptions.

Thirteen studies examined cortisol levels during seizures (34% of the total sample) (Abbott, Browning, & Davidson, 1980; Aminoff, Simon, & Wiedemann, 1984; Bazil, Short, Crispin, & Zheng, 2000; Culebras, Miller, Bertram, & Koch, 1987; Devinsky, Emoto, Nadi, & Theodore, 1993; Gallagher, Flanigin, King, & Littleton, 1987; Pritchard, Wannamaker, Sagel, Nair, & DeVillier, 1983; Pritchard, Wannamaker, Sagel, & Daniel, 1985; Rao, Stefan, & Bauer, 1989; Stoffel-Wagner et al., 1998; Takeshita, Kawahara, Nagabuchi, Mizukawa, & Hazama, 1986; Tuveri et al., 2008; Zhang & Liu, 2008), but differed in methodological factors related to sampling procedures. Nine studies (making up 69% of the studies in this section) examined serum cortisol levels (Abbott et al., 1980; Gallagher et al., 1987; Pritchard et al., 1983; Pritchard et al., 1985; Rao et al., 1989; Stoffel-Wagner et al., 1998; Takeshita et al., 1986; Tuveri et al., 2008; Zhang & Liu, 2008); two studies (15% of the studies in this section) analyzed plasma cortisol levels (Aminoff et al., 1984; Culebras et al., 1987); one study (8%) examined cortisol in cerebrospinal fluid (Devinsky et al., 1993); and the remaining study (8%) analyzed salivary cortisol (Bazil et al., 2000). Additionally, the time of sample collection was different in each study (see Table 3).

Table 3. Summary of results of studies examining the effects of seizures on cortisol levels.

Reference	Sample	Sex	Mean age in years (range)	Epilepsy type, semiology	Seizure frequency (monthly)	AEDs	C fluid	Time after event	C results
Abbott et al. (1980)	EG1: 5 E EG2: 26 E CG: 4 healthy	EG1: 4♂, 1♀ EG2: 16♂, 10♀ CG: 4♂	EG1: X = 33.2 (19-78) EG2: ne CG: ne	EG1: Grand mal EG2: ne	ne	ne	serum	+30, 60 and 120 min 9:00 a.m. – 6:00 p.m.	EG2 > CG
Aminoff et al. (1984)	20 E	18♂, 2♀	X= 45 (23-62)	GTCS, no depression	ne	3 PHT, 1 PHT + PB	plasma	+10, 30 min, 1, 2, 3, 4, 24 h after seizures	↑ C 60-120 min after seizures
Bazil et al. (2000)	EG: 11 E CG: ne	ne	EG: X = 41; SEM = 3 (26–55) CG: X = 38; SEM = 2 (33–46)	TLE, CPS, SGS	ne	yes, ne	saliva	2, 5, 8, 11, 14, 17, 20, 23 h.	↑ AUC after seizures Baseline: n.s.d. EG and CG
Culebras et al. (1987)	EG: 15 E CG1: 15 stressed CG2: 15 non-stressed	EG: 15 ♂ CG1: 15 ♂ CG2: 15 ♂	EG: 48 (32-65) CG1: 54 CG2: 54	TCS	ne	yes (n=10), ne	plasma	+30 (n = 8), +60 min after generalized seizures	EG: +60 min: ↑ C > CG1 and CG2 E (n = 8): no recovery C: CGs: CG1 > CG2
Devinsky et al. (1993)	EG: 25 E CG: 11 healthy	EG: 16♂, 9♀	EG: 30.3; SD = 6.8 (11-44) CG: 30.8; SD = 9.0 (19-49)	CPS or GTC	ne	CBZ, PHT, VPA	CSF	interictal (> 2h) postictal (< 2h)	n.s.d. corr. + C and PHT
Gallagher et al. (1987)	EG: 17 E	7♀, 9♂	ne	Drug-resistant TLE (2 RTLE, 8 LTLE, 5 bilateral)	> 6 (n = 6) 1 < seizures < 4 (n = 9)	ne, amygdala, hippocampus electrical stimulation	serum	2:00 p.m. – 4:00 p.m.	7 non-responders C seizures > C no seizures
Pritchard et al. (1983)	EG1: 23 EG2: 5	EG1: 23♂ EG2: 3♂, 2♀	EG1: ne EG2: 33	EG1: TLE (CPS, 20 also GTCS) EG2: CPS	ne	EG1: PHT, CBZ, PB, PMD, VPA (monotherapy or polytherapy) EG2: PHT + PMD, CBZ, or PB	serum	9:00 a.m. – 11:00 a.m.	↑ C pre-seizures n.s.d. ↑ C postictal
Pritchard et al. (1985)	EG: 6 E CG: 6 PNES	3♂, 3♀	ne	5 CPS, 1 TCS	ne		serum	In rest and +15, 30, 45, 60 min after seizures	C ↑ after seizures in respect to PNES, 3 patients ↑ C before seizures
Rao et al. (1989)	EG: 6 E CG1: 6 PNES CG2: 28 healthy	EG+CG1: 5♂, 7♀ CG2: 14♂, 14♀	X= 27.3 (13-47)	4 CPS, 2 grand mal	ne	2 CBZ+VAL, 3 CBZ, 1 CBZ + CLZ + PMD	serum	every 15 min for 2 h after seizures	↑ C postictal EG: ↓ back to baseline CG1: no recovery Half-life C: 123 ± 18 min
Stoffel-Wagner et al. (1998)	EG1: 22 TLE ♀ EG2: 26 TLE ♂ CG1: 60 healthy CG2: 106 healthy	EG1: 22 ♀ EG2: 26 ♂ CG1: 60 ♀ CG2: 106 ♂	EG1: 31.8; SEM=1.4 EG2: 33.9; SEM=1.4 CG1: 32.9; SEM=1.5 CG2: 33.9; SEM=1.2	TLE (focal and SGS) LTLE: 13♀ 13♂ RTLE: 9♀ 13♂	ne	CBZ monotherapy or polytherapy	serum	8:00 a.m. – 10:00 a.m. fast	n.s.d. EGs vs CGs

Table 3. Continued.

Reference	Sample	Sex	Mean age in years (range)	Epilepsy type, semiology	Seizure frequency (monthly)	AEDs	C fluid	Time after event	C results
Takeshita et al. (1986)	EG1: 30 E, GTCS EG2: 9 E, CPS EG3: 10 E, minor seizures	EG1: 17♀, 13♂ EG2: 5♀, 4♂ EG3: 1♀, 9♂	X = 34.6 (13-77)	EG1: GTCS EG2: CPS EG3: myoclonic, SPS (minor seizures)	ne	AEDs	serum	+15, +30 min, +2, +24 h after seizure onset	GTCS: ↑ C +30 min. CPS: ↑ C Others: n.s.d. Psychomotor seizures: ↑ C +15-30 2 h after: ↓ C
Tuveri et al. (2008)	EG: 17 CG: 13 healthy	EG: 17 ♀ CG: 13 ♀	EG: 28.2; SD = 1.6 CG: 26.5; SD = 1.7	7 SPS, 7 CPS, 3 IE + GE	X = 5.82 (2-11)	14 EIAED 3 NEIAED 5 CBZ, 2 VPA, 3 OXC, 3 CBZ+LEV, 2 CBZ + TPM, 1 VPA+LTG, 1 CBZ+LTG	serum	08:00 a.m. – 09:00 a.m. fast, cycle days 7, 11, 15, 19, 23, 27	n.s.d. EG vs CG
Zhang and Liu (2008)	EG1: 28 E EG2: 8 E, induced seizures (bemegride) CG: 11 PNES	ne	X = 21.14; SD = 6.90 (16 - 40)	EG1: 28 SGS or *PSSG* EG2: 8 SPS	ne	ne	serum	awakening (08:00 a.m.), sleep (00:00 a.m.), during seizures	↓ C before seizures ↑ C during seizures ↑↑ C after seizures n.s.d. EG1 vs EG2

Abbreviations. AEDs = antiepileptic drugs; AUC = area under curve; C = cortisol; CBZ = carbamazepine; CG = control group; corr. = correlation; CPS = complex partial seizures; CSF= cerebrospinal fluid; CLZ= clonazepam; E = epilepsy; EIAED = enzyme inducer AEDs; G = group; GE = generalized epilepsy; GTCS = generalized tonic-clonic seizures: IE = idiopathic epilepsy; LEV= levetiracetam; LTG = lamotrigine; LTLE = left temporal lobe epilepsy; n.s.d.= no significant differences; ne = no specify; NEIAED = non-enzyme inducer AEDs; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; PMD = primidone; PNES = psychogenic non-epileptic seizures; TCS = tonic-clonic seizures; PSSG = partial seizures with secondary generalization; RTLE = right temporal lobe epilepsy; SGS = secondary generalized seizures; SPS= simple partial seizures; TLE = temporal lobe epilepsy; TPM= topiramate; VPA = valproic acid.

3.5. Studies examining stress and cortisol levels in people with epilepsy (Table 4)

Only three studies examined stress in people with epilepsy from different approaches (making up 8% of the total sample) (Allendorfer et al., 2014; den Heijer et al., 2018; van Campen et al., 2016). All the studies measured cortisol levels in saliva and included patients treated with AEDs. However, whereas two of these studies examined the relationship between perceived stress and morning cortisol levels (den Heijer et al., 2018; van Campen et al., 2016), the third included a stressor to stimulate the cortisol response to stress (Allendorfer et al., 2014).

Table 4. Summary of results of studies examining stress effects on cortisol levels in people with epilepsy.

Reference	Sample	Sex	Mean age in years (range)	Epilepsy type, semiology	Seizure frequency (monthly)	AEDs	C fluid	Time after event	Results
Allendorfer et al. (2014)[1]	EG: 23 (LTLE-sz; n = 13 and LTLE+sz; n = 10) GC: 23 healthy	EG: 6♂, 17♀ CG: matched	X = 40; SEM = 11 (21–59)	LTLE	LTLE−sz: seizure-free LTLE+sz: more than 1,1 seizure	X = 1.9; SD = 0.8	saliva	-30, -15 min pre-, immediately, +15, +30, +45, +60 min after scanner.	C reactivity: EG > CG LTLE+sz group: corr. + C reactivity and seizure frequency Basal C: EG > C
den Heijer et al. (2018)[2]	EG: 17 E (6 stress-sensitive seizures)	10♂, 7♀	X = 39; SEM = 15 (21-64)	3 LTLE, 9 RTLE, 2 LFLE, 2 RFLE, 1 bilateral FLE	X = 12.7 (0.1-150)	1 LEV, 2 CBZ, 1 LTG, 2 no AEDs, 11 polytherapy	saliva	Morning, at 15 min intervals during the first 5 h	Stress-sensitive seizures group: corr. – C and global functional brain connectivity. Non stress-sensitive seizures group: no corr.
van Campen et al. (2016)[2]	EG: 21 E (9 stress-sensitive seizures)	12♂, 9♀	X = 39.8 (20-69)	14 TLE (4LTLE, 9 RTLE, 1 unknown) 6 FLE (3 left, 2 right, 1 bilateral) 1 occipital (left)	X = 13.2 (0.1-150)	4 no AEDs 4 monotherapy (1 LEV, 2 CBZ, 1 LTG) 9 polytherapy (2-3 AEDs)	saliva	Morning, at 15 min intervals during the first 5 h	Stress-sensitive seizures group: corr. + C and interictal epileptiform discharges

[1]All participants underwent fMRI with control math task and stress math task. Both control and stress tasks involved subtraction and auditory performance feedback, but the stressful task was more difficult subtraction and feedback was negative (compared to positive feedback during control task).

[2]Patients report an association between seizures and stress.

Abbreviations. AEDs = antiepileptic drugs; C = cortisol; CBZ = carbamazepine; CG = control group; corr. = correlation; E = epilepsy; FLE = frontal lobe epilepsy; G = group; LEV= levetiracetam; LTG = lamotrigine; LTLE = left temporal lobe epilepsy; LTLE-sz = left temporal lobe epilepsy without seizures; LTLE+sz = left temporal lobe epilepsy with seizures; ne = no specify; RTLE = right temporal lobe epilepsy; TLE = temporal lobe epilepsy.

4. Discussion

This review collects data on cortisol levels in adults with epilepsy. Thirty-eight studies were identified that assessed cortisol levels in basal conditions or in stressful situations such as seizures; some of the studies considered the effects of pharmacological treatments on cortisol. Only 12 studies were published in the past decade, with studies focused on stressful situations being the most recent. In 45% of the studies examined, basal cortisol levels are higher in people with epilepsy than in healthy people. These studies are the most homogeneous in terms of patients' characteristics, and one of them is not obscured by AED effects. Pharmacological treatments could contribute to explaining the variability in the studies because decreases or increases in cortisol levels in people with epilepsy, compared to healthy controls, are found depending on the AED used. Seizures are related to increases in cortisol levels in 77% of the studies, and in patients with stress-related seizures, morning cortisol levels are negatively related to functional brain connectivity and positively related to seizure frequency. Additionally, cortisol reactivity to a laboratory stressor is higher in people with epilepsy than in healthy participants. These findings fit the consideration of epilepsy as a model of chronic stress in humans, with the new episode of acute stress having a sensitizing effect.

The articles included were classified in four categories depending on their main objectives, but some of them might fit several categories (Allendorfer et al., 2014; Galimberti et al., 2005; Isojrvi, 1990; Ostrowska et al., 1988). Therefore, results will be discussed from an integrative view.

When basal cortisol levels of people with epilepsy and healthy people were compared, five studies showed increased cortisol levels in patients with epilepsy (Afifi et al., 2011; Allendorfer et al., 2014; Galimberti et al., 2005; Gallagher et al., 1984; Majoie et al., 2011), whereas five found a lack of significant differences (Bakvis et al., 2009; Cavallo et al., 1984; Galli et al., 1996; Isojrvi, 1990; Molaie et al., 1987), and one study found lower cortisol levels in patients with epilepsy (Ostrowska et al., 1988). No differences were found between patients with epilepsy and a control group of patients with PNES (Novakova et al., 2017). The heterogenous characteristics of the sample (e.g., age, epilepsy type, and AED consumption) could explain, at least in part, the variability in the results. Interestingly, studies that found increased cortisol levels in patients with epilepsy were the most homogeneous in terms of age (young individuals with age-matched controls) (Afifi et al., 2011; Allendorfer et al., 2014; Galimberti et al., 2005; Gallagher et al., 1984; Majoie et al., 2011) and epilepsy type (Allendorfer et al., 2014; Gallagher

et al.,1984). Although the influence of AEDs on cortisol levels in patients with epilepsy cannot be ruled out in most studies, the Afifi et al. (2011) results are noteworthy because their study had the largest sample size (40 patients) that was not obscured by AED effects.

Studies that compared basal cortisol levels of subgroups of people with epilepsy found higher cortisol levels in patients with a poor prognosis than in patients with a good prognosis (Calabrese et al., 1993), and no differences in cortisol levels between patients with and without sleep problems (Laakso et al., 1993). This variability in the results indicates that clinical factors could modulate cortisol levels, and it points to the need for further research to discriminate between relevant and spurious variables.

Regarding changes in basal cortisol levels after therapeutic approaches, the three studies that examined cortisol changes after surgery showed a lack of significant changes (Bauer et al., 2000a, 2000b; Gallagher et al., 1984). However, it should be noted that surgery achieved total seizure freedom in 50-63% of the cases in these studies (Bauer et al., 2000a, 2000b; Gallagher et al., 1984). Although the relationship between seizure freedom and cortisol changes after seizures was considered in the studies by Bauer et al. (2000a, 2000b), it was not analyzed in the Gallagher et al. (1984) study. More recently, Majoie et al. (2011) found higher cortisol levels in patients with epilepsy than in healthy controls before a 28-week VNS treatment. However, cortisol levels were normalized after stimulation in terms of reducing seizure frequency, as in other studies (Galimberti et al., 2005). Although the results should be considered cautiously, it is plausible that therapeutic approaches could affect cortisol levels to the extent that the treatment is effective in controlling seizures.

It is worth noting that only one study included relationships between cortisol levels and neuropsychological variables (Busch et al., 2012). Results show that cortisol levels were negatively related to long-term verbal and visual memory (Busch et al., 2012). These results are consistent with the consideration of the hippocampus as a region rich in GR receptors and particularly vulnerable to repeated stress (Pavlides, Watanabe, Magarin, & McEwen, 1995), as well as the disruption of long-term potentiation found after stress in animals with pilocarpine-induced epilepsy (Maggio et al., 2017). High cortisol levels could be a consequence of the HPA axis' inability to provide feedback, which is supported by the high rates of nonsuppression after the dexamethasone test in people with epilepsy (Robertson, Coppen, & Trimble, 1986). In studies examining emotional factors, cortisol levels were positively related to depression scores (Devinsky et al., 1991), trait anxiety (Busch et al., 2012), and antisocial behavior (Devinsky et

al., 1991), consistent with higher cortisol levels found in patients with epilepsy and depression (Afifi et al., 2011). Recently, significant relationships were found between memory performance and cortisol and trait anxiety in drug-resistant patients (Cano-López et al., 2019), and so overlapped effects of cognitive and affective factors are plausible.

Part of the variability in the results could be attributed to AED treatments because there is some consensus about assuming that AEDs can affect cortisol levels differently depending on the AED used.

In the case of carbamazepine treatment, the results were heterogeneous (Galimberti et al., 2005; Isojrvi, 1990; Marek et al., 2010; Rozza et al., 1987). On the one hand, no significant changes in cortisol levels were found after monotherapy carbamazepine treatment (Isojrvi, 1990), or there was no relationship between carbamazepine and cortisol levels in a mixed sample of patients treated with mono- and polytherapy (Galimberti et al., 2005). On the other hand, a single dose of 300-1800 mg/day of carbamazepine monotherapy was associated with higher levels of cortisol in patients than in to healthy participants, independently of seizure frequency and duration (Marek et al., 2010). These results remained significant when carbamazepine was combined with phenobarbital (Rozza et al., 1987). These findings are consistent with those found in healthy individuals, in whom carbamazepine administration induced hypercortisolism because of the inefficacy of the negative feedback mechanism of the HPA axis at the pituitary level (Perini et al., 1992). It should be pointed out that the studies carried out by Isojrvi (1990) and Galimberti et al. (2005) included only women, whereas Marek et al. (2010) and Rozza et al. (1987) included a sample composed predominantly of men. Thus, synergetic effects of sex hormones cannot be ruled out.

Decreases in cortisol levels have been found in the first year of phenytoin monotherapy treatment (Beastall et al., 1985; Ostrowska et al., 1988), with lamotrigine monotherapy (Hill et al., 2011), and after treatment with a combination of newer AEDs (clonazepam, lamotrigine, and levetiracetam) and conventional AEDs, compared to treatment with conventional AEDs alone (Morimoto et al., 2018).

Regarding phenytoin, Beastall et al. (1985) found lower cortisol levels in women with epilepsy treated with phenytoin monotherapy than in healthy women, but not in male patients treated with phenytoin and phenobarbital. Ostrowska et al. (1988) also found lower cortisol levels in patients after three and six months of treatment with 200-300 mg/day of phenytoin, compared to healthy participants, with cortisol returning to baseline after 12 months of

treatment. Phenytoin increases 6-β-hydroxylase levels, favoring cortisol metabolization and urinary secretion (Fleishaker, Pearson, & Peters, 1995). In the central nervous system, phenytoin blocks sodium and T-type calcium channels, attenuating atrophy of hippocampal pyramidal neurons associated with elevated glucocorticoid levels typical of chronic stress (Magariños, McEwen, Flügge, & Fuchs, 1996). Although this remains speculative, phenytoin may produce a buffering effect on GR receptors along with an increase in cortisol metabolism, resulting in decreases in cortisol levels. With regard to lamotrigine, the only study that administered it in monotherapy showed lower cortisol levels in women with epilepsy than in healthy women in the luteal phase of the menstrual cycle, but not in the follicular phase (Hill et al., 2011). In healthy people, lamotrigine had no effect on basal cortisol levels, although it inhibited the cortisol response to a psychosocial stressor (Makatsori et al., 2004). The effects of different AEDs on cortisol levels did not seem to depend on whether or not they were strong enzyme inducing drugs (Galimberti et al., 2005). When examining differences in cortisol levels between patients treated with newer AEDs combined with conventional AEDs and those treated with conventional AEDs alone, a significant decrease in serum cortisol levels in relation to the increase in serum albumin was found in the group treated with the combined treatment (Morimoto et al., 2018).

With this in mind, seizures could be considered a stressful event due to their impact on cortisol levels. Seizures were related to increases in cortisol levels in most of the studies analyzed (Abbott et al., 1980; Aminoff et al., 1984; Bazil et al., 2000; Culebras et al., 1987; Gallagher et al., 1987; Galimberti et al., 2005; Pritchard et al., 1985, 1983; Rao et al., 1989; Takeshita et al., 1986; Zhang & Liu, 2008). It should be noted that all these studies, except the study by Bazil et al. (2000), measured cortisol levels in serum, plasma, or cerebrospinal fluid, using invasive procedures that may trigger a cortisol response that overlaps with the effects of seizures.

Increases in cortisol levels were found before complex partial seizures and generalized tonic-clonic seizures (Pritchard et al., 1985), but decreases in cortisol levels were found before simple partial seizures and secondary generalized seizures (Zhang & Liu, 2008). It is possible that, depending on the seizure type, patients perceive certain signs as a prelude to a seizure, which could favor an anticipatory cortisol response (Engert et al., 2013; Gaab, Rohleder, Nater, & Ehlert, 2005).

After seizures, cortisol increases were found with a wide variety of seizures (Abbott et al., 1980; Aminoff et al., 1984; Bazil et al., 2000; Culebras et al., 1987; Pritchard et al., 1985, 1983; Rao et al., 1989; Takeshita et al., 1986; Zhang & Liu, 2008). The main difference between studies was the postictal period, during which cortisol levels return to baseline. Some studies found high cortisol levels from 15 to 120 min after seizure onset (Aminoff et al., 1984; Pritchard et al., 1985, 1983), and the half-life of these high serum levels was 123 ± 18 min (Rao et al., 1989). However, Takeshita et al. (1986) found response peaks 30 min after the onset of tonic-clonic seizures or other seizures with a high motor component, recovering basal levels at 120 min. Accordingly, in studies focused on the stress response in healthy people, the cortisol peak occurs 30 min after the onset of the stressor (Kirschbaum, Pirke, & Hellhammer, 1993).

Only three studies found no significant changes in cortisol levels after seizures (Devinsky et al., 1993; Stoffel-Wagner et al., 1998; Tuveri et al., 2008). Methodological aspects related to the time of sample collection may explain, at least in part, this lack of significant results. The studies carried out by Stoffel-Wagner et al. (1998) and Tuveri et al. (2008) were performed between 8 and 10 am, after a period of fasting, as baseline measurements, without considering the seizure time as a reference point. Devinsky et al. (1993) examined cortisol levels between 7 and 8:30 am, after a period of fasting, in the control group, whereas patients had several measurements at varying times after different seizures. Circadian cortisol rhythms, with higher levels in the morning (Pruessner et al., 1997), may overlap possible differences between groups.

This capability of seizures to increase cortisol levels makes it especially interesting to examine the cortisol response to acute stress in patients with epilepsy, but only three studies examined self-reported stress or the acute stress response in this population (Allendorfer et al., 2014; den Heijer et al., 2018; van Campen et al., 2016). Results showed that high morning cortisol levels significantly correlated with lower functional global connectivity measures of the whole brain and increased interictal epileptiform discharges, but only in patients with self-reported stress-related seizures (den Heijer et al., 2018; van Campen et al., 2016). In both studies, cortisol samples were collected after awakening at 15-min intervals during the first five hours on one or two consecutive days (den Heijer et al., 2018; van Campen et al., 2016). The time interval examined overlapped with the cortisol awakening response (CAR), the marked increase in cortisol levels in the first 30-45 min after morning awakening, previously identified as a key parameter in the study of chronic stress states (Schulz, Kirschbaum, Prüßner, & Hellhammer, 1998; Wüst et al., 2000). Studies collecting cortisol samples in the afternoon, when fluctuations are minor, are needed to determine whether these associations are stable

throughout the daily cortisol profile. Interestingly, only one study examined the cortisol response to a laboratory stressor in patients with left TLE and healthy controls. The results showed greater cortisol reactivity in patients that was positively related to seizure frequency in patients with poor seizure control (Allendorfer et al., 2014). Despite the promising results of this study, to our knowledge, no other studies have been conducted on this issue. If these results were confirmed with standardized stressors in future studies, it might be possible to explain the mechanisms underlying the interaction between stress and epilepsy. A review carried out by Allendorfer and Szaflarski (2014) emphasized the lack of studies examining whether psychosocial interventions focused on managing and coping with perceived stress can reduce seizure frequency. In this regard, Haut et al. (2018), in a randomized controlled trial, found that both progressive muscle relaxation with diaphragmatic breathing and a controlled focused-attention activity with extremity movements reduced seizure frequency compared to baseline in people with drug-resistant epilepsy.

Overall, studies included in the present review indicate that, at least in certain patients, epilepsy is able to modify basal cortisol levels and probably has a sensitizing effect on the HPA axis for future seizures. Clarification of relevant clinical variables to detect high-risk patients with altered cortisol levels should be emphasized, and AEDs are a source of variability that should be taken into account. Therapeutic approaches such as surgery or VNS seem to modify cortisol levels depending on their efficiency in seizure reduction. More homogeneous results are found in cortisol levels after seizures, with increases similar to those found after acute stress administration or self-reported stress before spontaneous seizures. However, studies point to several considerations for future research.

First, the epilepsy type was quite heterogeneous across studies, contributing to the variability in the results found, despite the fact that 11 of the 38 studies included in this review (29%) included a homogenous sample of patients with TLE (Allendorfer et al., 2014; Bauer et al., 2000a; Bauer et al., 2000b; Bazil et al., 2000; Busch et al., 2012; Gallagher et al., 1984, 1987; Galli et al., 1996; Pritchard et al., 1983; Stoffel-Wagner et al., 1998). In TLE patients, most of the studies indicated that cortisol levels were higher at baseline than in healthy controls (Allendorfer et al., 2014; Gallagher et al., 1984), were related to memory and anxiety (Busch et al., 2012), increased after seizures (Bazil et al., 2000; Pritchard et al., 1983), and had higher reactivity to acute stress than in healthy people (Allendorfer et al., 2014). Second, methodological considerations that could at least partly explain the variability in the results include small sample sizes or scarce descriptive data about epilepsy-related factors. Third,

cortisol levels were analyzed in different fluids such as cerebrospinal fluid, serum, plasma, and saliva, and so the results for total cortisol were intermixed with those for free cortisol (saliva). Although total and free cortisol concentrations are significantly correlated in the general population, the balance between the two concentrations depends on the concentration of transport proteins such as cortisol-binding globulin (CBG) (Gozansky, Lynn, Laudenslager, & Kohrt, 2005). Additionally, there is a tendency to collect cortisol samples in the morning (Afifi et al., 2011; Bauer et al., 2000a, 2000b; den Heijer et al., 2018; Devinsky et al., 1991; Galimberti et al., 2005; Hill et al., 2011; Isojrvi, 1990; Morimoto et al., 2018; Ostrowska et al., 1988; Pritchard et al., 1983; Stoffel-Wagner et al., 1998; Tuveri et al., 2008; van Campen et al., 2016), probably to coincide with other neurological assessments. Cortisol levels follow a 24-h circadian rhythm, with a morning circadian peak within the first 30 minutes after awakening and slowly declining levels in the late afternoon, evening, and night (Pruessner et al., 1997). In fact, the CAR has also been proposed as an indicator of health alterations related to stress, and its measurement should meet certain requirements (Stalder et al., 2016). Other aspects to consider when measuring cortisol levels are related to the effects of sex, age, smoking, physical exercise, menstrual cycle, or contraceptives on this hormone, all of which should be controlled to avoid confusion. Finally, in the present review, we excluded studies that measured other HPA axis hormones without examining cortisol levels. The few studies that manipulated cortisol levels with suppression tests carried out with drugs that could interact with AEDs were also excluded. However, given the interest in this issue, it is especially useful to elucidate the possible diagnostic role of the cortisol response, its possible involvement in the pathological process of epilepsy, its interaction with stress processes, and the factors that could modulate it.

Despite this, the present review highlights that epilepsy could be considered a chronic stress model in humans, which might be useful in the clinical management of people with epilepsy. The detailed results, furthermore, point to several questions that could be useful for future research. Among them, apart from methodological issues, heterogeneous results for basal cortisol levels emphasize the need to more closely examine clinical variables in order to explain individual differences among patients. Sex differences in AED effects suggest a differential role of sex hormones. Moreover, due to the scarce number of studies focused on cognitive-emotional relationships with cortisol levels, as well as on acute stress induction in adults with epilepsy, there is a need for further research on these topics.

CAPÍTULO 3

Objetivos e hipótesis

1. Objetivos e hipótesis

Como se ha expuesto en los capítulos anteriores, el deterioro de la memoria es una de las quejas más frecuentes en personas con epilepsia (Helmstaedter, 2013; Hoppe et al., 2007; Lee et al., 2002; Thompson et al., 2016). Aunque numerosos estudios han explorado el papel de factores directamente relacionados con las crisis epilépticas sobre el funcionamiento mnésico (Baxendale et al., 2008; Seidenberg et al., 2007; Vingerhoets, 2006), otros factores han sido escasamente estudiados. Por una parte, entre ellos, destacan los relacionados con el sustrato neural de la memoria como la morfología del hipocampo a lo largo de su eje anterior-posterior (Pauli et al., 2006), la activación funcional durante el procesamiento cognitivo (Berl et al., 2005), y la edad en el momento de la cirugía del lóbulo temporal (Thompson et al., 2015). Por otra parte, encontramos factores que podrían considerarse indicadores del bienestar del individuo como los niveles de cortisol (Busch et al., 2012) y la afectividad negativa (Helmstaedter et al., 2004; Miller et al., 2016b), cuyo estudio adquiere especial relevancia en una población potencialmente sometida a estrés crónico. El deterioro de la memoria, potencialmente asociado a los factores considerados anteriormente, podría ser uno de los principales factores implicados en la calidad de vida de esta población (Perrine et al., 1995). Sin embargo, hasta donde sabemos, no se ha analizado de forma global la contribución relativa de factores psicobiológicos y sociales, incluyendo variables cognitivas como la memoria, sobre la calidad de vida en una misma muestra formada exclusivamente por pacientes con epilepsia farmacorresistente. Estos pacientes experimentan la mayor parte de la carga de la enfermedad (World Health Organization, 2014), motivo por el cual la presente Tesis se centra en dicha población.

En esta Tesis realizamos cinco estudios con el fin de clarificar los factores intervinientes en el funcionamiento mnésico en pacientes adultos con epilepsia farmacorresistente y el impacto de esta función cognitiva en la calidad de vida de esta población. Los objetivos y las hipótesis de esta Tesis se presentan a continuación.

Objetivo general 1. Clarificar el papel de las alteraciones hipocampales a lo largo de su eje anterior-posterior y del patrón de activación funcional durante la codificación mnésica y el procesamiento del lenguaje en regiones de interés sobre el rendimiento mnésico en pacientes con epilepsia farmacorresistente.

- **Objetivo específico 1.1.** Determinar la asociación entre la morfología del hipocampo a lo largo de su eje anterior-posterior y el rendimiento mnésico en pacientes con ELT.

- **Objetivo específico 1.2.** Examinar si la morfología del hipocampo a lo largo de su eje anterior-posterior se asocia con la activación funcional del lóbulo temporal medial durante la codificación mnésica, y si esta última se relaciona con el rendimiento en memoria en pacientes con ELT.

- **Objetivo específico 1.3**. Estudiar la influencia de la asimetría hemisférica (típica o atípica) durante el procesamiento del lenguaje en el rendimiento en memoria y otros dominios cognitivos, considerando el papel de factores mediadores (i.e., lateralización del área epileptógena, tipo de epilepsia, edad de inicio de la epilepsia, frecuencia de crisis, número de FAEs, sexo y dominancia manual).

Considerando la literatura previa que indica que la pérdida celular en la región CA1 del hipocampo, correspondiente a la cabeza del hipocampo, es la más característica de la ELT mesial (Pauli et al., 2006) y que los pacientes con ELT suelen presentar déficits en memoria (Helmstaedter y Kockelmann, 2006), hipotetizamos que los pacientes con mayor atrofia anterior en el hipocampo (versus posterior) presentarán peor rendimiento mnésico, ya sea de forma directa o a través de una baja activación funcional en el lóbulo temporal medial, durante la codificación mnésica. Respecto al patrón de activación funcional durante el procesamiento del lenguaje, hipotetizamos que los pacientes con asimetría hemisférica atípica presentarán peor rendimiento que aquellos con asimetría hemisférica típica en tareas verbales, pero también en tareas no verbales para las cuales el hemisferio derecho es típicamente dominante, de acuerdo con el fenómeno conocido como *crowding* (Jokeit y Ebner, 2002).

Los objetivos específicos 1.1 y 1.2 se abordarán en el Estudio 1, mientras que el propósito del Estudio 2 es responder al objetivo específico 1.3.

Objetivo general 2. Determinar si la edad en el momento de la cirugía es un predictor fiable de la evolución mnésica de pacientes sometidos a cirugía del lóbulo temporal desde una perspectiva multivariada e integral, considerando la asociación entre la memoria y otros dominios cognitivos.

- **Objetivo específico 2.1.** Examinar si los pacientes que presentan mejorías en su competencia verbal (tanto en memoria como en otros dominios cognitivos) tras la

cirugía y aquellos que presentan un empeoramiento significativo difieren en su edad en el momento de la cirugía.

- **Objetivo específico 2.2.** Estudiar el papel predictivo de la edad en el momento de la cirugía en la evolución en memoria verbal, considerando la influencia de otros posibles predictores (i.e., lateralización del área epileptógena, tipo de cirugía y frecuencia de crisis).

De acuerdo con estudios previos (Jambaqué et al., 2007; Thompson et al., 2015), hipotetizamos que los pacientes con un perfil de mejoría en su competencia verbal tras la cirugía tendrán menor edad que aquellos que presentan empeoramientos en los dominios verbales tras la cirugía. A su vez, se hipotetiza que menor edad en el momento de la cirugía será un predictor significativo de mejoría en memoria verbal tras la cirugía, aun controlando la influencia de otros factores no considerados en estudios previos juntamente con la edad de la cirugía.

Estos objetivos se abordarán en el Estudio 3.

Objetivo general 3. Determinar la influencia de los niveles de cortisol y de la afectividad negativa (ansiedad rasgo y depresión) en el funcionamiento mnésico de pacientes con epilepsia farmacorresistente, considerando el papel de otros potenciales factores influyentes.

- **Objetivo específico 3.1.** Analizar las diferencias en los niveles de cortisol entre pacientes con alto rendimiento mnésico y pacientes con bajo rendimiento mnésico, considerando la influencia de otros factores (i.e., tipo de epilepsia y lateralización del área epileptógena).

- **Objetivo específico 3.2.** Estudiar si los niveles de cortisol y la afectividad negativa son predictores significativos del rendimiento mnésico, controlando otros posibles predictores (i.e., lateralización del área epileptógena, tipo de epilepsia y frecuencia de crisis).

Hipotetizamos que los pacientes con bajo rendimiento mnésico presentarán mayores niveles de cortisol respecto a pacientes con alto rendimiento mnésico (Busch et al., 2012), especialmente aquellos con foco epileptógeno temporal izquierdo, que tienen mayor riesgo de deterioro mnésico (Jokeit et al., 2001). En esta línea, y en base a los hallazgos previos en

personas sanas (Fonda et al., 2005; Lee et al., 2007) y en otras poblaciones clínicas (Hinkelmann et al., 2009; Rubinow et al., 1984) expuestos en los capítulos anteriores, esperamos encontrar una asociación negativa entre los niveles de cortisol y la ejecución en tareas de memoria. En lo que respecta a la afectividad negativa, hipotetizamos que las altas puntuaciones en ansiedad rasgo (Miller et al., 2016b) y en depresión (Helmstaedter et al., 2004; Paradiso et al., 2001) se asociarán a un peor rendimiento en memoria.

Estos objetivos se abordarán en el Estudio 4.

Objetivo general 4. Clarificar el papel del rendimiento mnésico sobre la calidad de vida de pacientes con epilepsia farmacorresistente, considerando la influencia de variables relacionadas con las crisis epilépticas y de otros factores psicobiológicos y sociales no directamente relacionados con las crisis.

- **Objetivo específico 4.1.** Analizar si el rendimiento en memoria se asocia significativamente con la calidad de vida global, controlando la contribución relativa de otros factores influyentes.

- **Objetivo específico 4.2.** Examinar la sensibilidad de las diferentes subescalas de calidad de vida al rendimiento mnésico y a otros factores influyentes.

Se hipotetiza que los pacientes con peor rendimiento mnésico percibirán una calidad de vida más pobre respecto a aquellos con alto rendimiento mnésico (Perrine et al., 1995), y que esta relación se mantendrá aun controlando la contribución relativa de otros factores influyentes. En cuanto al objetivo específico 4.2, debido a la escasez de estudios previos, no se establecen hipótesis específicas a este respecto.

El propósito del Estudio 5 es responder a estos objetivos.

CHAPTER 4

Study 1

Hippocampal morphology along the anterior-posterior axis and its relationship to memory encoding and performance in temporal lobe epilepsy[1]

[1] Manuscript in preparation and internal revision.

1. Introduction

Temporal lobe epilepsy (TLE) is the most common type of drug-resistant epilepsy in adults (Téllez-Zenteno & Hernández-Ronquillo, 2012). It is frequently associated with memory impairments; particularly verbal deficits in patients with left TLE (LTLE) and visual deficits in those with right TLE (RTLE) (Willment & Golby, 2013), which affect their quality of life (Cano-López et al., 2018b).

Poor memory performance has been linked to hippocampal atrophy, describing an association of left hippocampal volume with verbal memory deficits (Alessio et al., 2004; Kilpatrick et al., 1997) and right hippocampal volume with visual memory deficits (Baxendale et al., 1998a). Using functional magnetic resonance imaging (fMRI), we described efficient and inefficient patterns of functional memory reorganization (Richardson et al., 2003, 2004; Powell et al., 2007; Bonelli et al., 2010; Sidhu et al., 2013).

Memory functional reorganization could be a compensatory effort elicited by mesiotemporal structural deficits. There is, however, little knowledge on the relationship between structural damage and memory encoding. Previous studies found an association of severity of mesiotemporal sclerosis with less activation in the affected hippocampus and more activation in the contralateral hippocampus on memory encoding tasks (Richardson et al., 2004; Powell et al., 2007). These relationships were explored considering the hippocampus as a whole. However, hippocampal sclerosis (HS) does not affect the hippocampus uniformly and different subtypes exist (Blümcke et al., 2013). It is unknown whether selective damage of the hippocampal head or body and tail differ in memory performance and relate to diverging memory functional reorganisation. A more-detailed understanding of hippocampal structural-functional interactions may help to better classify TLE phenotypes (Coras & Blümcke, 2015) and understand why some people with TLE are more likely to have memory deficits compared to others.

Here, we analysed hippocampal surface-shape patterns along the anterior-posterior axis with high-resolution magnetic resonance imaging (Bernhardt, Kim, & Bernasconi, 2013) and related them to fMRI memory encoding activation and memory performance. We aimed to determine whether there were differences in functional memory encoding and memory performance between TLE patients with atrophy mainly affecting the hippocampal head in respect to those with atrophy of the hippocampal tail. Integration of structural, functional and

behavioural views could contribute to identify TLE phenotypes with higher risk of memory deficits.

2. Material and methods

2.1. Participants

We included consecutive patients being evaluated for epilepsy surgery with medically refractory TLE confirmed by multidisciplinary presurgical assessment. All subjects underwent a standardised neuropsychological evaluation, 3T structural and functional MRI on the same scanner. Excluded were patients with lesions (e.g. cavernoma, dysplasia or tumours) within or in close proximity to the hippocampus that could alter hippocampal morphology (HS was not excluded), scans of insufficient quality, and those that were not fluent English speakers.

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

2.2. Neuropsychological evaluation

All patients underwent a standardized neuropsychological assessment. Handedness was determined using the Edinburgh Handedness Inventory (Oldfield, 1971). Verbal and visual learning was assessed using the British Memory and Information Processing Battery (BMIPB) (Coughlan, Oddy, Crawford, 2007), previously found to be sensitive to the integrity of temporal structures (Baxendale, Thompson, Harkness, & Duncan, 2006). In the list learning task, participants listen to a list of 15 words and asked to recall as many words as possible over five trials. The total number of correctly recalled items was computed as an indicator of verbal learning. In the design learning task, an abstract design with nine components was presented and participants were asked to reproduce it over five trials. The total number of components recalled was computed as an indicator of visual learning. Verbal and visual learning direct scores were transformed into z-scores according to normative data (Coughlan et al., 2007).

2.3. Hippocampal segmentation (Figure 1)

Hippocampal segmentations were performed using a manual refinement of automated segmentations. First, we extracted the initial hippocampal masks using Hipposeg (Winston et al., 2013), an automated parcellation software specifically developed in people with epilepsy.

Hipposeg has shown to delineate the hippocampus with no more variability than expert human raters and be robust to atrophic hippocampus (Winston et al., 2013). Second, one blinded rater (TP) received anonymized hippocampal masks and corrected misclassifications according to a well-established protocol (Cook et al., 1992). To determine the intra-rater variability of this manual refinement of automated segmentation, one blinded rater manually corrected Hipposeg segmentation in randomly selected 10 TLE patients on two different trials 3 months apart and compared the resulting masks using Dice coefficients (Dice, 1945). To assess inter-rater variability, a second blinded rater corrected Hipposeg segmentations of 10 randomly selected TLE patients using the same segmentation protocol. A high intra-rater (0.98 ± 0.01) and inter-rater (0.96 ± 0.02) reliability demonstrate a high consistency of the combined manual-automated method, exceeding the reliability reported for an entirely manual method (intra-rater 0.89 ± 0.02, inter-rater 0.83 ± 0.02) (Winston et al., 2013).

Volumes of extracted hippocampi were corrected for total intracranial volume (TIV) as described previously (Winston et al., 2013). TIV was calculated using a parcellation algorithm based on Geodesic Information Flows (Cardoso et al., 2015). Generated TIV masks were visually checked and corrected by one rater.

2.4. Hippocampal shape analysis (Figure 1)

The binary hippocampal segmentations were transformed to 3D surface meshes and parametrised with a spherical harmonics point distribution model (SPHARM-PDM) (Styner et al., 2006), according to an established protocol (Manning et al., 2015). A mean mesh template was generated from 39 healthy controls and all hippocampal surfaces were rigidly aligned to this mesh. We visually checked hippocampal shapes to ensure the absence of surface mesh and alignment failures. Pre-processing of the left and the right hippocampus was performed separately. Anterior (head) and posterior (body together with tail) hippocampal regions were outlined on volumetric MRI based on anatomically landmarks and projected to the hippocampal surface, generating a regional surface atlas (see Figure S1). Displacement values were computed using a point to mesh approach computing the normal distance between the mean template surface and each point on an individual's hippocampal surface mesh, and a mean displacement value was calculated for the anterior and posterior region. A negative displacement value (inward displacement) was indicative of atrophy, while a positive displacement value (outward displacement) was indicative of hypertrophy. An anterior-posterior deformation index of each hippocampus was computed by using the following

formula: (anterior displacement value – posterior displacement value)/ (|anterior displacement value + posterior displacement value|). Higher scores indicated less atrophy of the hippocampus head (vs body and tail), while lower scores indicated more atrophy of the hippocampus head (vs body and tail).

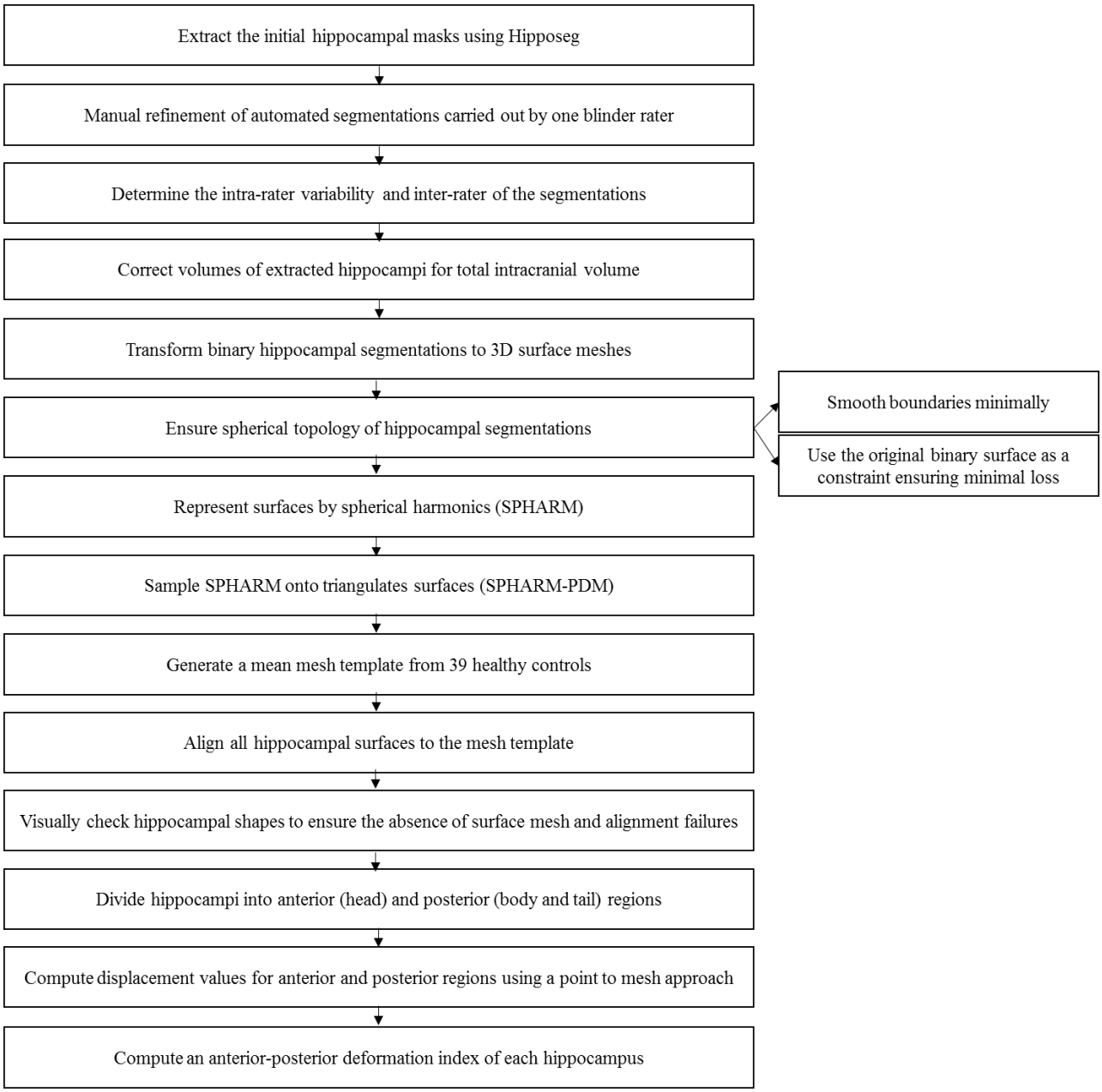

Figure 1. Summary of the hippocampal segmentation and shape analysis procedure.

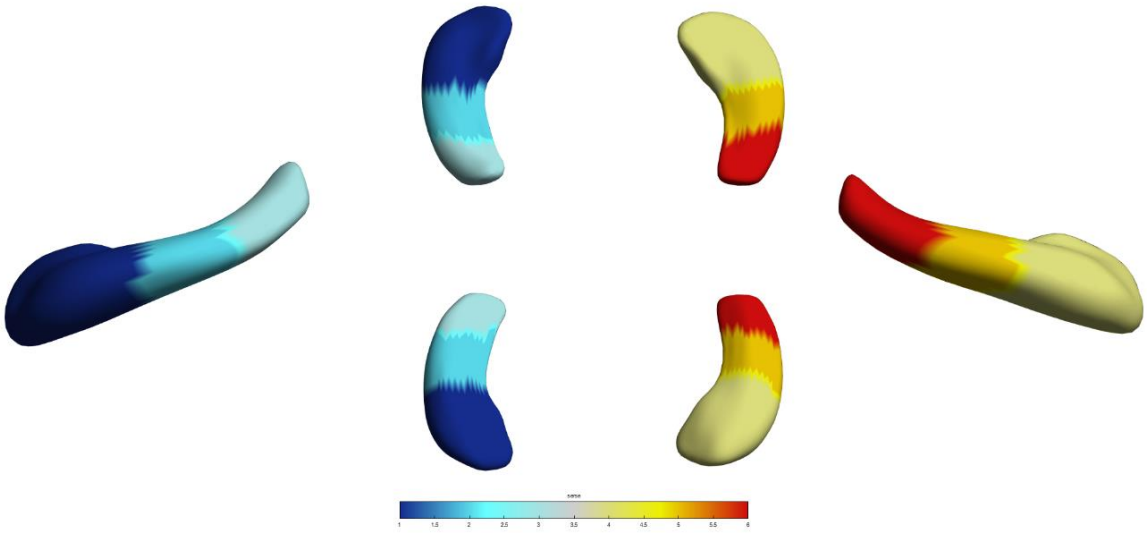

Figure S1. Hippocampal parcellation.

2.5. MRI acquisition

All scans were performed on a 3 T General Electric Excite HDx MRI scanner with a gradient strength of 40 m/Tm and slew rate 150Tm/s. For structural MRI, coronal T1W 3D fast spoiled gradient echo images were acquired with repetition time/echo time/number of excitations = 6.6/2.8/450 ms; matrix 256x256x196; slice thickness 1.1 mm. For the functional MRI, gradient-echo planar images were acquired, providing blood oxygen level-dependent contrast. Each volume comprised 36 contiguous oblique axial slices, slice thickness 2.5 mm (0.3 mm gap), field of view 24 cm, matrix 96 x 96 interpolated to 128 x 128 during image reconstruction, in-plane resolution 2.5 mm x 2.5 mm, SENSE factor 2.5, echo time 25 ms, repetition time 2.75 s. The field of view covered the temporal and frontal lobes with slices aligned with the long axis of the hippocampus.

2.6. Memory encoding fMRI paradigm and data preprocessing

We used a well-established memory encoding fMRI paradigm as described in detail previously (Sidhu et al. 2013, 2016). Briefly, we used a paradigm with two material types, visual stimuli (faces) and verbal stimuli (words) to analyse brain activation during verbal and visual encoding. Each item was presented for 3 s in 60 s blocks viewed via a mirror, using a different inter-stimulus interval (3 s) to the repetition time (2.75 s) to introduce jitter and facilitate random sampling. A total of 10 blocks were presented (100 faces and 100 words). Patients were instructed to memorize items for subsequent out-of-scanner recall. Forty minutes

after scanning, face and word recognition were tested out of the scanner by two separate recognition tasks. We computed the number of words remembered (WR) and faces remembered (FR).

Data were preprocessed using statistical parametric mapping (SPM 8; Wellcome Trust Centre for Imaging Neuroscience). Scans from each subject were realigned using the mean image as a reference to remove any minor motion-related signal change, and coregistered with the anatomical image. The resulting data set was segmented, normalized into standard anatomical space (using a scanner specific template created from 30 healthy control subjects, 15 patients with left HS and 15 patients with right HS using the high-resolution whole brain echo planar image), and smoothed with a Gaussian kernel of 8 mm full-width at half-maximum.

2.7. Data analyses

First, The Kolmogorov–Smirnov test was carried out to examine the normality of the data. Differences between RTLE and LTLE patients in descriptive, clinical and cognitive variables were examined using t-test for independent samples or the chi-square test where appropriate. Pearson correlations were used to examine the associations between the anterior-posterior deformation index of the hippocampus ipsilateral to the epileptic focus and memory performance in each group. These statistical analyses were carried out using SPSS 22.0 and a two-tailed $p < 0.05$ was considered significant.

To analyse fMRI data, we compared the encoding-related responses for stimuli that were subsequently remembered with a second-level event-related random-effects analysis (Sidhu et al., 2013, 2015a, 2016). At the first level, for each subject, delta functions of FR and WR were convolved with the canonical HRF and its temporal derivative, including movement parameters as confounds. The generated WR and FR contrast images for each subject were used in the second-level analyses.

At second-level, we performed simple regressions models of anterior-posterior deformation index of the hippocampus ipsilateral to the epileptic focus with WR and FR whole brain activations, and WR and FR activations with verbal and visual learning, respectively, in each group.

All results are shown corrected for multiple comparisons (family-wise error (FWE), $p < .05$). Due to our a-priori hypothesis to detect functional changes within the hippocampus, medial temporal lobe activations are shown corrected for multiple comparisons using a small volume correction within a sphere of 6mm (FWE $p < 0.05$).

All these latter analyses were performed using SPM 8 (Wellcome Trust Centre for Imaging Neuroscience).

3. Results

3.1. Participants characteristics

The sample was composed of 58 patients with drug-resistant TLE (median age: 40.05, range: 17-65 years), 27 with RTLE and 31 with LTLE, who underwent a presurgical evaluation at the National Hospital for Neurology and Neurosurgery, London, U.K.

There were no clinical or demographic differences between RTLE and LTLE patients (Table 1) except for a lower proportion of men in the RTLE group ($p = 0.05$). However, no differences in the anterior-posterior deformation index of the right or left hippocampi were found depending on sex ($p > 0.08$). RTLE patients had lower visual learning scores than LTLE patients ($p = 0.03$).

Table 1. Characteristics of the total sample and groups of patients with LTLE and RTLE, expressed in mean (SD) or n (%), and differences between groups

Characteristics	Total ($N = 58$)	RTLE (n = 27)	LTLE (n = 31)	*p*
Age	40.05 (9.68)	40.37 (10.87)	39.77 (8.68)	0.82
Sex				0.05
Female	35 (60.3%)	20 (74.1%)	15 (48.4%)	
Male	23 (39.7%)	7 (25.9%)	16 (51.6%)	
Handedness				0.33
Left	8 (13.8%)	5 (18.5%)	3 (9.7%)	
Right	50 (86.2%)	22 (81.5%)	28 (90.3%)	
Age at epilepsy onset	17.10 (11.19)	17.87 (12.19)	16.43 (10.40)	0.63
Epilepsy duration	22.95 (13.05)	22.50 (13.21)	23.34 (13.10)	0.81
HS				0.72
Yes	40 (69.0%)	18 (66.7%)	22 (71.0%)	
No	18 (31.0%)	9 (33.3%)	9 (29.0%)	
Type of seizures				
SPS	27 (46.6%)	11 (40.7%)	16 (51.6%)	0.41
CPS	54 (93.1%)	25 (92.6%)	29 (93.5%)	0.89
SGS	35 (60.3%)	17 (63.0%)	18 (58.1%)	0.70
Seizures per month				
SPS	14.89 (44.87)	8.37 (25.92)	20.90 (57.01)	0.33
CPS	8.37 (10.46)	8.31 (11.65)	8.43 (9.56)	0.97
SGS	0.26 (0.70)	0.42 (1.03)	0.13 (0.24)	0.20
CPS + SGS	8.13 (10.35)	7.97 (11.44)	8.26 (9.48)	0.92
Total	20.96 (45.01)	15.41 (25.78)	25.79 (56.75)	0.39
Number of AEDs	2.47 (0.78)	2.63 (0.69)	2.32 (0.83)	0.14
Learning scores				
Verbal learning	-0.62 (1.01)	-0.67 (0.98)	-0.57 (1.06)	0.71
Visual learning	-0.53 (1.28)	-0.73 (1.07)	-0.10 (1.02)	0.03

Note. HS: hippocampal sclerosis, SPS: simple partial seizure, CPS: complex partial seizure, GTCS: secondary generalized seizures, SGS: Secondary generalized seizures.

3.2. RTLE (Table 2)

In RTLE patients, no correlations were found between the anterior-posterior deformation index of the hippocampus ipsilateral to the epileptic focus and verbal or visual memory performance ($r(27) = -0.02$, $p = 0.94$, and $r(27) = -0.07$, $p = 0.71$, respectively).

In this group, more atrophy of the right hippocampal head was associated with less activation during verbal encoding within the right fusiform gyrus ($p_{FWE\text{-}corr} = 0.054$), and the left fusiform gyrus ($p_{FWE\text{-}corr} = 0.070$) (Figure 2A). It was also associated with less activation during visual encoding within the right hippocampus body ($p_{FWE\text{-}corr} = 0.008$) and the left fusiform gyrus ($p_{FWE\text{-}corr} = 0.019$). (Figure 2B).

Out-of-scanner verbal learning scores tended to be related to WR activations within the right hippocampus tail ($p_{FWE\text{-}corr} = 0.072$) (Figure 3A), but were negatively related to activation within the right superior frontal gyrus (orbital part) ($p_{FWE\text{-}corr} = 0.021$). Moreover, visual learning scores were positively associated with left-sided FR activations within the hippocampus head ($p_{FWE\text{-}corr} = 0.019$) and the amygdala ($p_{FWE\text{-}corr} = 0.023$) (Figure 3B).

No other significant correlations were found.

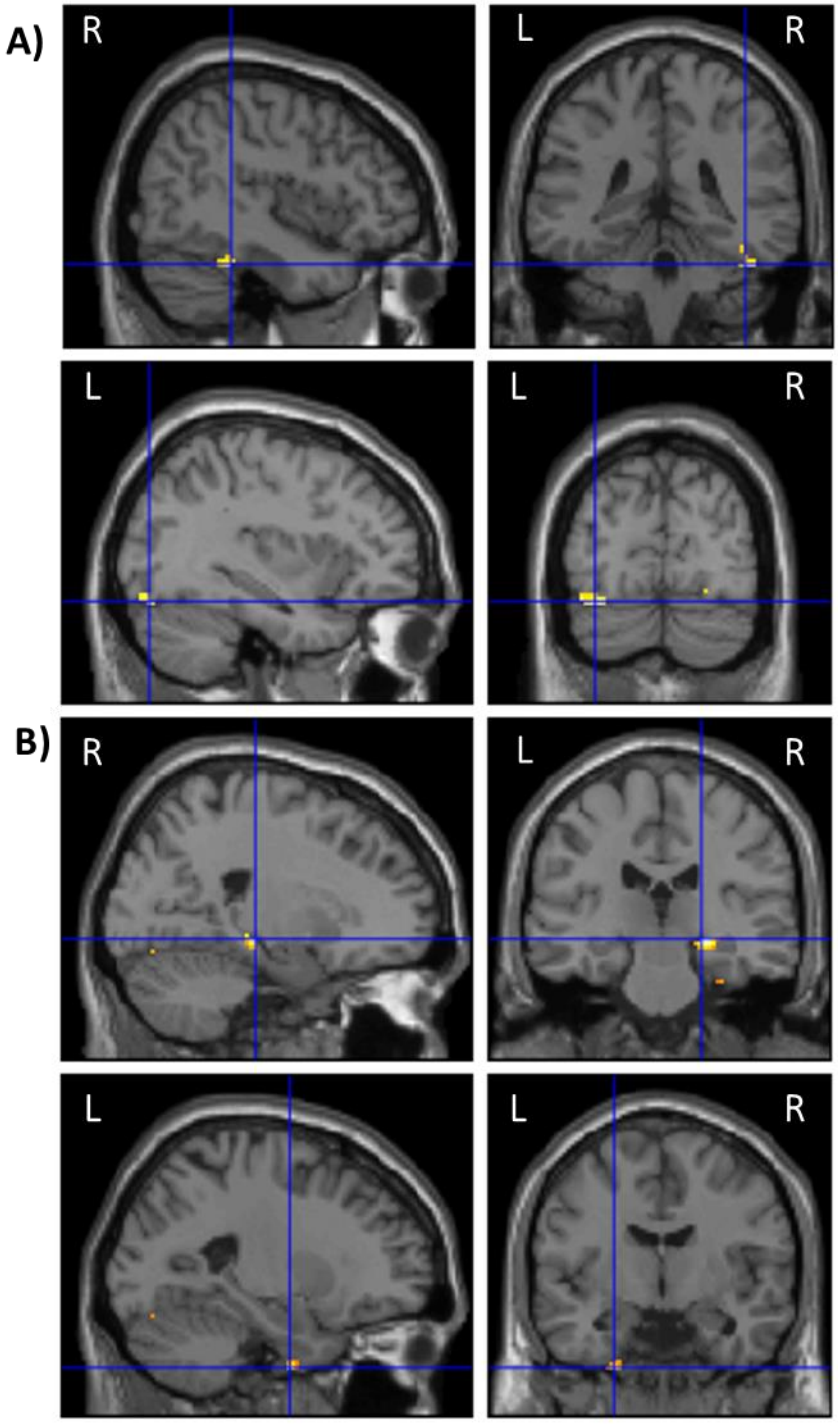

Figure 2. Correlations of atrophy pattern of the right hippocampus with functional activation during memory encoding in RTLE patients displayed at a threshold of $p < 0.05$, uncorrected. A) Correlations of more atrophy of the hippocampal head with less WR activation within the right fusiform gyrus (top row) and the left fusiform gyrus (bottom row). B) Correlations of more atrophy of the hippocampal head with less FR activation within the right hippocampus body (top row) and the left fusiform gyrus (bottom row). L = left; R = right.

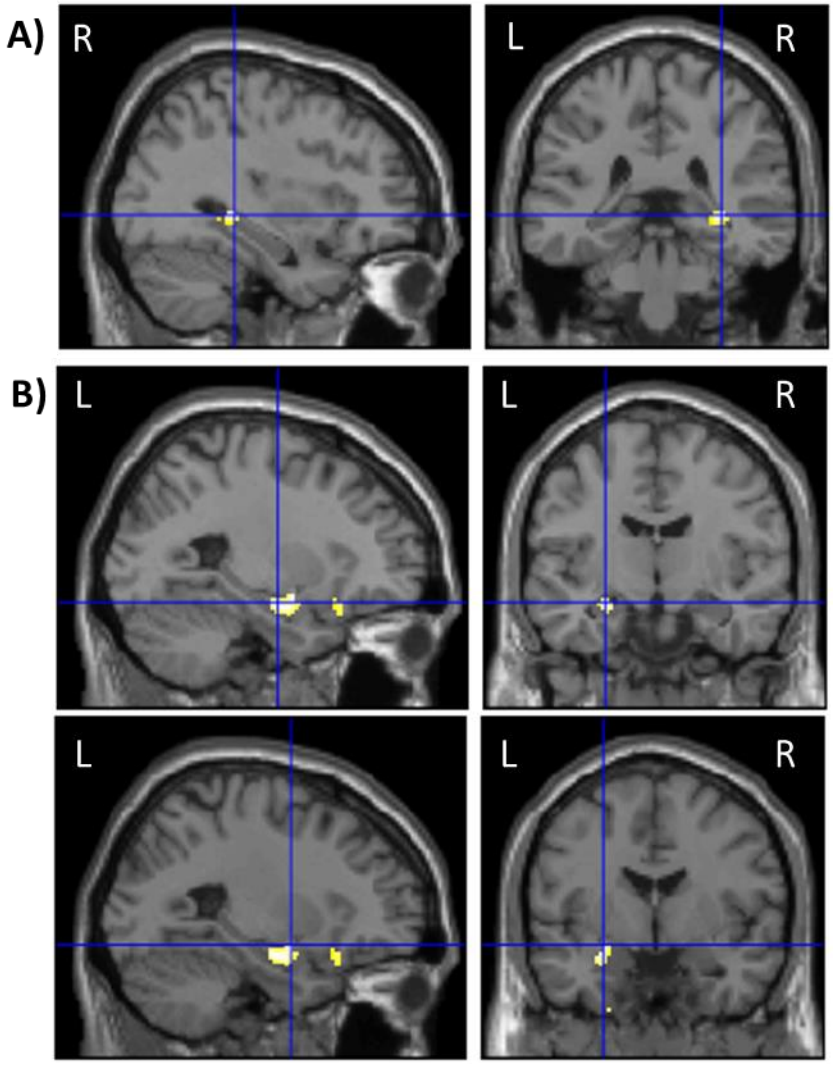

Figure 3. Correlations of memory performance with functional activation during memory encoding in RTLE patients displayed at a threshold of $p < 0.05$, uncorrected. A) Positive correlation of verbal learning with WR activations within the right hippocampus tail. B) Positive correlation of visual learning and FR activations within the left hippocampal head (top row) and the left amygdala (bottom row). L = left; R = right.

3.3. LTLE (Table 2)

In LTLE patients, more atrophy of the left hippocampal head was related to lower visual learning scores ($r(31) = 0.35$, $p = 0.05$). No correlations were found between the anterior-posterior deformation index of the left hippocampus and verbal learning ($r(31) = -0.26$, $p = 0.16$).

In this group, more atrophy of the left hippocampal head was related to less activation during verbal encoding within the right amygdala ($p_{FWE\text{-}corr} = 0.026$), the left parahippocampal gyrus ($p_{FWE\text{-}corr} = 0.031$) and the left hippocampus head ($p_{FWE\text{-}corr} = 0.044$) (Figure 4A), as well as to less activation during visual encoding within the left fusiform gyrus ($p_{FWE\text{-}corr} = 0.022$) (Figure 4B).

Although verbal learning scores were not significantly related to whole brain WR activations, visual learning scores were negatively related to FR activations within the right parahippocampal gyrus ($p_{FWE\text{-}corr} = 0.007$).

No other significant correlations were found.

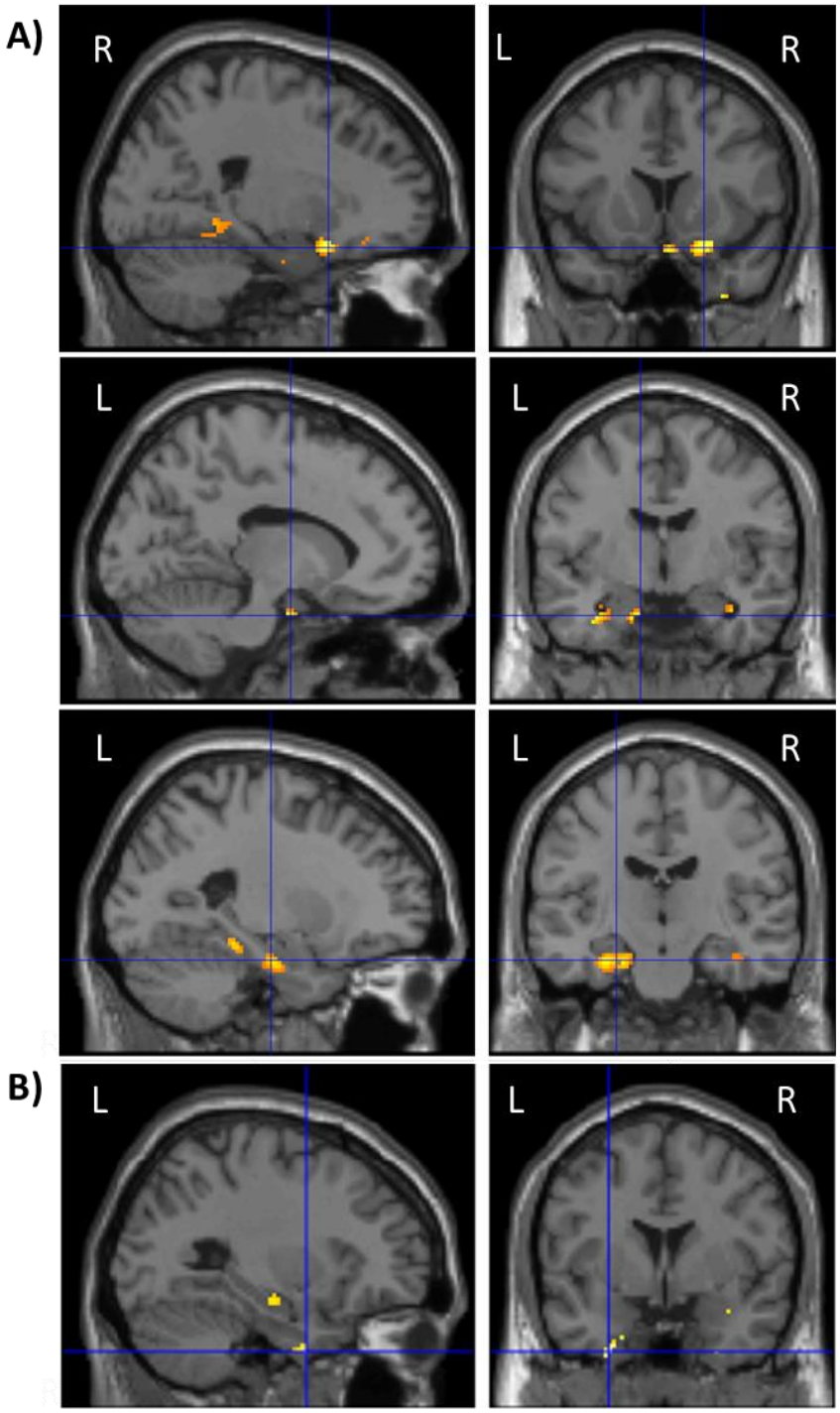

Figure 4. Correlations of atrophy pattern of the left hippocampus with functional activation during memory encoding in LTLE patients displayed at a threshold of $p < 0.05$, uncorrected. A) Correlations of more atrophy of the hippocampal head with less WR activation within the right amygdala (top row), the left parahippocampal gyrus (second row) and the left hippocampus head (bottom row). B) Correlations of more atrophy of the hippocampal head with less FR activation within the left fusiform gyrus. L = left; R = right.

Table 2. Associations of whole brain memory activations with anterior-posterior deformation values and learning scores in RTLE and LTLE patients. Medial temporal lobe activations are shown corrected for multiple comparisons using an SVC within a sphere of 6mm (FWE $p < 0.05$)

Group	Design	Covariate	Contrast	Region	k_E	z-score	$p_{FWE-corr}$	Coordinates (x,y,z)
RTLE	WR	More atrophy of the R hippocampus head	Positive	ns				
			Negative	R fusiform G	34	2.76	0.054	44,-38,-28
				L fusiform G	31	2.64	0.070	-34,-80,-18
		Verbal learning	Positive	R Hippocampus tail	43	2.64	0.072	34,-34,-2
			Negative	R Sup Frontal G (orbital part)	2783	5.12	0.021	18,28,-24
	FR	More atrophy of the R hippocampus head	Positive	ns				
			Negative	R Hippocampus body	42	3.50	0.008	22,-24,-8
				L Fusiform G	20	3.19	0.019	-24,-6,-46
		Visual learning	Positive	L Hippocampus head	101	3.19	0.019	-26,-10,-16
				L Amygdala	40	3.12	0.023	-26,-2,-12
			Negative	ns				
LTLE	WR	More atrophy of the L hippocampus head	Positive	ns				
			Negative	R Amygdala	20	2.86	0.026	36,0,-24
				L Parahippocampal G	29	2.80	0.031	-12,-6,-26
				L Hippocampus	90	2.52	0.044	-20,-12,-24
		Verbal learning	Positive	ns				
			Negative	ns				
	FR	More atrophy of the L hippocampus head	Positive	ns				
			Negative	L Fusiform G	19	2.82	0.022	-28,2,-42
		Visual learning	Positive	ns				
			Negative	R Parahippocampal G	50	3.27	0.007	24,10,-30

MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); AP= anterior-posterior; def. = deformation; FR = faces remembered; G = gyrus; Inf = inferior; L = left; R= right; Sup = superior; WR = words remembered.

4. Discussion

In the current study, we demonstrate that the anterior-posterior hippocampal surface-shape patterns are associated with poor visual memory in LTLE patients, although are not related to memory performance in RTLE patients. However, a disturbed structural integrity of the hippocampal head is related to less activation within the ipsilateral and contralateral medial temporal structures during memory encoding in both LTLE and RTLE patients. This functional activation seems to modulate verbal and visual learning through a pattern of associations dependent on the side of seizure focus. To our knowledge, this is the first study to investigate whether relative damage of the anterior or posterior hippocampus is linked to memory performance and to diverging functional activation during memory encoding.

RTLE patients presented worse visual learning than LTLE patients, without differences in verbal learning. These results are partially according to the material-specific model that states that visual deficits are usually observed in patients with seizure focus within right hemisphere (Smith & Milner, 1981), while patients with seizure focus within the left hemisphere are more likely to have verbal deficits (Frisk & Milner, 1990).

In RTLE patients, the atrophy pattern of the right hippocampus was not directly related to memory performance. Previous studies focused on the sub-regionally contribution of the hippocampus to memory encoding were based on histological cell counts, in which only limited slices from the anterior half of the hippocampus are analysed, limiting the establishment of conclusions. Schematically, the hippocampal head is most likely to correspond to atrophy in the cornus ammonis (CA) 1 subfield in these studies. A lack of relationships between neuronal cell counts in right CA1 and memory performance has been found (Baxendale et al., 1998b; Coras et al., 2014; Sass et al., 1995; Witt et al., 2014), but also a positive relationship (Comper et al., 2017; Pauli et al., 2006). Memory performance has also been associated with neuronal cell loss in CA3 and the dentate gyrus (DG) (Pauli et al., 2006), CA2, CA3, and CA4 (Zentner et al., 1999), or in CA4 affecting also CA3 and DG (Coras et al., 2014). Both the lack of significant relationships of memory performance with the atrophy pattern of the right hippocampus in our study and its heterogeneous relationships with specific hippocampal subfields in previous studies point to the possible modulating role of functional changes associated with hippocampal atrophy.

In fact, more atrophy of the right hippocampal head was related to less medial temporal activation during memory encoding. Patients with more atrophy of the right hippocampal head showed less activation within both fusiform gyri during verbal encoding, and less activation within the right hippocampus body and the left fusiform gyrus during visual encoding. Additionally, lower right temporal medial activation was associated with worse verbal learning, while lower left temporal medial activation was related to worse visual learning, suggesting interhemispheric compensation mechanisms. In contrast, a relationship was found between poor verbal learning and activation within the right superior frontal gyrus, which was not associated with the atrophy pattern. Considering the hippocampus as a whole, Powell et al. (2007) found that more severe right hippocampal pathology leads to less activation in the damaged hippocampus, but greater activation in the contralateral hippocampus -an inefficient activation pattern for visual recall. Our results suggest that the structural integrity of the right hippocampal head is critical for the functional memory encoding network in the ipsilateral and contralateral medial temporal lobes. These results argue against a traditional fully lateralised model of material-specific memory, supporting that a more bilateral representation of memory encoding within medial temporal lobes in RTLE patients could be adaptive, as we previously reported only during visual encoding (Sidhu et al., 2013).

In LTLE patients, the atrophy pattern of the left hippocampus was not related to verbal learning. In previous histopathological studies, poor verbal memory has been linked to neuronal cell loss in CA1 (Baxendale et al., 1998b; Sass et al., 1995), but also in CA3 and the hilar area (Sass et al., 1990, 1992). Histopathological studies have not explored in most cases the link between neuronal cell loss in the left hippocampus and visual memory (Baxendale et al., 1998b; Sass et al., 1995). However, we found that patients with more atrophy in the left hippocampal head were more likely to have a poor visual memory. Visual memory has been identified as a bilateral process, which may largely be mediated by the verbalization of the information to be learned (van Asselen et al., 2006). Our results may help to better classify LTLE phenotypes, identifying those with a more diffuse pattern of memory impairments.

More atrophy in the left hippocampal head was also related to less medial temporal activation during memory encoding. Specifically, patients with more atrophy of the left hippocampal head had less activation within the right amygdala, the left parahippocampal gyrus, and the left hippocampal head during verbal encoding, and less activation within the left fusiform gyrus during visual encoding. In this group, the results are more intriguing since none of these activations shows an association with memory performance. In contrast, the only

association found was a negative relationship between visual learning performance and right medial temporal activation, which was not associated with the atrophy pattern. Richardson et al. (2004) found that more severe hippocampal pathology was related to less activation in the damaged hippocampus and more activation in the contralateral hippocampus in LTLE patients during verbal encoding – an inefficient activation pattern for verbal memory. However, our results suggest that the structural integrity of the left hippocampal head is critical for the functional verbal encoding network in both medial temporal lobes. These changes seem to be subtle since they do not translate into changes in verbal learning performance. As far as we know, no studies have analysed these relationships during visual encoding in LTLE patients. Our results indicate that the disruption of the left hippocampal head is directly linked to worse visual learning performance, and this performance is not mediated by the functional activation associated with the hippocampal atrophy pattern.

Some limitations should be considered. Firstly, the analysis method was restricted to the hippocampal surface, so hippocampal subfields hidden in depth (CA4) could not be explored. Secondly, given the cross-sectional design of our study, it is not possible to describe functional activation as functional memory reorganization. Finally, patients were treated with AEDs, which could influence memory performance, although this influence cannot be eliminated, should not be different between patient groups.

Taken together, our findings suggest that a disturbed structural integrity predominantly of the hippocampal head interferes with the functional memory encoding network in the ipsilateral and contralateral medial temporal lobes. This functional activation translates into poor memory performance in RTLE patients, but not in LTLE patients, in whom more atrophy in the left hippocampal head is directly related to poor visual memory. Considering that the hippocampal head is usually included in a standard anterior temporal lobe resection (Baxendale, Thompson, & Kitchen, 2000), these results could explain why surgical removal of the anterior temporal lobe frequently leads to postsurgical memory deficits (Cano-López et al., 2017).

CHAPTER 5

Study 2

Typical asymmetry in the hemispheric activation during an fMRI verbal comprehension paradigm is related to better performance in verbal and non-verbal tasks in patients with epilepsy [1]

[1] Published in: Cano-López, I., Calvo, A., Boget, T., Carreño, M., Donaire, A., Setoain, X., ... & Bargalló, N. (2018a). Typical asymmetry in the hemispheric activation during an fMRI verbal comprehension paradigm is related to better performance in verbal and non-verbal tasks in patients with epilepsy. *NeuroImage: Clinical*, *20*, 742-752.

1. Introduction

Some 30% of patients with epilepsy have drug-resistant epilepsy (Barr & Morrison, 2014), in which brain injury around eloquent language areas can induce inter-hemispheric language reorganisation (Tzourio-Mazoyer et al., 2017). As a result, patients with epilepsy have bilateral or right-hemispheric language lateralization more frequently than the general population (Hamberger & Cole, 2011). This pattern of language lateralization was defined as atypical in classic studies based on the Wada test, considering left-hemispheric lateralization as the typical pattern (Mateer & Dodrill, 1983).

Several factors have been proposed as possible mediators of this atypical pattern, such as age at epilepsy onset (Brázdil, Zákopčan, Kuba, Fanfrdlová, & Rektor, 2003; Miró et al., 2014), gender (Adcock, Wise, Oxbury, Oxbury, & Matthews, 2003; Helmstaedter, Kurthen, Linke, & Elger, 1997), handedness (Corballis, Badzakova-Trajkov, & Häberling, 2012), and location of seizure focus (Duke et al., 2012). The explicative mechanism has not yet been fully explained (Piervincenzi et al., 2016).

Although a certain consensus exists about language reorganization in patients with left hemisphere (LH) focus, the cognitive implications of this remain unclear. Using the Wada test, atypical language lateralization in patients with LH focus was related to decreases in non-verbal functions, but preserved verbal abilities (Loring et al., 1999; Strauss et al., 1990). Using an fMRI language paradigm, Berl et al. (2005) showed that those with atypical hemispheric asymmetry had lower scores in performance intelligence quotient (IQ) than those with typical asymmetry, although performances in verbal tasks are similar. However, Thivard et al. (2005) found better performance in verbal fluency and delayed verbal memory in those with atypical patterns of activation (considering that as a compensatory mechanism).

fMRI allows us to approach this problem in a non-invasive way (Benjamin et al., 2017), although results are far from homogeneous due to the high variability in the paradigms used (Tzourio-Mazoyer et al., 2017). Among them, a single phonemic verbal fluency paradigm has been one of the most frequently used. However, this paradigm could favor left frontal lobe activation corresponding to Broca's area, and less prominent activation of the medial or superior temporal lobes (Bonelli et al., 2012). Verbal comprehension paradigms would provide better information about semantic and syntactic processing (Ni et al., 2000), so it is likely to show higher sensitivity in temporal lobe epilepsy (TLE) – the most frequent type of drug-resistant epilepsy (Téllez-Zenteno & Hernández-Ronquillo, 2012). Additionally, verbal comprehension

paradigms are a little less dependent on the active performance of the patient, thus the patient only has to listen and understand a short story and the task is carried out covertly. The non-excessive complexity of this paradigm could avoid poor activation patterns as a result of underperformance (Miró et al., 2014).

The current study assesses the relationship between asymmetry in the hemispheric activation during an fMRI verbal comprehension paradigm and performance in verbal and non-verbal tasks when considering possible mediator factors. According to the 'crowding' phenomenon, higher right hemisphere (RH) activation during language processing could imply a competition of cognitive resources in the performance of the same task, disrupting cognitive performance (Jokeit & Ebner, 2002). Considering that chronic epilepsy could imply a progressive cognitive deterioration, and that previous studies have found that cognitive variables are interrelated (Cano-López et al., 2017) and depend on a functional brain network (Dinkelacker et al., 2015), we hypothesize that higher RH activation during verbal comprehension could disrupt performance in various cognitive domains. For that, firstly, a positive relationship is expected between typical hemispheric asymmetry and performance in verbal tasks, but also in non-verbal tasks for which the RH is typically dominant, in the total sample. Secondly, in patients with LH focus, more frequent atypical asymmetry than in patients with RH focus is hypothesized, and this will be related to lower performance in verbal and non-verbal tasks. Finally, the role of side of seizure focus, location of seizure focus, age at epilepsy onset, seizure frequency, number of antiepileptic drugs (AEDs), gender, and handedness on fMRI activation patterns, and the impact of these factors and fMRI activation patterns on performance in verbal and non-verbal tasks are examined.

This study contributes to understanding the relationship between the asymmetry in fMRI activation and the cognitive profile of patients who are candidates for epilepsy surgery, which could be useful in the clinical management of such patients. Whereas prior studies primarily used fMRI paradigms that favor frontal lobe activation and less prominent activation of the medial or superior temporal lobes, we used a verbal comprehension paradigm previously demonstrated to reliably activate receptive language areas. Additionally, we include more cognitive domains than previous studies to more comprehensively analyse this issue.

2. Material and methods

2.1. Sample

The sample was composed of 47 adult patients with drug-resistant epilepsy that were candidates for epilepsy surgery (mean age ± *SD*: 33.72 ± 12.15, range: 18-61).

2.2. Procedure

This study was conducted in the Epilepsy Unit at the Hospital Clínic of Barcelona between 2008 and 2017 in accordance with the Declaration of Helsinki. Informed consent was obtained from participants in the study.

Medical history provided characteristics of the patients such as gender, age, level of education, handedness, age at epilepsy onset, duration of epilepsy (years), frequency of seizures (seizures per month), pre-surgical number of AEDs and type of AEDs.

Pre-surgical assessment included the diagnosis of drug-resistant epilepsy, as well as the lateralization and location of the epileptogenic area. Assessment was made by the multidisciplinary team staff members based on an evaluation that included: seizure history and semiology; neurologic examination; long-term video-EEG monitoring; 3-Tesla magnetic resonance imaging (MRI); fluorodeoxyglucose (FDG)-positron emission tomography (PET); single photon emission computed tomography (SPECT); psychiatric assessment; language fMRI assessment; and neuropsychological evaluation.

Considering this assessment, patients were divided into groups based on the side of seizure focus –LH focus (80.9%) and RH focus (19.1%), and the location of seizure focus –temporal (72.3%) and extratemporal (27.7%).

2.3. Neuropsychological assessment

2.3.1. IQ outcome

This was estimated by means the verbal subtests (vocabulary and digit span) and performance subtests (block design and digit symbol) of the Wechsler Adult Intelligence Scale-3rd Edition (Wechsler et al., 1997a). Z-scores of each subtest were computed.

2.3.2. Executive functions

The Trail Making Test (TMT; Reitan & Wolfson, 1985) was used to measure various executive functions (working memory, attention, planning and set shifting) that require motor skills and visual-spatial processing. In part A, participants were requested to draw a line to connect 25 circles with successive numbers and in the correct order, while in part B letters and numbers had to be linked. Z-scores for both parts were computed.

2.3.3. Logical memory

Evaluated by means Logical Memory I and II subtests of the Wechsler Memory Scale-3rd Edition (Wechsler, 1997b), consisting of immediate and delayed recall of two short stories. Z-scores of immediate and delayed logical memory were computed.

2.3.4. Verbal learning and memory

The Rey Auditory Verbal Learning Test (Rey, 1964) was used to evaluate the patient's ability to encode, consolidate, and retrieve verbal information. It consisted of five trials of learning a list of 15 words. Verbal learning was computed by summing the total number of correctly reproduced words over the five learning trials, and long-term verbal memory was computed as the total number of correctly recalled words 30 minutes after the list presentation. These scores were transformed into z-scores following the normative data.

2.3.5. Visual memory

Evaluated using the Visual Reproduction I and II subtests of the Wechsler Memory Scale-Revised (Wechsler, 1987). Participants were instructed to draw geometric designs from memory after seeing them for a brief period of time. Z-scores of immediate and delayed visual memory were computed.

2.3.6. Naming functions

The Boston Naming Test (Kaplan, Goodglass, & Weintraub, 2001) was used to assess visual confrontation naming. Semantic and phonemic cues were provided in the case of no response or incorrect response. The total score was computed as the number of cards correctly named without phonemic cues and with 60 being the maximum score, and it was transformed into z-scores following the normative data of Aranciva et al. (2011).

2.3.7. Phonemic fluency

The total number of words generated in one minute for the letters F, A, and S was obtained (Spreen & Benton, 1977). The total score was computed as the sum of all admissible words for the three letters, and it was transformed into z-scores following the normative data of Tombaugh, Kozak, and Rees (1999).

2.3.8. Semantic fluency

Participants were asked to 'think of the names of as many animals that they could in one minute (Rosen, 1980). The total score was computed as the sum of admissible words for this semantic category, and it was transformed into z-scores following the normative data of Tombaugh et al. (1999).

2.4. Language fMRI acquisition and analyses

The study was performed at the Magnetic Resonance Image Core Facility at IDIBAPS located in the Diagnostic Imaging Centre at Hospital Clinic (CDIC) using the blood-oxygen level-dependent (BOLD) fMRI signal. All scans were performed on a 3 T Siemens MAGNETOM TIM Trio scanner (Siemens Medical Systems, Germany), using an 8-channel head coil for radio frequency transmission and signal reception. Each subject underwent a 3D structural scan high-resolution T1-weighted MPRAGE sequence. Acquisition consisted of a set of 240 adjacent sagittal images with a slice thickness of voxel size 1x1x1 mm, using a spoiled

gradient echo sequence (TR:2300 ms, TE:298 ms, NEX:1, flip angle: 90º, FOV: 256 x 256). fMRI images were acquired in the axial plane with an EPI sequence (TR:3000 ms, TE: 30 ms, flip angle: 90º, pixel matrix: 3.75x3.75 mm, slice thickness: 3 mm).

We used an fMRI adaptation of the logical memory test of the Wechsler Memory Scale-3rd Edition (Wechsler, 1997b) to analyse brain activation during verbal comprehension. The experimental design was an AB 'boxcar' with the 30-s verbal comprehension task (A) alternating with 30 s of control task (B) for a total of six cycles (over 3 min). In the verbal comprehension task, participants were instructed to listen and understand a short story, while the control task consisted of listening to the language content of the story digitally backwards. After the acquisition, participants were asked about the story to control their performance in the task.

Data were analysed using statistical parametric mapping (SPM 12; Wellcome Trust Centre for Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm/). Scans from each subject were realigned using the mean image as a reference to remove any minor motion-related signal change, and coregistered with the anatomical image. The resulting data set was segmented, and scans were spatially normalised into standard space (3 x 3 x 3 mm; Montreal Neurology Institute, MNI coordinates) and spatially smoothed with a Gaussian kernel of 8 mm FWHM.

After data pre-processing, statistical analyses were performed at the single-subject level using the general linear model implemented in SPM (Friston et al., 1994). Condition-specific effects were estimated by creating boxcar functions of task against control. Statistical parametrical maps were created and thresholded using *a* p-value of 0.001, uncorrected for multiple comparisons (T value > 3.26). The contrast image (verbal comprehension relative to baseline) for each subject was then entered into a second level one-sample t-test to analyse activations in the ROIs. The ROIs included superior temporal gyrus (Brodmann's area (BA) 22), middle temporal gyrus (BA 21), temporal pole (BA 38), angular gyrus (BA 39) and auditory cortex (BA 41) in both hemispheres. Selection of ROIs was based on lesion and imaging data implicating them in language processing (Ahmad, Balsamo, Sachs, Xu, & Gaillard, 2003), and was supported by SPM maps, which are not based on a priori assumptions, using Wake Forest University (WFU) PickAtlas Tool Version 2.4 (http://fmri.wfubmc.edu/software/PickAtlas) software (Maldjian, Laurienti, Kraft, & Burdette et al., 2003). We report all ROIs activations corrected for multiple comparisons [family wise error (FWE)], $p < 0.05$. Parametrical maps were inspected for their validity and all participants

activated ROIs. Using these parametrical maps, we computed the sum of the activated voxels in the ROIs volumes.

Laterality indexes (LIs) that reflect the interhemispheric difference between voxel counts in left and right homologous ROIs were calculated for each ROI using the bootstrap method of the SPM toolbox (Wilke & Lidzba, 2007). Activation was considered 'left-sided' if the LI was > 0.2; 'right-sided' if the LI was smaller than -0.2; and bilateral if the LI ranged between 0.2 and -0.2 (Ahmad et al., 2003; Lee, Pouratian, Bookheimer, & Martin, 2010). Asymmetry in the hemispheric activation was categorised as: 'typical' -unilateral left preponderance (LI > 0.2) and 'atypical'-bilateral (LI between -0.2 and 0.2) or unilateral right preponderance (LI < -0.2), as in previous studies that include the same paradigm (Chaudhary et al., 2017; Gaillard et al., 2007) or other auditory paradigms that require verbal comprehension (Berl et al., 2005). Thus, the higher LI, the higher degree of LH activation.

2.5. Statistical analyses

The Kolmogorov-Smirnov test was carried out to examine the normality of the data. T-tests for independent samples were then performed for between-group comparisons based on the asymmetry in the hemispheric activation (typical or atypical) on demographic (age) and epilepsy-related variables (age at epilepsy onset, epilepsy duration, number of AEDs and frequency of seizures per month), according to Levene's test for equality of variance. The chi-square test was used to study the differences between these groups in categorical variables such as gender, educational level, handedness, epilepsy type (comparing the frequency of frontal lobe epilepsy (FLE), TLE, parietal lobe epilepsy, occipital lobe epilepsy and multifocal epilepsy), location of seizure focus (temporal or extratemporal), side of seizure focus, etiology of the pathology (comparing the frequency of hippocampal sclerosis (HS), focal cortical dysplasia, tumor, gliosis, heterotopia, general atrophy, encephalocele, encephalomalacia, subcortical lesions and non-specific pathology), presence of HS versus all other pathologies, frequency of use of each type of AED, seizure type, and presence of psychiatric disorders.

To check the impact of the side of seizure focus and the location of seizure focus on LI, univariate ANOVAs were carried out in the total sample. Univariate ANOVAs were also performed in the subgroup of TLE, including the presence of HS as between-subject factor. Secondary analyses were carried out to evaluate the differences in age at epilepsy onset, gender,

and handedness depending on the side of seizure focus, the location of seizure focus or the presence of HS (in TLE subgroup), using chi-square test or t-test for independent samples where appropriate. When significant differences in these variables were found, they were included as covariates in the previous ANOVAs.

To evaluate the possible predictors of LI, hierarchical regressions were carried out, including LI as a dependent variable, and two separate blocks of independent variables (block 1: gender and handedness; and block 2: side of seizure focus, age at epilepsy onset, seizure frequency and number of AEDs).

To analyse the impact of the asymmetry in the hemispheric activation (typical or atypical) and the side of seizure focus (LH or RH focus) on cognitive performance, univariate ANOVAs were carried out in the total sample, including the hemispheric activation and the side of seizure focus as between-subject factors, and cognitive scores as dependent variables. These ANOVAs were repeated in the subgroup of TLE, including also the presence of HS as a between-subject factor.

Spearman correlations were performed to establish the association between LI and cognitive performance in the total sample, in groups based on the location of seizure focus, and in groups based on the side of seizure focus. Multiple testing correction controlling the False Discovery Rate (FDR) was applied in these correlations (Benjamini & Yekutieli, 2001). The FDR was set to 0.10, which implies that the proportion of significant associations which are actually false discoveries is limited no more than 10%, as in other neuropsychological studies (Gallagher et al., 2014).

To evaluate the role of possible predictors of cognitive performance, hierarchical regressions were carried out on the total sample, including cognitive scores as dependent variables and three separate blocks of independent variables (block 1: gender and handedness; block 2: side of seizure focus, location of seizure focus, and age at epilepsy onset; and block 3: LI).

Statistical analysis was carried out using SPSS 22.0 and two-tailed tests with p set to 0.05 considered as significant.

3. Results

3.1. fMRI results

Significant activation was demonstrated in the bilateral superior temporal gyrus, middle temporal gyrus and angular gyrus, as well as in the right temporal pole and auditory cortex during the verbal comprehension fMRI paradigm (Figure 1 and Table 2).

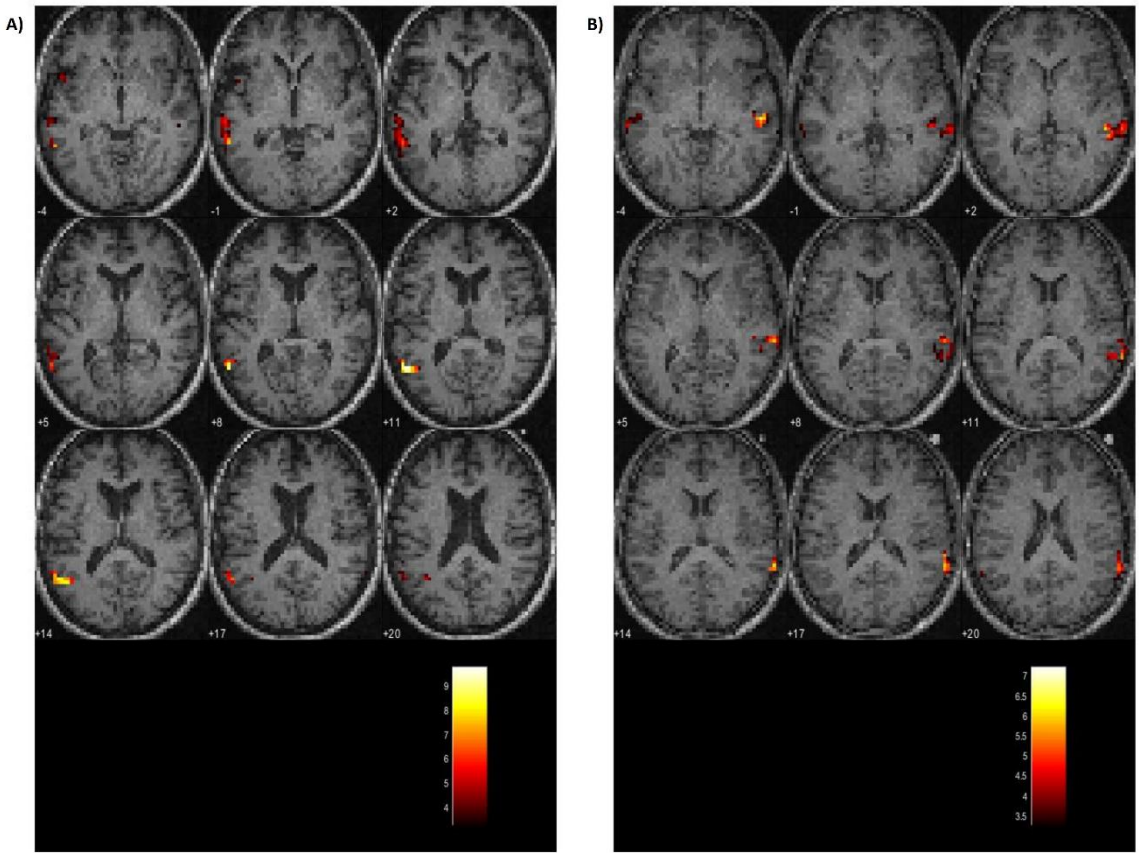

Figure 1. Structural axial images fused with the activation maps in ROIs during an fMRI verbal comprehension paradigm in two patients. Patient A had a RH epileptic focus and presented typical hemispheric asymmetry (LI = 0.80). Patient B had a LH epileptic focus and presented atypical hemispheric asymmetry (LI = -0.65).

3.2.Characteristics of patients based on LI and LI predictors.

Using LI classification criteria, 23 patients had left-sided activation (48.9%), 19 patients had right-sided activation (40.4%) and 5 patients had bilateral activation (10.6%). Thus, patients were distributed into two groups of hemispheric asymmetry (Table 1): typical (48.9%) and atypical (51.1%).

Table 1. Characteristics of the total sample (mean ± SD or %) and groups with typical and atypical hemispheric asymmetry

Characteristics	Total	Typical asymmetry	Atypical asymmetry	*p*
Age	33.72 ± 12.15	35.26 ± 13.57	32.25 ± 10.69	0.40
Gender				
Female	22 (46.8%)	10 (43.5%)	12 (50.0%)	0.65
Male	25 (53.2%)	13 (56.5%)	12 (50.0%)	
Educational level				0.11
Primary education	23 (48.9%)	9 (39.1%)	14 (58.3%)	
Secondary education	7 (14.9%)	2 (8.7%)	5 (20.8%)	
Lower-university education	10 (21.3%)	8 (34.8%)	2 (8.3%)	
University education	7 (14.9%)	4 (17.4%)	3 (12.5%)	
Handedness				0.24
Right	25 (53.2%)	13 (56.5%)	12 (50.0%)	
Left	20 (42.6%)	8 (34.8%)	12 (50.0%)	
Ambidextrous	2 (4.3%)	2 (8.7%)	0 (0.0%)	
Epilepsy type				0.24
FLE	8 (17.0%)	1 (4.3%)	7 (29.2%)	
TLE	34 (72.3%)	20 (87.0%)	14 (58.3%)	
PLE	1 (2.1%)	0 (0.0%)	1 (4.2%)	
OLE	1 (2.1%)	1 (4.3%)	0 (0.0%)	
Multifocal	3 (6.4%)	1 (4.3%)	2 (8.3%)	
Location of seizure focus				0.03
Temporal	34 (72.3%)	20 (87.0%)	14 (58.3%)	
Extratemporal	13 (27.7%)	3 (13.0%)	10 (41.7%)	
Side of seizure focus				0.05
RH	9 (19.1%)	7 (30.4%)	2 (8.3%)	
LH	38 (80.9%)	16 (69.6%)	22 (91.7%)	
Age at epilepsy onset	11.91 ± 11.02	9.70 ± 8.82	14.13 ± 12.66	0.18
Epilepsy duration	21.83 ± 13.86	25.57 ± 16.19	18.09 ± 10.07	0.07
Etiology of pathology				0.20
HS	17 (36.2%)	8 (34.8%)	9 (37.5%)	
Focal cortical dysplasia	10 (21.3%)	6 (26.1%)	4 (16.7%)	
Tumor	2 (4.2%)	1 (4.3%)	1 (4.2%)	
Gliosis	3 (6.4%)	0 (0.0%)	3 (12.5%)	
Heterotopia	3 (6.4%)	3 (13.0%)	0 (0.0%)	
General atrophy	4 (8.5%)	1 (4.3%)	3 (12.5%)	
Encephalocele	1 (2.1%)	0 (0.0%)	1 (4.2%)	
Encephalomalacia	1 (2.1%)	0 (0.0%)	1 (4.2%)	
Subcortical lesions	1 (2.1%)	0 (0.0%)	1 (4.2%)	
Non-specific pathology	5 (10.6%)	4 (17.4%)	1 (4.2%)	

Table 1 (cont.)

Characteristics	Total	Typical asymmetry	Atypical asymmetry	*p*
Presence of HS				0.85
Yes	17 (36.2%)	8 (34.8%)	9 (37.5%)	
No	30 (63.8%)	15 (65.2%)	15 (62.5%)	
Number of AEDs	2.75 ± 0.84	2.64 ± 0.66	2.86 ± 0.99	0.38
Type of AEDs				
Levetiracetam	20 (42.6%)	12 (52.2%)	8 (33.3%)	0.19
Lacosamide	19 (40.4%)	8 (34.8%)	11 (45.8%)	0.44
Carbamazepine	14 (29.8%)	6 (26.1%)	8 (33.3%)	0.59
Eslicarbazepine	6 (12.8%)	4 (17.4%)	2 (8.3%)	0.35
Sodium valproate	5 (10.6%)	3 (13.0%)	2 (8.3%)	0.60
Lamotrigine	3 (6.4%)	1 (4.3%)	2 (8.3%)	0.58
Perampanel	1 (2.1%)	0 (0.0%)	1 (4.2%)	0.32
Clobazam	14 (29.8%)	9 (39.1%)	5 (20.8%)	0.17
Zonisamide	3 (6.4%)	1 (4.3%)	2 (8.3%)	0.58
Clonazepam	3 (6.4%)	2 (8.7%)	1 (4.2%)	0.53
Oxcarbazepine	11 (23.4%)	6 (26.1%)	5 (20.8%)	0.67
Phenobarbital	5 (10.6%)	1 (4.3%)	4 (16.7%)	0.16
Topiramat	7 (14.9%)	3 (13.0%)	4 (16.7%)	0.73
Phenytoin	3 (6.4%)	0 (0.0%)	3 (12.5%)	0.08
Pregabalin	5 (10.6%)	2 (8.7%)	3 (12.5%)	0.67
Retigabine	1 (2.1%)	0 (0.0%)	1 (4.2%)	0.32
Seizures per month	15.68 ± 16.67	12.45 ± 14.40	18.63 ± 18.39	0.22
Seizure type				0.36
SPS	4 (8.5%)	2 (8.7%)	2 (8.3%)	
CPS	18 (38.3%)	9 (39.1%)	9 (37.5%)	
GTCS	4 (8.5%)	1 (4.3%)	3 (12.5%)	
SPS + CPS	6 (12.8%)	5 (21.7%)	1 (4.2%)	
SPS + GTCS	1 (2.1%)	0 (0.0%)	1 (4.2%)	
CPS + GTCS	9 (19.1%)	5 (21.7%)	4 (16.7%)	
SPS + CPS + GTCS	5 (10.6%)	1 (4.3%)	4 (16.7%)	
Psychiatric disorder				0.85
Yes	17 (36.2%)	8 (34.8%)	9 (37.5%)	
No	30 (63.8%)	15 (65.2%)	15 (62.5%)	

Note. CPS: complex partial seizure, FLE: frontal lobe epilepsy, GTCS: secondary generalized seizures, HS: hippocampal sclerosis, ILE: insular epilepsy, LH: left hemisphere, OLE: occipital lobe epilepsy, PLE: parietal lobe epilepsy, RH: right hemisphere, SPS: simple partial seizure, TLE: temporal lobe epilepsy.

Table 2. fMRI activation peaks for the main effects of verbal comprehension in the total sample in ROIs shown corrected for multiple comparisons (FWE) $p < 0.05$

Z-score	Corrected p-value (FWE)	Coordinates (x, y, z) in MNI space	Region
4.68	0.001	-54, -1, -13	Left superior temporal gyrus (BA 22)
4.49	0.002	-54, -10, -7	Left superior temporal gyrus (BA 22)
5.46	0.0001	48, -19, -7	Right superior temporal gyrus (BA 22)
4.75	0.001	54, -4, -13	Right superior temporal gyrus (BA 22)
3.79	0.031	57, -19, -7	Right superior temporal gyrus (BA 22)
4.18	0.007	-54, -46, 2	Left middle temporal gyrus (BA 21)
3.95	0.018	60, -37, -1	Right middle temporal gyrus (BA 21)
3.92	0.020	54, -4, -19	Right middle temporal gyrus (BA 21)
4.62	0.001	54, 8, -19	Right temporal pole (BA 38)
4.56	0.002	-57, -49, 11	Left angular gyrus (BA 39)
4.29	0.005	-54, -58, 14	Left angular gyrus (BA 39)
3.80	0.030	-39, -55, 20	Left angular gyrus (BA 39)
4.96	0.0001	63, -49, 14	Right angular gyrus (BA 39)
4.22	0.006	42, -34, 5	Right auditory cortex (BA 41)

MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); BA, Brodmann's area; ns, not significant.

No significant differences between these groups were found in age, age at epilepsy onset, epilepsy duration, number of AEDs, and frequency of seizures. Additionally, there were no significant differences between these groups in gender, educational level, handedness, epilepsy type, etiology of the pathology, presence of HS versus all other pathologies, frequency of use of each type of AED, seizure type and presence of psychiatric disorders. However, a significant difference was found for the side of seizure focus, with a higher proportion of patients with LH focus having atypical hemispheric asymmetry. Accordingly, patients with LH focus have lower LI than patients with RH focus ($F(1,46) = 6.31$, $p = 0.016$, $n^2_p = 0.12$; LI = -0.06 ± 0.08 *versus* LI = 0.42 ± 0.17, respectively). Groups with LH and RH focus did not differ in age at epilepsy onset, gender, nor handedness.

A significant difference was also found for the location of seizure focus, with a higher proportion of patients with an extratemporal focus having atypical hemispheric asymmetry. These groups did not differ in age at epilepsy onset and gender, but in the group of patients with an extratemporal focus, there was a higher proportion of left-handedness patients (76.9%) than in the group with temporal focus (29.4%) ($\chi^2 = 8.68$, $p = 0.003$). For that, to analyse the effect

of the location of seizure focus on LI, handedness was included as covariate, and no significant effects were found ($F(1,46) = 2.40$, $p = 0.13$, $n^2_p = 0.05$), so the location of seizure focus was not included as possible predictor of LI in the regression analysis. Additionally, in the subgroup of 34 patients with TLE, patients without HS (n = 18) tended to have higher LI than those with HS (n = 16) ($F(1,33) = 3.40$, $p = 0.07$, $n^2_p = 0.10$; LI = 0.28 ± 0.51 *versus* LI = -0.05 ± 0.53, respectively). These patients did not differ in age at epilepsy onset, gender, nor handedness.

In the total sample, higher LI was predicted by right-handedness and RH focus, while age at epilepsy onset, seizure frequency, number of AEDs and gender were not significant predictors (Table 3).

Table 3. Hierarchical regression analyses investigating the effect of gender, handedness, side of seizure focus and age at epilepsy onset on LI

	LI (indicating typical hemispheric asymmetry)						
	Std β	*p*	Δ R^2	*p*	Adj. R^2	*F*	*p*
Block 1			0.06	0.28	0.02	1.44	0.25
Gender	-0.11	0.49					
Handedness	0.40	0.02*					
Block 2			0.21	0.01*	0.21	2.78	0.03*
Side of seizure focus	0.38	0.02*					
Age at epilepsy onset	-0.26	0.12					
Seizure frequency	0.08	0.63					
Number of AEDs	-0.14	0.39					

*: $p < .05$

3.3. Cognitive performance depending on asymmetry in hemispheric activation and side of seizure focus

Significant effects of 'asymmetry in the hemispheric activation' were found in the digit symbol task and verbal learning in the total sample, patients with typical hemispheric asymmetry having better performance in both tasks ($F(1,41) = 7.03$, $p = 0.01$, $n^2_p = 0.16$, and $F(1,42) = 6.56$, $p = 0.014$, $n^2_p = 0.14$, respectively) (Figure 2).

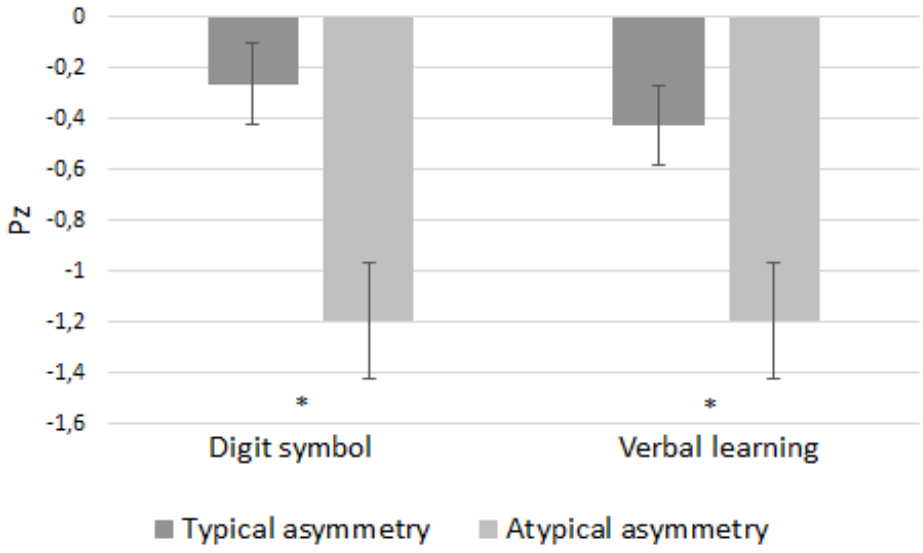

Figure 2. Performance in Digit symbol task and verbal learning (z-scores) depending asymmetry in hemispheric activation during verbal comprehension.

These significant effects remained in the subgroup of patients with TLE (n = 34) (for all, $p < 0.032$). Additionally, in this subgroup, patients without HS (n = 18) had higher scores in delayed logical memory and long-term verbal memory than those with HS (n = 16) ($F(1,33) = 4.46$, $p = 0.04$, $n^2_p = 0.16$ and $F(1,33) = 4.98$, $p = 0.034$, $n^2_p = 0.15$, respectively). Given the limited patients in our study with an extratemporal focus (n = 13), we cannot analyse the effect of the asymmetry in the hemispheric activation on cognitive performance in this subgroup.

No significant effects of the side of seizure focus on any cognitive task were found.

3.4.LI, cognitive performance, and predictor factors

Positive associations were found between LI and immediate logical memory ($r = 0.30$, $p = 0.04$), delayed logical memory ($r = 0.36$, $p = 0.01$), block design ($r = 0.36$, $p = 0.018$), digit symbol ($r = 0.53$, $p < 0.0001$), TMT A ($r = 0.34$, $p = 0.026$), immediate visual memory ($r = 0.37$, $p = 0.01$), delayed visual memory ($r = 0.32$, $p = 0.028$), and verbal learning ($r = 0.36$, $p = 0.02$) (Figure 3). All correlations passed FDR multiple testing correction.

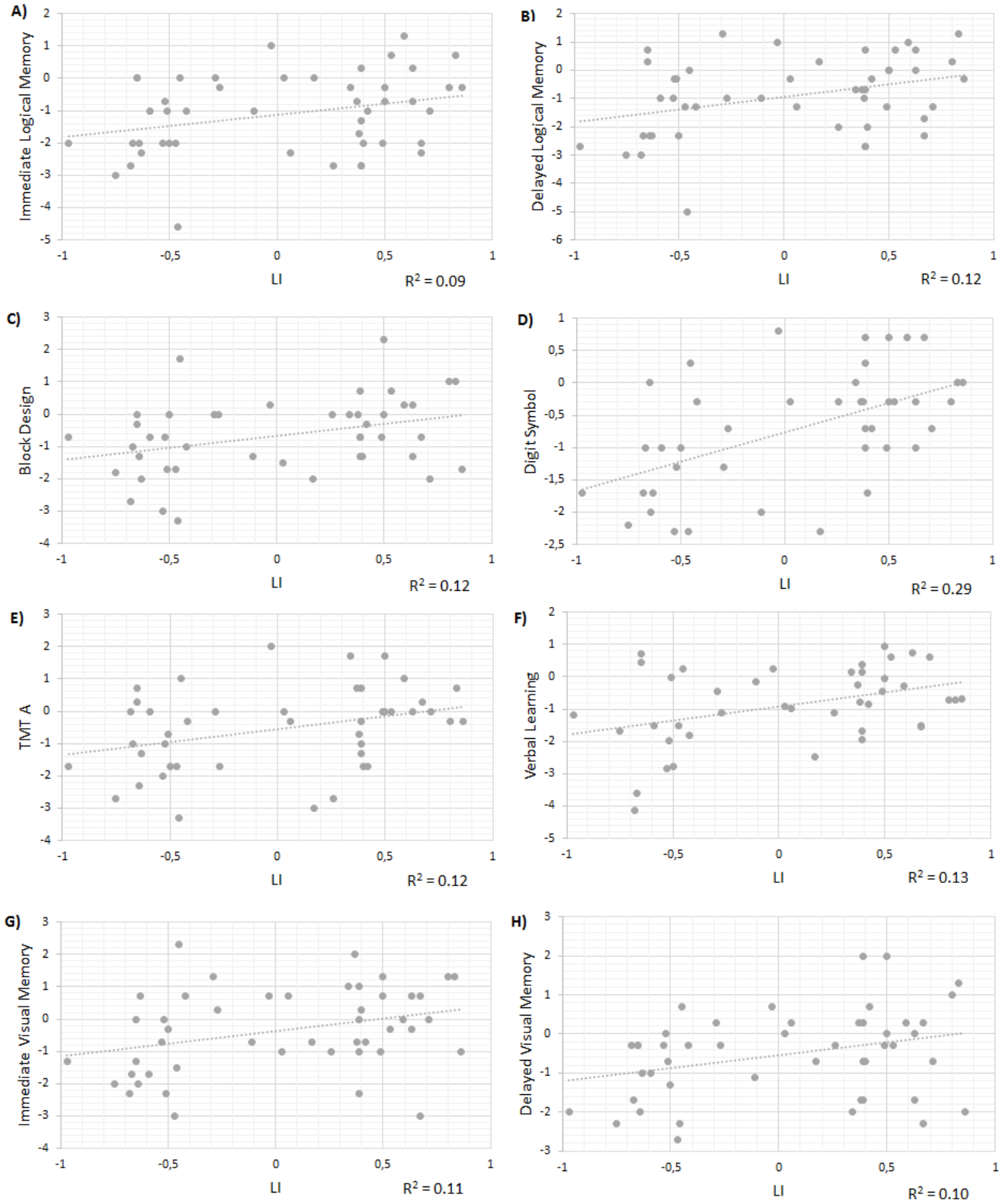

Figure 3. Associations between LI and cognitive performance (z-scores) in the total sample.

In the subgroup of patients with TLE (n = 34), LI was also significantly related to immediate logical memory (r = 0.32, p = 0.05), delayed logical memory (r = 0.37, p = 0.03), digit symbol (r = 0.48, p = 0.005), immediate visual memory (r = 0.33, p = 0.05), and delayed visual memory (r = 0.34, p = 0.05). Only the association between LI and digit symbol remained significant with FDR < 0.10 in this subgroup (Figure S1). In patients with extratemporal focus (n = 13), LI was not related to performance in any cognitive task.

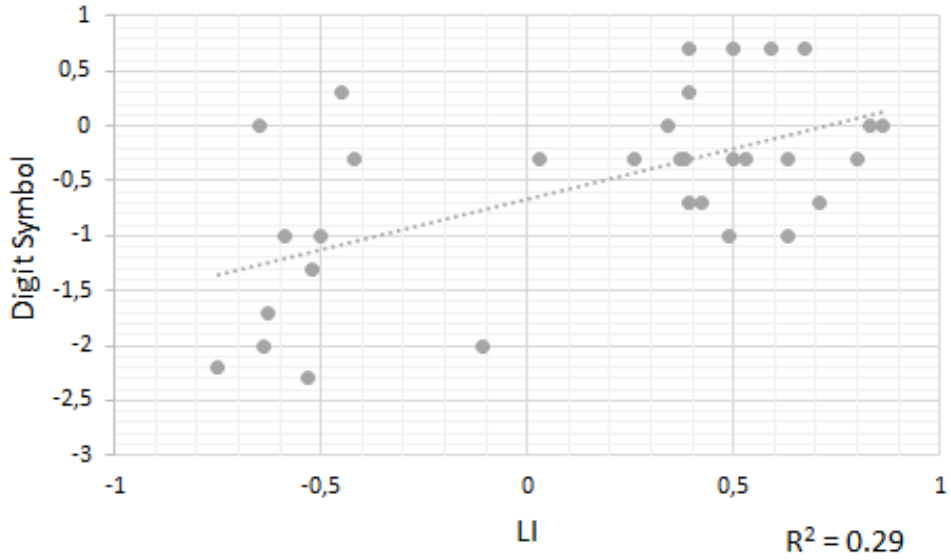

Figure S1. Associations between LI and performance in the digit symbol task (z-scores) in patients with TLE.

In the subgroup of patients with LH focus (n = 38), higher LI was related to better performance in immediate logical memory (r = 0.32, p = 0.05), delayed logical memory (r = 0.36, p = 0.027), digit symbol task (r = 0.45, p = 0.009), verbal learning (r = 0.43, p = 0.01), long-term verbal memory (r = 0.36, p = 0.03), and immediate visual memory (r = 0.38, p = 0.02). Only correlations between LI and digit symbol task, verbal learning and immediate visual memory passed FDR multiple testing correction in this subgroup (Figure S2). In patients with RH focus (n = 9), LI was positively related to performance in TMT A (r = 0.70, p = 0.04), but this correlation did not survive at FDR < 0.10.

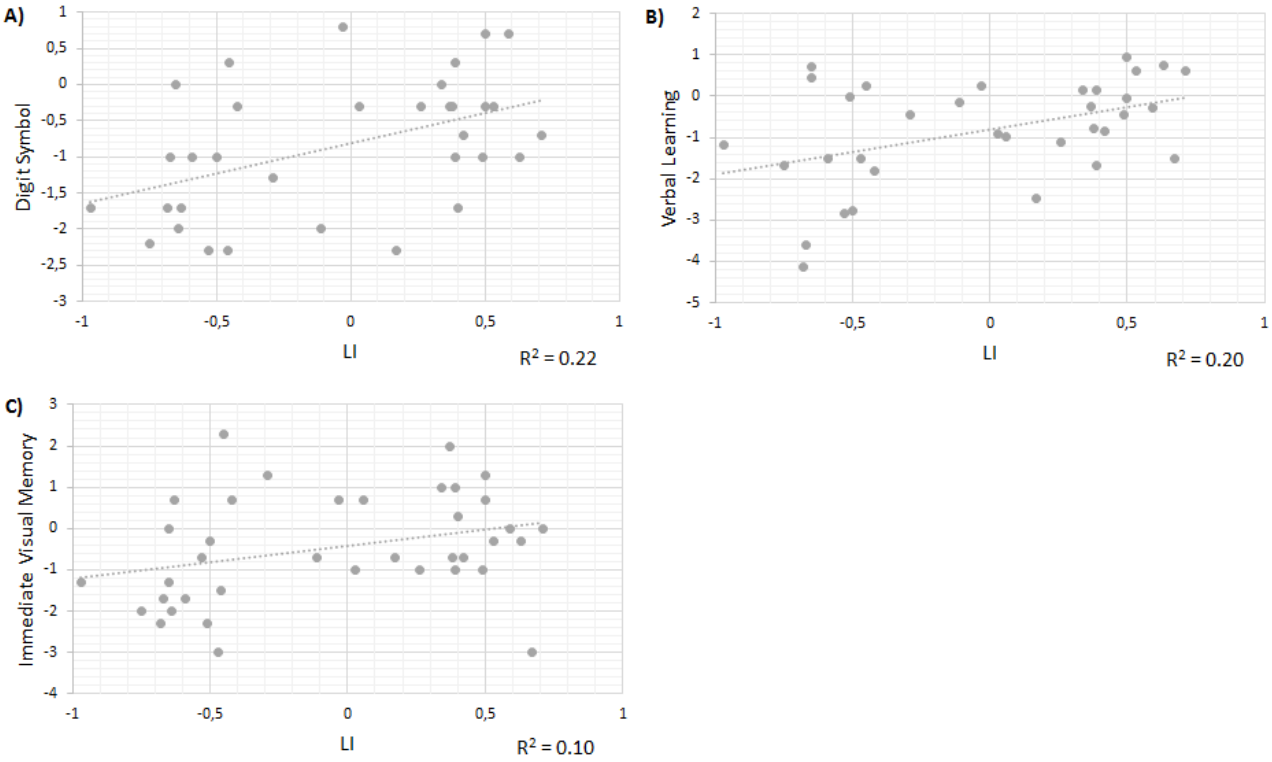

Figure S2. Associations between LI and cognitive performance (z-scores) in patients with LH focus.

Hierarchical regressions (Table 4) revealed that female gender and higher LI were significant predictors of better performance in delayed logical memory and in TMT A. RH focus and higher LI significantly predicted higher long-term verbal memory scores. Additionally, female gender was a significant predictor of better performance in the block design task, and higher LI was a significant predictor of better performance in digit symbol task. Handedness, location of seizure focus and age at epilepsy onset did not predict cognitive performance. No predictors were found for other cognitive tasks.

Table 4. Hierarchical regression analyses investigating the effect of gender, handedness, side of seizure focus, location of seizure focus, age at epilepsy onset and LI on cognitive performance

	Block design						
	Std β	*p*	Δ R^2	*p*	Adj. R^2	*F*	*p*
Block 1			0.13	0.07	0.08	2.85	0.07
Gender	0.33	0.03*					
Handedness	0.03	0.85					
Block 2			0.15	0.07	0.18	2.79	0.03*
Side of seizure focus	0.18	0.25					
Location of seizure focus	-0.20	0.21					
Age at epilepsy onset	0.15	0.34					
Block 3			0.04	0.15	0.20	2.75	0.03*
LI	0.24	0.15					
	Digit symbol						
	Std β	*p*	Δ R^2	*p*	Adj. R^2	*F*	*p*
Block 1			0.04	0.49	-0.01	0.73	0.49
Gender	0.22	0.14					
Handedness	-0.15	0.37					
Block 2			0.19	0.05*	0.12	2.05	0.10
Side of seizure focus	0.10	0.51					
Location of seizure focus	-0.25	0.12					
Age at epilepsy onset	0.10	0.47					
Block 3			0.16	0.01*	0.28	3.64	0.01*
LI	0.48	0.01*					
	TMT A						
	Std β	*p*	Δ R^2	*p*	Adj. R^2	*F*	*p*
Block 1			0.09	0.16	0.04	1.91	0.16
Gender	0.35	0.03*					
Handedness	-0.22	0.26					
Block 2			0.09	0.26	0.07	1.63	0.18
Side of seizure focus	-0.10	0.54					
Location of seizure focus	-0.27	0.11					
Age at epilepsy onset	0.12	0.45					
Block 3			0.10	0.03*	0.16	2.36	0.05*
LI	0.39	0.03*					
	Delayed logical memory						
	Std β	*p*	Δ R^2	*p*	Adj. R^2	*F*	*p*
Block 1			0.13	0.05*	0.09	3.26	0.05*
Gender	0.36	0.02*					
Handedness	-0.04	0.81					
Block 2			0.08	0.26	0.12	2.18	0.08
Side of seizure focus	0.04	0.81					
Location of seizure focus	-0.14	0.37					
Age at epilepsy onset	0.26	0.09					
Block 3			0.12	0.02*	0.21	3.01	0.02*
LI	0.37	0.02*					

Table 4 (cont.)

	Long-term verbal memory						
	Std β	*p*	Δ R^2	*p*	Adj. R^2	*F*	*p*
Block 1			0.07	0.25	0.02	1.43	0.25
Gender	0.29	0.06					
Handedness	-0.20	0.29					
Block 2			0.13	0.17	0.08	1.68	0.17
Side of seizure focus	-0.39	0.02*					
Location of seizure focus	-0.25	0.15					
Age at epilepsy onset	0.28	0.10					
Block 3			0.13	0.02*	0.20	2.66	0.03*
LI	0.43	0.02*					

*: $p < .05$

4. Discussion

The current study indicates that typical asymmetry in the hemispheric activation in a verbal comprehension paradigm is related to better cognitive performance in patients with epilepsy. Patients with LH focus have more frequently atypical hemispheric asymmetry, showing lower LI than patients with RH focus, and this is related to worse cognitive performance. Right-handedness and RH focus are significant predictors of typical hemispheric asymmetry, and LI, side of seizure focus and gender significantly predict cognitive performance.

fMRI verbal comprehension paradigm was effective to activate reliably receptive language areas, according to previous studies (Thivard et al., 2005; Ives-Deliperi, Butler, & Meintjes, 2013). Patients with typical and atypical asymmetry in the hemispheric activation did not differ in gender and age at epilepsy onset. Previous studies are inconsistent, some of them found that women (Helmstaedter et al., 1997) and patients with early age at epilepsy onset (Brázdil et al., 2003) were more likely to show atypical language lateralization in Wada tests. Other fMRI studies have found no differences based on gender (Adcock et al., 2003) or age at epilepsy onset (Thivard et al., 2005; Janszky, Mertens, Janszky, Ebner, & Woermann, 2006). It has even been suggested that shifts in language lateralization can occur in adolescence or adulthood (Hertz-Pannier, 2002). Although this reasoning remains speculative, our results suggest that the adult brain may be more plastic than commonly thought, and repeated seizures could imply slowly progressive structural disturbances, contributing to greater RH activation

during language processing due to the damage in the LH. According to previous studies, patients with LH focus had significantly lower LI (Adcock et al., 2003; Janszky et al., 2003), independently of the age at epilepsy onset, gender, and handedness.

Patients with an extratemporal focus had more frequently atypical hemispheric asymmetry, but also more frequently left-handedness than patients with a temporal focus. When handedness was controlled, no differences in LI were found depending on the location of seizure focus. Previous studies have found that left TLE may have more wide-ranging consequences on distributed language processing areas than left FLE (Duke et al., 2012). Given the limited patients in our study with FLE, we cannot exclude a specific frontal seizure focus effect on LI. Consequently, our group of patients with extratemporal focus included different epilepsy types, which could explain the lack of differences found. In fact, Berl et al. (2005) also found no differences in LI between patients with temporal and extratemporal focus. Additionally, patients with TLE with HS tended to have lower LI than those without HS and, consequently, more atypical asymmetry during verbal comprehension processing, according to previous studies (Duke et al., 2012; Weber et al., 2006). Mesial TLE with HS is a particularly severe focal epilepsy syndrome associated with high degree of intractability with AEDs (Wieser, ILAE Commision on Neurosurgery of Epilepsy, 2004), and may be more closely associated with disturbances of cortical function than other forms of focal epilepsy (Weber et al., 2006). In this sense, a mesial temporal focus may have an indirect effect on consolidation of language networks trough altered verbal memory processing (Duke et al., 2012).

Right-handedness and RH focus significantly predicted higher LI (and, consequently, higher LH activation), according to previous studies examining the role of handedness (Corballis et al., 2012), side of seizure focus (Adcock et al., 2003; Janszky et al., 2003) or both (Stewart et al., 2014). Surprisingly, seizure frequency was not related to LI. A possible explanation could be that it is the chronic exposure to seizures, rather than their frequency, that is related to LI.

fMRI activation pattern had implications on cognitive performance: patients with typical hemispheric asymmetry perform better in the digit symbol task and in verbal learning in the total sample and in the subgroup of patients with TLE. As expected, in this subgroup, patients with HS had worse performance in verbal memory than those without HS (Miller, Muñoz, & Finmore, 1993).

Despite these meaningful distinctions when classifying asymmetry patterns, the degree of asymmetry may have clinical implications (Bonelli et al., 2012), and so we analysed the relationships between LI and cognitive scores and found that higher LI was associated with better scores in a wide variety of verbal and non-verbal tasks, such as immediate and delayed logical memory, block design, digit symbol, TMT A, immediate and delayed visual memory, and verbal learning in the total sample. The relationship between LI and performance in digit symbol remained in the subgroup of patients with TLE, while no significant relationships were found in the subgroup of patients with an extratemporal focus. In healthy participants, atypical fMRI activation patterns have also been related to poor performances in verbal memory and spatial domains (Mellet et al., 2014). Contrarily, Thivard et al. (2005) found higher verbal memory in patients with epilepsy with atypical hemispheric asymmetry than in those with typical asymmetry, although the first group was composed of only seven patients and this limits any conclusions. As far as we know, no studies have analysed the potential role of the location of seizure focus in the relationships between LI and cognitive performance. Our results suggest that atypical hemispheric asymmetry in receptive language areas during verbal comprehension may be related to cognitive dysfunction mainly in patients with TLE. It should be noted that this group includes patients with HS, and the hippocampus is integrated into different cognitive systems by multiple reciprocal connections (Eichenbaum, Schoenbaum, Young, & Bunsey, 1996), so functional disturbances originating in the hippocampus could affect language networks, and this could be related to a variety of cognitive impairments not directly related to the temporal lobe. However, due to the small number of patients with an extratemporal focus, our findings should be interpreted with caution.

The fact that, in our study, LI was related to verbal functions and non-verbal functions emphasises that cognitive variables are interrelated (Cano-López et al., 2017), depending on a functional brain network (Dinkelacker et al., 2015). Chronic epilepsy could imply an additional indirect impairment of functional compensation in non-epileptic areas, being the explicative mechanism of progressive cognitive deterioration in these patients (Elger et al., 2004). In fact, chronic epilepsy lasting more than two decades is related to a worsening in cognitive functions (Jokeit & Ebner, 2002).

Considering that patients with LH focus presented lower LI than those with RH focus, we analysed these groups separately. In patients with RH focus, no significant relationships between LI and cognitive performance were found, although this group was composed of only

nine patients and this limited the establishment of any firm conclusions. In patients with LH focus, higher LI was related to better scores in digit symbol, verbal learning, and immediate visual memory. Using the Wada test, Strauss et al. (1990) found that patients with atypical language dominance and early age at epilepsy onset performed more poorly than those with typical dominance on a wide variety of non-verbal tasks, despite the preservation of verbal functions. In contrast, we found worse performances in non-verbal tasks, as well as in verbal functions in patients with LH focus and atypical hemispheric asymmetry. The later age at epilepsy onset of our sample could imply that greater RH activation during language processing was less adaptive in terms of cognitive performance.

In line with our results, Berl et al. (2005) found that adults and children with LH focus and typical hemispheric asymmetry had higher performance IQ than those with atypical asymmetry. However, our sample only included adult patients in order to reduce variability, and we assessed visual memory and executive functions apart from IQ and verbal domains. Our findings suggest that atypical hemispheric asymmetry during verbal comprehension, which is more frequent in patients with LH focus, could imply a competition of cognitive resources in the performance of the same task, disrupting cognitive performance, even in non-verbal tasks, for which the RH is typically dominant. This phenomenon was described as 'crowding', and occurs when 'one hemisphere tries to do more than it had originally been meant to do' (Teuber, 1974). This effect implicitly assumes two separate lesions in patients with LH focus and atypical hemispheric asymmetry: one structural (in the LH) and the other functional (in the RH) (Satz, Orsini, Saslow, & Henry, 1985). Although this remains speculative, our results suggest that the atypical hemispheric asymmetry during verbal comprehension in these patients could reflect variations in the global organization of the brain instead of exclusively in the organization of language.

It should be noted that patients with drug-resistant epilepsy may be impaired on multiple cognitive domains, which can be driven by important factors unrelated to hemispheric asymmetry during verbal comprehension. RH focus was also a significant predictor of better long-term verbal memory performance, according to previous studies that consistently have associated verbal memory deficits with left TLE (for review, see Tramoni-Negre et al., 2017). Additionally, gender was a significant predictor of performance in delayed logical memory, in the TMT A, and in the block design task (with higher scores in women than men, independently of fMRI activation). Berger, Oltmanns, Holtkamp, and Bengner (2017) found similar gender

differences in verbal tasks in patients with LH focus. However, block design and TMT A requires visual and motor abilities, and in studies with healthy participants, men presented higher scores than women in these type of tasks (Boghi et al., 2006), in contrast with our results. As far as we know, no studies have examined gender differences in performance of this task in patients with epilepsy. Even after controlling for gender, handedness, side of seizure focus, location of seizure focus and age at epilepsy onset, higher LI was a significant predictor of performance in logical memory, long-term verbal memory, TMT A and digit symbol task.

Our study has limitations. Firstly, although all the patients presented drug-resistant epilepsy, the group was quite diverse in terms of the exact localisation of epileptic focus. Secondly, large sample sizes could provide more information about groups, thereby ensuring statistical power. Thirdly, the fMRI paradigm was carried out covertly, and, although participants were asked about the story after the acquisition, no records on this performance were available, so performance in the neuropsychological assessment was used as an approximate measure of task adherence and general motivation. Fourthly, there are important challenges associated with concluding language lateralization based on a single paradigm (Seghier et al., 2008), since some patients may have typical asymmetry on one language paradigm, but atypical asymmetry on another paradigm that involves a different language network depending on the location of the pathology. In this sense, the lack of healthy controls to determine LI in this study should be noted as a limitation. Finally, our results should be taken with caution, since cognitive performance could be influenced by important factors such as the amount of inter-ictal discharge activity on the day of testing (for review, see Drane et al., 2016).

In conclusion, using a verbal comprehension paradigm that reliably activates receptive areas, typical hemispheric asymmetry is related to better cognitive performance, not only in language-related cognitive functions but also in non-verbal functions in patients with drug-resistant epilepsy. Additionally, we found that patients with LH focus can have more preponderant RH activation during verbal comprehension, and that could imply a competition of cognitive resources in the performance of the same task and a disruption in cognitive performance. These findings emphasize the need to consider cognitive functions as related processes and network dependent, and could be useful in the clinical management of these patients.

CHAPTER 6

Study 3

Age at surgery as a predictor of cognitive improvements in patients with drug-resistant temporal epilepsy [1]

[1] Published in: Cano-López, I., Vázquez, J. F., Campos, A., Gutiérrez, A., Garcés, M., Gómez-Ibáñez, A., ... & Villanueva, V. (2017). Age at surgery as a predictor of cognitive improvements in patients with drug-resistant temporal epilepsy. *Epilepsy & Behavior, 70*, 10-17.

1. Introduction

Epilepsy is a condition that affects more than 50 million people worldwide (World Health Organization, 2016). While most patients with epilepsy achieve adequate seizure control with antiepileptic drugs (AEDs), approximately 30% of patients continue to have seizures despite appropriate trials of two or more AEDs (Barr & Morrison, 2014; de Tisi et al., 2011; Kwan, Schachter, & Brodie, 2011). In these cases, surgery may be a suitable treatment to achieve seizure control (Helmstaedter, 2004; Kwan et al., 2010).

The goal of epilepsy surgery is to remove the epileptogenic region while preserving as much functional tissue as possible (Helmstaedter, 2013). Surgery for temporal lobe epilepsy (TLE) represents the most frequent surgical procedure (Witt et al., 2015) and usually involves resection of various structures of the temporal lobe, including the hippocampus, amygdala, entorhinal cortex, and temporal neocortex (Jobst & Cascino, 2015). Surgery for TLE is an effective procedure (Schomer & Lewis, 2012) that decreases the number of seizures in approximately 70% of patients (de Tisi et al., 2011; Sherman et al., 2011). Despite these advantages, the surgery may produce various sequelae in patients, including impairments in verbal and non-verbal memory, language, attention, and visual-constructive function (Helmstaedter, 2013). Among these cognitive domains, verbal memory disruption is one of the most frequently reported complaints by patients (Helmstaedter, 2013; Lee et al., 2002; Thompson et al., 2016; Hoppe et al., 2007). Various factors have been suggested to explain cognitive performance changes after surgery, although their predictive capability has not been confirmed (Ji et al., 2015). These proposed factors include variables of the patient such as gender (Gleissner et al., 2005; Helmstaedter, 1999, 2004); characteristics of the epilepsy course such as age at onset, duration, seizure-free period, and frequency of seizures (Ji et al., 2015; Sidhu et al., 2015b); as well as variables related to surgical procedures such as type of surgery and age at surgery (Helmstaedter, 2004; Jobst & Cascino, 2015). In addition to the identification of relevant factors, notable efforts have been made to minimize variability in cognitive performance due to confounding variables (such as the practice effect). From among these efforts, the reliable change index (RCI) has been widely used to detect if cognitive changes are clinically relevant (Chelune, Naugle, Luders, Sedlak, & Awad, 1993; Hermann et al., 1996; Jacobson & Truax, 1991; Loring, Kapur, Meador, & Morrell, 2015).

It is crucial to determine the appropriate age of the patient to perform epilepsy surgery in order to optimize seizure control and minimize cognitive sequelae. Age at surgery has been

identified as an important modulator of the cognitive reserve capacity of the patient (Helmstaedter, 2004, 2013) since there are critical phases of cerebral functional plasticity such as childhood until language acquisition at 6 years of age, puberty until 15 years, and a decline from 30 years of age (Gleissner et al., 2005; Helmstaedter, 1999). Although neural plasticity could be compromised in adult patients and the risk of cognitive decline after surgery is a frequent concern in older patients (Thompson et al., 2015), few studies have analyzed the importance of age at surgery in the verbal memory of adult patients with TLE and the results are inconsistent. The relationship between verbal memory and age at surgery has been studied using two strategies: comparing age groups and considering age as a continuous variable from a regression approach. In studies where verbal memory is compared in groups of patients classified by age, poorer performance and more frequent declines have been found in patients older than 50 in comparison with younger patients (Thompson et al., 2015). However, an absence of significant differences has also been reported (Grivas et al., 2006). Other studies with the same methodological strategy have suggested an age effect depending on the hemisphere, showing lower declines in older patients than in younger patients with left-sided TLE (L-TLE) and no differences in those with right-sided TLE (R-TLE) (Chapin et al., 2013). Studies that considered age at surgery as a continuous variable capable of predicting changes in verbal memory after surgery are also inconsistent. Wagner et al. (2013) found that the age at surgery explained, among other factors, changes in verbal learning but not verbal recall. However, Baxendale et al. (2006) found that age at surgery, as well as the preoperative IQ, were predictors of verbal memory only in patients with R-TLE. Other factors that were not considered (such as seizure frequency and patients with atypical dominance) could explain, at least in part, the discrepancy in results.

The aim of this study was to determine if age at surgery is a reliable predictor of verbal memory competence in typically lateralized TLE, considering other factors such as hemisphere, type of surgery, seizure frequency, and epilepsy duration.

2. Material and methods

2.1. Sample

The inclusion criteria of the study comprised: 1) patients with a diagnosis of drug-resistant TLE who underwent resective epilepsy surgery; 2) a chronological age of at least 18 years; 3) typical language dominance; 4) and a neuropsychological assessment performed prior to surgery and 1 year after the surgery. The initial sample was composed of 67 adult patients with drug-resistant TLE who underwent surgical treatment. Four patients with atypical language dominance and two patients with postsurgical neuropsychological assessment after 1 year were excluded to reduce the variability of the sample. Therefore, the final sample included 61 patients (30 women and 31 men).

Participants were divided in two groups according to the hemisphere of surgery: R-TLE and L-TLE. Descriptive statistics are shown in Table 1.

Table 1. Characteristics of the total sample and groups based on resected hemisphere (M ± SD or %).

Characteristics	Total (N = 61)	L-TLE (n = 34)	R-TLE (n =27)	*p*
Age	40.33 ± 12.70	41.71 ± 13.16	38.59 ± 12.11	.35
Sex				.71
Female	30 (49.2%)	16 (47.1%)	14 (51.9%)	
Male	31 (50.8%)	18 (52.9%)	13 (48.1%)	
Educational level				.51
Early childhood education	4 (6.6%)	2 (5.9%)	2 (7.4%)	
Primary education	31 (50.8%)	20 (58.8%)	11 (40.7%)	
Secondary education	10 (16.4%)	6 (17.6%)	4 (14.8%)	
Lower-university education	11 (18.0%)	4 (11.8%)	7 (25.9%)	
University education	5 (8.2%)	2 (5.9%)	3 (11.1%)	
Verbal IQ	94.15 ± 18.05	94.62 ± 17.44	93.54 ± 19.15	.82
Performance IQ	102.98 ± 16.03	101.09 ± 16.48	105.70 ± 15.31	.29
Age at epilepsy onset	14.26 ± 10.76	15.94 ± 11.35	12.15 ± 9.77	.17
Age at surgery	38.87 ± 12.39	40.09 ± 13.04	37.32 ± 11.58	.39
Years of epilepsy	24.61 ± 13.32	24.16 ± 14.27	25.18 ± 12.26	.77
Etiology of pathology				.07
Hippocampal sclerosis	31 (50.8%)	18 (52.9%)	13 (48.1%)	
Cavernous angioma	4 (6.6%)	2 (5.9%)	2 (7.4%)	
Cortical malformations	3 (4.9%)	3 (8.8%)	0 (0.0%)	
Hippocampal sclerosis + dysplasia	3 (4.9%)	0 (0.0%)	3 (11.1%)	
Tumor	6 (9.8%)	3 (8.8%)	3 (11.1%)	
Non-specific pathology	7 (11.5%)	6 (17.6%)	1 (3.7%)	
Non-assessable	5 (8.2%)	1 (2.9%)	4 (14.8%)	
Number of AEDs	6.08 ± 2.25	6.07 ± 2.40	6.10 ± 2.07	.97
Pre-surgical seizures per month	12.84 ± 23.72	10.53 ± 20.03	15.76 ± 27.81	.73
Surgical approach				.50
TL	11 (18.0%)	6 (17.6%)	5 (18.5%)	
TL + AH	42 (68.9%)	22 (64.7%)	20 (74.1%)	
Lesionectomy	8 (13.1%)	6 (17.6%)	2 (7.4%)	
Type of surgery				.43
With AH	42 (68.9%)	22 (64.7%)	20 (74.1%)	
Without AH	19 (31.1%)	12 (35.3%)	7 (25.9%)	
Engel I	53 (86.9%)	31 (91.2%)	22 (81.5%)	.27
Postsurgical seizures per month	0.24 ± 0.83	0.08 ± 0.38	0.44 ± 1.16	.19

2.2. Procedure

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Hospital Universitario y Politécnico La Fe. Signed informed consent was obtained from all participants.

Medical history provided characteristics of the patients such as sex, age, level of education, age at epilepsy onset, duration of epilepsy (years), frequency of seizures (seizures per month), and pre-surgical number of AEDs.

Pre-surgical assessment included the diagnosis of TLE and the lateralization of the epileptogenic area. Assessment was made by staff members of the multidisciplinary team based on a comprehensive evaluation that included seizure history and semiology, neurologic examination, long-term video-EEG monitoring, 3-Tesla magnetic resonance imaging (MRI), fluorodeoxyglucose (FDG)-positron emission tomography (PET), single photon emission computed tomography (SPECT), psychiatric assessment, and neuropsychological evaluation for all patients. If there were concerns about post-surgical memory outcome, not solved with prior evaluation, a Wada test was performed to help in the decision-making process. Presurgical assessment was discussed at a multidisciplinary surgical conference, where decisions about the possibility and type of surgery were made.

Surgery was carried out after the evaluation — the most frequent type of intervention being temporal lobectomy (TL) plus amygdalohippocampectomy (AH) (68.9%), following by TL without AH (18.0%), and lesionectomy guided with intraoperative electrocorticography (13.1%).

All patients repeated the same neuropsychological assessment 1 year after surgery (as described below). In addition, post-surgical seizure outcome was assessed by a neurologist using the Engel Epilepsy Surgery Outcome Scale (Engel, Van Ness, Rasmussen, & Ojemann, 1993).

2.3. Neuropsychological assessment

2.3.1. Handedness

This was examined using the Edinburgh Handedness Inventory (EHI; Oldfield, 1971). Participants were classified as left-handed (EHI: −100 to −61), ambidextrous (EHI: −60 to +60),

or right-handed (EHI: +61 to + 100) (Dragovic, 2004). According to this inventory and the side of epilepsy, patients were classified by dominant (for language) and non-dominant TLE.

2.3.2. IQ outcome

This was assessed using the Wechsler Adult Intelligence Scale-3rd Edition (WAIS-III; Wechsler, 1997a), which provides a verbal IQ and a performance IQ. The verbal subtests include vocabulary, similarities, arithmetic, digit span, information, and comprehension. The performance subtests include picture completion, digit symbol, block design, matrix reasoning, and picture arrangement. The average time of administration of the 11 subtests is 60 min, ranging from 45 to 75 min. Verbal IQ and performance IQ were computed as percentile scores.

2.3.3. Verbal memory

The Spanish Complutense Verbal Learning Test (TAVEC; Benedet & Alejandre, 1998) was used to assess episodic verbal memory. This is a Spanish version of the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) and is more sensitive than other tests such as Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987) for evaluating verbal memory loss after brain injury (Chirivella, Ferri, Villodre, & Noe, 2003). The TAVEC consists of three shopping lists: a learning list (list A), an interference list (list B), and a recognition list (list C). Short-term verbal memory and long-term verbal memory (20 min after the last presentation of the learning list) were computed.

2.3.4. Naming functions

The 60-item version of the Boston Naming Test (BNT; Kaplan et al., 2001) was used to assess visual confrontation naming. Semantic and phonemic cues are provided to patients in the case of no response or incorrect response. The total score was computed as the number of cards correctly named without phonemic cues: 60 being the maximum score.

2.3.5. Phonemic fluency

The total number of words generated in one minute for the letters F, A, and S was obtained following the instructions in Spreen & Benton (1977). The total score was computed as the sum of all admissible words for the three letters.

2.3.6. Semantic fluency

Participants were asked to 'think of the names of as many animals that they could' in 1 min, following the instructions used by Rosen (1980). The total score was computed as the sum of admissible words for this semantic category.

2.3.7. Immediate visual memory

This was evaluated using the immediate visual memory subtest of the Revised-Barcelona Test (BCN-R; Peña-Casanova, 2005). The test has been standardized and validated in a Spanish population. This subtest consists of the presentation of ten figures for 10 s each and participants had to recognize them from among four alternatives. Total score was computed as the sum of correct answers and therefore the maximum score was ten points.

2.4. Statistical analysis

The Kolmogorov–Smirnov test was carried out to examine the normality of the data. When data distribution was not normal (as the case of the Boston Naming Test), logarithmic transformation was performed to homogeneously apply a parametric statistical approach. Afterwards, t-tests for independent samples were performed for between-group comparisons based on the hemisphere of surgery in descriptive and pre-surgical variables, according to Levene's tests for equality of variance. The chi-square test was used to study the differences between frequencies in descriptive variables in the total sample. To check cognitive variations after the surgery, repeated measures ANOVAs 2 × 2 with Hemisphere (L-TLE/R-TLE) and the Moment (pre-/post-surgery) as within-subject factor were performed for each task. When a factor was significant in repeated measures ANOVAs, Bonferroni adjustments for the *p* values

were performed as post hoc analysis. In addition, univariate ANCOVAs considering pre-surgical scores as covariates were carried out for post-surgical scores.

Meaningful cognitive changes were evaluated with the RCIs (Jacobson & Truax, 1991). These provide an index of reliable alteration in test performance that cannot be attributed to common sources of measurement error inherent in test–retest protocols — such as the practice effect or regression to the mean (Davies, Risse, & Gates, 2005). Due to the lack of a control group in our study, these indices were derived from the normative data and reliability data of the tests. In the case of the TAVEC, the test–retest reliability was 0.94, and the SD was 2.95 for the short-term verbal memory and 2.75 for the long-term verbal memory (Benedet & Alejandre, 1998). In the case of the BNT, the test–retest reliability was 0.86 (Sachs et al., 2012) and the SD was 3.47 (Kaplan et al., 2001). For the phonemic fluency test, the test–retest reliability was 0.83 and the SD was 13.1 (Tombaugh et al., 1999). For the semantic fluency test, the test–retest reliability was 0.56 (Bird, Papadopoulou, Ricciardelli, Rossor, & Cipolotti, 2004) and the SD was 5 (Tombaugh et al., 1999). In the case of the BCN-R test, the test–retest reliability was 0.96 (Serra-Mayoral, & Peña-Casanova, 2006) and the SD was 8.17 (Peña-Casanova, 2005). In the cases of the TAVEC and BNT, in which there were no normative data for the total sample, normative data of a similar age group to the mean of our sample was used. The reliable change criterion to exceed the 95th centile of the RCI was ± 2.00 for the short-term verbal memory, ± 1.87 for the long-term verbal memory, ± 3.60 for the BNT, ± 14.97 for the phonemic fluency task, ± 9.19 for the semantic fluency task, and ± 4.53 for the BCN-R. Differences in the frequency of reliable decline, reliable improvement, or no reliable changes between patients with L-TLE and R-TLE were analyzed using the chi-square test.

To estimate the magnitude of the cognitive changes, RCI criteria were subtracted from cognitive score differences to control for practice effects and to obtain $changes_p$ scores for each cognitive task. To analyze the role of seizure freedom in these $changes_p$, a t-test for independent samples was performed for between-group comparisons based on the Engel index (Engel 1 or not Engel 1) in cognitive $changes_p$. Spearman correlations were also performed to establish the association among cognitive $changes_p$ in different tasks. Due to the relationships among verbal changes of different variables of verbal tasks, a cluster analysis was forced to two groups over z-scores of the $changes_p$ in verbal variables. There were two types of variables related to these clusters: verbal performance and clinical/demographic variables. To establish the clinical and demographic variables involved in these $changes_p$, we performed t-tests for independent

samples with this group of clusters as independent variables, and age, age at surgery, and duration of epilepsy before surgery as dependent variables.

To evaluate the role of these factors as predictors, hierarchical regressions were carried out in the total sample. $Changes_p$ of different cognitive tasks were included as dependent variables in the regression.

We sequentially entered three separate blocks of independent variables. Block 1 included the hemisphere and the type of surgery. Block 2 was comprised of pre-surgical frequency of partial seizures. Block 3 included age at surgery. After the entry of each block, we evaluated the adjusted R^2 change to determine the proportion of variance explained.

Statistical analysis was carried out using SPSS 22.0 and two-tailed tests with *p* set to 0.05 considered as significant.

3. Results

3.1. Sample characteristics and cognitive differences between R-TLE and L-TLE groups

The R-TLE and L-TLE groups presented similar demographic data, pre-surgical cognitive variables, characteristics of epilepsy and surgery, and post-surgical seizure outcome (Table 1). Overall surgical outcome was successful in the control of seizures since the percentage of patients classified as Engel I was 86.9% at 1 year after surgery.

After surgery, patients with R-TLE showed better evolution than patients with L-TLE (for all, $p < .001$) in short-term verbal memory, long-term verbal memory, and naming. No other cognitive differences by hemisphere were found for immediate visual memory, semantic fluency, or phonemic fluency. Cognitive scores are shown in Figure 1.

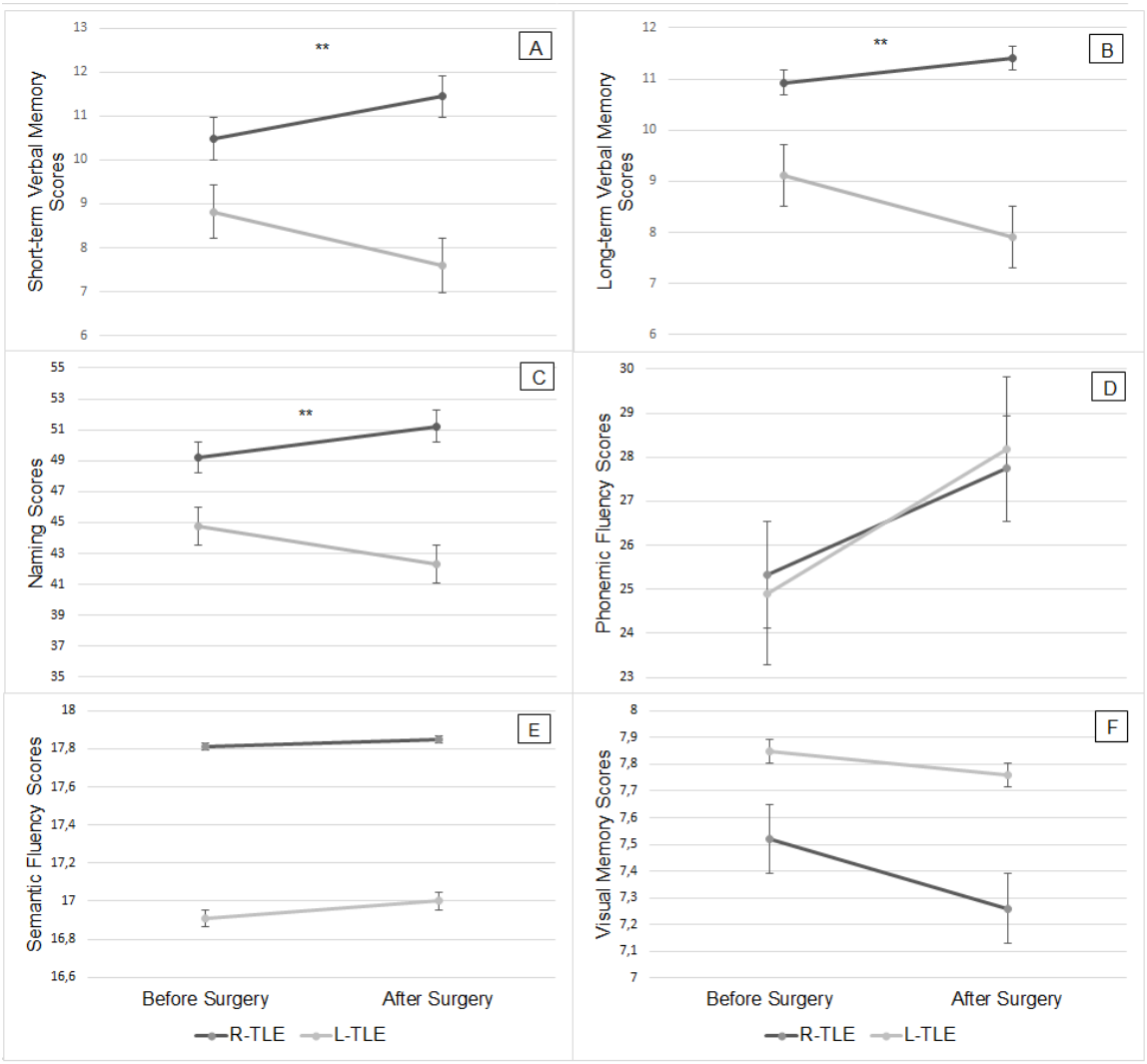

Figure 1. Cognitive scores before and after surgery in R-TLE and L-TLE groups. (A) Short-term verbal memory: main effect of the Hemisphere ($F(1,59) = 9.23$, $p = .004$, $\eta^2_p = .14$) and the Moment x Hemisphere interaction ($F(1,59) = 8.60$, $p = .005$, $\eta^2_p = .13$). (B) Long-term verbal memory: main effect of the Hemisphere ($F(1,59) = 8.01$, $p = .006$, $\eta^2_p = .12$) and the Moment x Hemisphere interaction ($F(1,59) = 4.86$, $p = .031$, $\eta^2_p = .08$). (C) Naming: main effect of the Hemisphere ($F(1,59) = 7.33$, $p = .009$, $\eta^2_p = .11$) and the Moment x Hemisphere interaction ($F(1,59) = 4.62$, $p = .04$, $\eta^2_p = .07$). (D) Phonemic fluency: main effect of the Moment ($F(1,59) = 6.96$, $p = .01$, $\eta^2_p = .106$). (E) Semantic fluency: ns. (F) Visual Memory: ns. *Note*. $^{**}p < .01$.

When RCIs were considered, patients with L-TLE also more frequently a strong reliable decline in short-term and long-term verbal memory and naming, in contrast to patients with R-TLE (for all, $p < .02$). In fact, 13 patients with L-TLE had a reliable short-term verbal memory decline in contrast to 1 patient with R-TLE; 15 patients with L-TLE had a reliable long-term verbal memory decline in contrast to 3 patients with R-TLE; and 13 patients had a reliable naming decline in contrast to 2 patients with R-TLE (percentages of patients who showed reliable changes are shown in Table 2). No other cognitive differences in reliable changes were found between the L-TLE and R-TLE groups. Table 3 and Figure 2 show the magnitude of the cognitive changes based on $changes_p$ scores. Additionally, there was improvement in the raw scores of the phonemic fluency after surgery ($p < .01$), independently of the resected hemisphere. The $changes_p$ of phonemic fluency were associated with seizure freedom, since the patients classified as Engel I showed significantly less worsening than other patients ($t(59) = 2.12$, $p = .038$).

Table 2. Frequencies, % and χ^2 probability (p) of the patients who showed reliable changes in scores of short-term verbal memory, long-term verbal memory and naming for the R-TLE and L-TLE groups after the surgery.

	Short-term Verbal memory					Long-term Verbal memory					Naming				
	R-TLE		L-TLE			R-TLE		L-TLE			R-TLE		L-TLE		
	N	%	*N*	%	*p*	*N*	%	*N*	%	*p*	*N*	%	*N*	%	*p*
Improvements	5	18.7	3	8.8	.006	8	29.6	6	17.6	.019	9	33.3	6	17.6	.018
No changes	21	77.8	18	52.9		16	59.3	13	38.2		16	59.3	15	44.1	
Worsening	1	3.7	13	38.2		3	11.1	15	44.1		2	7.4	13	38.2	

Table 3. Pre-surgical and post-surgical scores, differences, RCI criterion and $changes_p$ for all cognitive tasks (M ± SD).

	Pre-surgical score	Post-surgical score	Differences	RCI criterion	$Changes_p$
Short-term verbal memory	9.56 ± 3.80	9.30 ± 4.31	-0.26 ± 3.09	2.00 ± 0.00	-2.26 ± 3.09
Long-term verbal memory	9.92 ± 3.89	9.46 ± 4.36	-0.46 ± 3.06	1.87 ± 0.00	-2.33 ± 3.06
Naming	46.72 ± 10.93	46.26 ± 10.79	-0.46 ± 8.32	3.60 ± 0.00	-4.06 ± 8.33
Phonemic fluency	25.10 ± 13.08	27.98 ± 14.12	2.89 ± 8.28	14.97 ± 0.00	-12.08 ± 8.28
Semantic fluency	17.31 ± 5.68	17.38 ± 6.02	0.07 ± 4.59	9.19 ± 0.00	-9.12 ± 4.59
Immediate visual memory	7.71 ± 1.84	7.54 ± 1.72	-0.12 ± 1.45	4.53 ± 0.00	-4.65 ± 1.45

Note. Differences were calculated subtracting post-surgical scores from pre-surgical scores. $Changes_p$ were calculated subtracting RCI criterions from cognitive score differences.

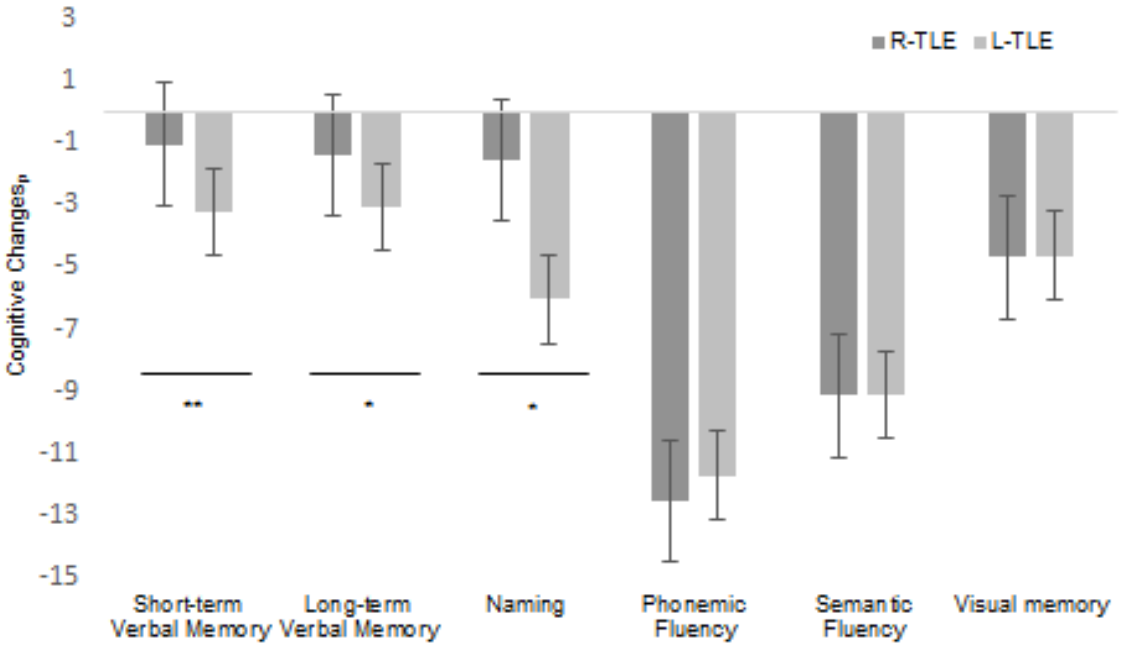

Figure 2. Cognitive changes after surgery based on changes$_p$ scores in patients with R-TLE and patients with L-TLE. *Note*. * $p < .05$; ** $p < .01$.

3.2. Profiles of verbal competence after surgery: age at surgery

In the total sample, significant correlations were found among changes$_p$ in different cognitive variables. Changes$_p$ in short-term verbal memory were positively related to changes$_p$ in naming, phonemic fluency, and long-term verbal memory ($r = 0.402$, $p < 0.001$; $r = 0.276$, $p < 0.03$ and $r = 0.681$, $p < 0.0001$, respectively). Changes$_p$ in long-term verbal memory also positively correlated to naming changes$_p$ ($r = 0.339$, $p < 0.007$). An interesting relationship was also found between naming and visual memory ($r = 0.321$, $p < 0.01$).

Due to this pattern of relationships among verbal changes$_p$ in different tasks, it is plausible to consider profiles of verbal competence. With this rationale, patients were distributed into two groups (clusters) who differed in the verbal performance (for all scales, $p < .02$): Cluster 1 (21 R-TLE and 18 L-TLE patients) with improvements in verbal competence; and Cluster 2 (6 R-TLE and 16 L-TLE patients) with a worsening in verbal domains (Figure 3). Interestingly, these two groups of patients also differed in age and age at surgery and nearly significantly in years of epilepsy before surgery. Patients in Cluster 1 were younger and younger at surgery, and had shorter durations of epilepsy before surgery than patients in Cluster 2 (Figure 3). Thus, the

younger the patients are at surgery, the greater improvements in verbal memory after surgery.

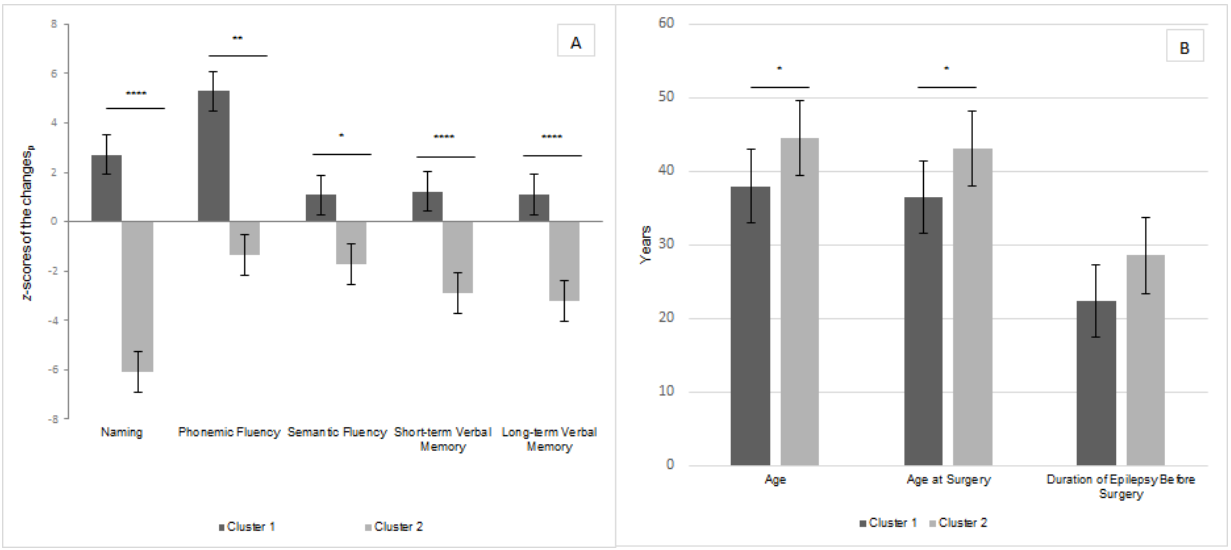

Figure 3. Characteristics of the Cluster 1 and Cluster 2. (A) Z scores of the changes$_p$ in verbal scores after the surgery with respect to presurgical scores. (B) Differences in demographic and clinical data: age ($t(59) = -2.00$, $p = .05$), age at surgery ($t(59) = -2.06$, $p = .04$) and duration of epilepsy before surgery ($t(59) = -1.76$, $p = 0.08$). Note. * $p < .05$; ** $p < .01$; *** $p < .001$; **** $p < .0001$.

3.3. Predictors of the cognitive changes after surgery

The results of the hierarchical regressions with cognitive changes$_p$ as dependent variables are shown in Table 4. The short-term verbal memory improvements after surgery were predicted by the lower pre-surgical frequency of partial seizures. The increases in long-term verbal memory were predicted by relative youth at surgery and the lower pre-surgical frequency of partial seizures. Finally, the naming improvements were not predicted by these variables.

No significant predictors were found for the phonemic fluency, semantic fluency, and visual memory changes.

Table 4. Hierarchical regression analyses investigating the effect of the frequency of seizures and age at surgery on cognitive changes$_p$.

	Short-term Verbal Memory				Long-term Verbal Memory				Naming			
	Std β	Δ R^2	Adj. R^2	*F*	Std β	Δ R^2	Adj. R^2	*F*	Std β	Δ R^2	Adj. R^2	*F*
Block 1		.13*				.11*				.13*		
Hemisphere	-0.37**				-0.25*				-0.25*			
Type of surgery	0.06				0.20				0.23*			
Block 2		.07*				.03				.03		
Frequency seizures	-0.30*				-0.23 (t)				-0.20			
Block 3		.01	.16	3.81**		.08*	.16	3.89**		.03	.12	3.08*
Age at surgery	-0.11				-0.30*				-0.18			

Note. * $p < .05$; ** $p < .01$; (t) tendency of $p < .06$.

4. Discussion

The results of the current study corroborate that right-sided surgery is a relevant factor for better cognitive evolution after surgery in verbal memory and naming in patients with typical language dominance and drug-resistant TLE. From a multivariate approach, a low age at surgery is related to a profile of improvements in verbal competence in these patients. In addition, low age at surgery and low pre-surgical frequency of seizures are relevant predictors of verbal memory improvements. To our knowledge, this is the first study to investigate cognitive outcome after TLE surgery considering cognitive functions as related processes. These results emphasize the importance of early intervention in order to minimize cognitive side-effects of epilepsy (independently of the resected hemisphere).

Surgery was successful in the control of seizures 1 year after surgery as 86.9% of the patients were seizure free. Despite this benefit, post-surgical cognitive deficits were found, according to the cognitive domain considered and the side of surgery. Verbal memory and naming were more sensitive than other cognitive domains to the side-effects of surgery, especially in patients with L-TLE. Patients with R-TLE showed better evolution in verbal memory and naming than patients with L- TLE after surgery. In fact, patients with L-TLE showed a reliable and strong worsening in these cognitive functions significantly more frequently than patients with R-TLE. These results support previous studies which found that verbal memory is one of the domains most sensitive to the negative effects of epilepsy (Helmstaedter, 2004; Vingerhoets, 2006) and are consistent with studies that found better

evolution in patients with R-TLE in verbal memory (Baxendale, Thompson, & Sander, 2013; Helmstaedter, Petzold, & Bien, 2011; Ives-Deliperi & Butler, 2012; Sidhu et al., 2016; Witt et al., 2015) and naming (Ives-Deliperi & Butler, 2012; Sherman et al., 2011).

No other cognitive differences based on the hemisphere of surgery were found in visual memory, semantic fluency, or phonemic fluency. Previous studies focused on visual memory evolution in this sample found unclear results (Helmstaedter, Brosch, Kurthen, & Elger, 2004; Sherman et al., 2011; Vaz, 2004; Witt et al., 2015) and this is probably due to the inconsistent role of the right temporal lobe (Helmstaedter et al., 2004). Our results are not in agreement with Bell et al. (2009) who showed a greater impairment in semantic fluency in patients with L-TLE with respect to patients with R-TLE when language dominance was not considered. The sample of the current study is composed of patients with typical hemispheric language dominance, and this could explain, at least in part, the discrepancies with the study of Bell et al. (2009). Additionally, we found a general improvement in phonemic fluency in the total sample, which was related to seizure freedom and in accordance with Helmstaedter et al. (2003) who found that seizure-free patients showed recovery of non-memory functions 1 year after surgery. Poor post-surgical seizure control has been associated with lower verbal fluency performance (Sarkis et al., 2013) in line with our results.

The results are interesting because the patients with R-TLE showed better evolution in verbal memory and naming by visual confrontation than patients with L-TLE, but both groups showed similar evolution in related processes such as semantic fluency and visual memory. Cognitive processes involved in each task can explain these results. The naming by visual confrontation of the Boston naming task implies access to visual storage and the subsequent assignation of a word or semantic load. However, the semantic fluency task consists in naming animals, not evoked by an image, and requires associative processes between elements of a category. It is possible that surgery could modify the pattern of relationships among cognitive processes. This idea is supported by the positive relationship found in the evolution of different cognitive domains.

The approach in previous studies mainly consisted in analyzing the evolution of cognitive functions as independent processes. Although the clinical relevance of this view is evident, few studies have employed a multivariate approach to predict cognitive changes after epilepsy treatment as related processes (Lancman et al., 2016) despite its use in other neurological diseases (Hayden et al., 2014). Recent data from task-fMRI support the idea that functional connectivity among different regions of the brain as a network could be an underlying

mechanism in which cognitive variables are interrelated (Bota et al., 2015; Dinkelacker et al., 2015; Garcia-Ramos et al., 2016). In fact, TLE has been recently understood as a network disease involving limbic and extralimbic brain regions (Bernhardt, Bonilha, & Gross, 2015; DeSalvo, Douw, Tanaka, Reinsberger, & Stufflebeam, 2014; Liao et al., 2016) and cognitive patterns are essential markers of the functioning of this network (Dinkelacker et al., 2015). Verbal competence is a complex process that requires optimal performance in multiple and frequently interrelated tasks (such as lexical access, verbal memory, fluency, and probably visual memory).

The identification of profiles of verbal competence while considering various processes such as fluency, memory, and naming should provide ecological validity to the neuropsychological evaluation and could contribute to clinical decision making. With this rationale, we identified two groups of patients who differed in their verbal profiles: one group with improvements in verbal competence after surgery; and the other with impairments. These groups also differed in clinical characteristics: patients with verbal improvements were younger and younger at surgery, and had shorter durations of epilepsy than patients with verbal impairments. These results are in accordance with those of Baxendale et al. (2006) who considered that greater age at surgery was a significant risk factor for post-surgical memory decline, suggesting that compensatory mechanisms and recovery of function are limited in these patients (Grivas et al., 2006). Additionally, these results support the previously reported association for younger age, greater functional plasticity, and better cognitive performance after surgery (Gleissner et al., 2005; Helmstaedter et al., 2004; Ji et al., 2015). Despite this, patients on average had epilepsy for approximately 20 years before being referred for a pre-surgical assessment (Haneef et al., 2010). A greater emphasis must be placed on early access to surgical treatment in these patients in order to minimize the cognitive side-effects of this effective treatment. It is worth noting that this effect was independent of the seizure frequency for long-term verbal memory.

Another issue to take into account is that a greater age at surgery and longer duration of epilepsy could also imply higher pre-surgical frequency of seizures and this, in turn, could contribute to cognitive changes. Although the long-term verbal memory improvements were significantly predicted by the lower age at surgery, these improvements also tended to be predicted by a lower frequency of partial seizures. In addition, the improvements in short-term verbal memory were predicted by a lower frequency of partial seizures. This association

between the frequency of seizures and cognitive decline has been previously reported (Baxendale, Thompson, & Duncan, 2012; Dodrill, 2004; Paradiso et al., 2001).

In sum, in the light of these data, age at surgery can be considered a reliable predictor of verbal memory changes after surgery. As greater age at surgery is associated with a higher occurrence of seizures, the role of this factor must be clarified. While short-term verbal memory is more sensitive to partial seizures during the period between epilepsy onset and surgery, this is not true for long-term memory.

Some limitations of our study should be considered. Firstly, additional neuropsychological data for some of the patients in the present study were available. However, as not all the individuals fulfilled all the neuropsychological protocol, the cognitive variables included are limited. Thus, the assessment of other cognitive domains is needed in order to establish if these preliminary results can be extrapolated. Secondly, greater sample sizes could provide more information about groups, thereby ensuring statistical power. In this regard, the number of variables to be included in the regression analysis as potential predictors is reduced in order to maintain an acceptable statistical power (Wilson Van Voorhis, & Morgan, 2007). Thirdly, the assessment of post-surgical changes on cognition has been carried out only once and, in this sense, longitudinal studies that consider long-term progress are needed.

Finally, the practice effect has been minimized by means of the RCI; and hemisphere and the type of surgery have been statistically controlled in the first block of the regression. However, the results must be read cautiously. Although the present study was aimed at examining the differences between patients who underwent temporal lobe resection from the left or right hemisphere rather than making comparisons between patients and healthy persons, a methodological issue must still be considered. Normative data of neuropsychological tests are frequently based on the general population, reducing the probability of reliable improvements in neurological patients. The inclusion in future research of appropriate control groups and/or the need for normative data of specific populations of patients are strongly supported.

The present study contributes to the corpus of data about the effects of surgical intervention on cognition in patients with typical hemispheric language dominance with TLE and the factors involved. Additionally, the employed approach emphasizes the need to consider cognitive functions as related processes and network dependent. Measuring surgical cognitive changes in patients with TLE presents a challenge, since these changes are dynamic and depend on various modulating factors (age at time of surgery being an important predictor of change in verbal memory). Therefore, our findings emphasize the relevance of early identification and treatment

of people with drug-resistant temporal epilepsy who are good surgical candidates for minimizing sequelae and so enhancing personal functionality and quality of life.

CHAPTER 7

Study 4

Cortisol and trait anxiety as relevant factors involved in memory performance in people with drug-resistant epilepsy[1]

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1. Introduction

People with drug-resistant epilepsy can be considered as exposed to a chronic stress condition involving unpredictable and uncontrollable seizures. In turn, stressful events could act as predisposing and precipitant factors of seizures. In addition, these patients present memory deficits (Helmstaedter, 2004; Vingerhoets, 2006), especially those with temporal lobe epilepsy (TLE) and hippocampal sclerosis (HS) (Helmstaedter & Elger, 2009), and a high prevalence of depression and anxiety (Kwon & Park, 2014; Mensah et al., 2007; Park, 2016).

In the last decade, research on cognitive and affective processes in relation to stress has received special attention, due to its capability to modify neural excitability, neurogenesis, and migration. In this context, cortisol, considered as the main stress hormone, is the final product of the hypothalamus–pituitary–adrenal (HPA)–axis activation, and has been proposed as an indicator of the neuroendocrine health status (Hellhammer et al., 2007) for cognitive and emotional processes (Adam & Kumari, 2009).

The role of cortisol levels in memory has been frequently studied in healthy individuals (Almela et al., 2011; Hidalgo et al., 2015; Lupien et al., 2005), as well as in patients with emotional disorders (Campbell, Marriott, Nahmias, & MacQueen, 2004; Wingenfeld & Wolf, 2011). Although the results point to complex interactions, several studies with healthy elderly people have linked increased basal cortisol levels with impairment in hippocampus-dependent learning and memory processes, suggesting that prolonged exposure to stressors may lead to decreased memory performance (Lupien et al., 2005; Lupien, McEwen, Gunnar, & Heim, 2009). Additionally, increased basal cortisol levels have been found in patients with emotional disorders – such as depression – that are also characterized by memory impairments (Wingenfeld & Wolf, 2011), as cortisol levels are related to these memory impairments (Campbell et al., 2004).

Even though stress, memory impairments, and affective alterations are common in epilepsy, few studies have focused on the potential interactions among these aspects in this disease. Thus, the role of cortisol on memory performance, anxiety, and depression remains unclear in this population and the few results are far from consistent. Devinsky et al. (1991) found a positive association between cortisol levels and depression. Afifi et al. (2011) reported higher cortisol levels in people with epilepsy and depression than in people with epilepsy without depression or healthy controls. To our knowledge, only Busch's study considers all

these variables in a sample of persons with epilepsy (Busch et al., 2012), showing that cortisol levels are negatively related to long-term verbal and visual memory, but positively related to trait anxiety scores (although not to depression or anxiety symptoms).

To establish more on the relationships between cortisol and cognitive and affective processes in people with drug-resistant epilepsy, this study analyzed the differences in afternoon cortisol levels for those with high and low immediate and delayed memory performance, considering the side of seizure focus, the epilepsy type (temporal or extratemporal), the presence of HS, and seizure frequency due to possible influence on memory performance. The above-mentioned studies were carried out in the morning, when circadian rhythms favor greater fluctuations of cortisol that could overlap target effects (Gadea, Gómez, González-Bono, Espert, & Salvador, 2005). To minimize these fluctuations, several cortisol samples were assessed in the afternoon. Moreover, such timing could also help characterize cortisol profiles in people with epilepsy by comparing them with those reported in the CIRCORT database (Miller et al., 2016a). The CIRCORT database provides normative reference values for the general population and is a useful tool for comparing adrenocortical functioning in epidemiological research and clinical practice. In addition, our study aimed to examine the relationships for cortisol levels with anxiety and depression in people with epilepsy. We hypothesized that patients with low memory performance would have higher cortisol levels than those with high memory performance, especially patients with left-hemisphere (LH) and temporal focus who are at higher risk of an accelerated forgetting of declarative memory (Jokeit, Daamen, Zang, Janszky, & Ebner, 2001). Thus, we hypothesized that cortisol levels would be negatively related to memory performance — but positively related to anxiety and depression scores.

2. Material and methods

2.1. Participants

In this cross-sectional study, patients were recruited from the Refractory Epilepsy Unit, Hospital Universitario y Politécnico La Fe (Valencia, Spain), between April 2015 and October 2017. Our reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines (Von Elm et al., 2007).

The inclusion criteria for the study comprised the following: 1) people with a diagnosis of drug-resistant focal epilepsy; 2) candidates for epilepsy surgery; 3) chronological age of at least 18 years; and 4) a neuropsychological assessment performed prior to surgery. Excluded were patients who as follows: 1) were older than 60 years; 2) had severe cognitive impairment that prevented a reliable neuropsychological evaluation; 3) had not completed primary education; 4) suffered an endocrine disease; 5) were not fluent Spanish speakers; and 6) declined to participate in the study. Characteristics of the sample are shown in Table 1.

Table 1. Characteristics of groups based on side of seizure focus, epilepsy type and memory competence (mean ± SD or n (%)) and differences between groups.

Characteristics	Side of seizure focus			Epilepsy type			Immediate memory competence			Delayed memory competence		
	LH (n = 27)	RH (n = 25)	*p*	TLE (n = 38)	ETLE (n = 14)	*p*	High (n =28)	Low (n =24)	*p*	High (n =28)	Low (n =24)	*p*
Age	37.33 ± 10.26	40.76 ± 10.13	.23	39.45 ± 10.99	37.71 ± 8.11	.59	41.21 ± 10.19	36.38 ± 9.89	.09	38.93 ± 9.33	39.04 ± 11.43	.97
Sex			.28			.26			.18			.18
Female	17 (63.0%)	12 (48.0%)		23 (60.5%)	6 (42.9%)		18 (64.3%)	11 (45.8%)		18 (64.3%)	11 (45.8%)	
Male	10 (37.0%)	13 (52.0%)		15 (39.5%)	8 (57.1%)		10 (35.7%)	13 (54.2%)		10 (35.7%)	13 (54.2%)	
Educational level			.16			.17			.31			.12
Primary	2 (7.4%)	3 (12.0%)		4 (10.5%)	1 (7.1%)		1 (3.6%)	4 (16.7%)		0 (0.0%)	5 (20.8%)	
Secondary	6 (22.2%)	9 (36.0%)		8 (21.1%)	7 (50.0%)		7 (25.0%)	8 (33.3%)		6 (21.4%)	9 (37.5%)	
Lower-university	10 (37.0%)	11 (44.0%)		16 (42.1%)	5 (35.7%)		13 (46.4%)	8 (33.3%)		13 (46.4%)	8 (33.3%)	
University	9 (33.3%)	2 (8.0%)		10 (26.3%)	1 (7.1%)		7 (25.0%)	4 (16.7%)		9 (32.1%)	2 (8.3%)	
Epilepsy type			.87			-			.77			.36
TLE[1]	20 (74.1%)	18 (72.0%)		38 (100.0%)	0 (0.0%)		20 (71.4%)	18 (75.0%)		19 (67.9%)	19 (79.2%)	
ETLE[2]	7 (25.9%)	7 (28.0%)		0 (0.0%)	14 (100.0%)		8 (28.6%)	6 (25.0%)		9 (32.1%)	5 (20.8%)	
Side of seizure focus			-			.87			.39			.39
LH[3]	27 (100.0%)	0 (0.0%)		20 (52.6%)	7 (50.0%)		13 (46.4%)	14 (58.3%)		13 (46.4%)	14 (58.3%)	
RH[4]	0 (0.0%)	25 (100.0%)		18 (47.4%)	7 (50.0%)		15 (53.6%)	10 (41.7%)		15 (53.6%)	10 (41.7%)	
Age at epilepsy onset	15.74 ± 11.76	15.84 ± 11.98	.98	17.58 ± 12.09	10.93 ± 9.52	.07	17.07 ± 12.60	14.29 ± 10.74	.40	16.11 ± 11.90	15.42 ± 11.82	.84
Epilepsy duration	21.59 ± 15.64	24.92 ± 14.19	.43	21.87 ± 15.57	26.79 ± 12.75	.30	24.14 ± 15.40	22.08 ± 14.56	.62	22.82 ± 15.14	23.63 ± 14.94	.85
Etiology of pathology												
HS[5]	8 (29.6%)	4 (16.0%)	.25	12 (31.6%)	0 (0.0%)	.02	4 (14.3%)	8 (33.3%)	.10	4 (14.3%)	8 (33.3%)	.10
FCD[6]	7 (25.9%)	4 (16.0%)	.39	5 (13.2%)	6 (42.9%)	.20	6 (21.4%)	5 (20.8%)	.96	5 (17.9%)	6 (25.0%)	.53
Tumor	2 (7.4%)	2 (8.0%)	.60	3 (7.9%)	1 (7.1%)	.80	2 (7.1%)	2 (8.3%)	.65	3 (10.7%)	1 (4.2%)	.65
Cavernoma	2 (7.4%)	1 (4.0%)	.61	2 (5.3%)	1 (7.1%)	.80	3 (10.7%)	0 (0.0%)	.10	3 (10.7%)	0 (0.0%)	.10
Glioma	3 (11.1%)	1 (4.0%)	.96	3 (7.9%)	1 (7.1%)	.93	1 (3.6%)	3 (12.5%)	.23	2 (7.1%)	2 (8.3%)	.87
Gliosis	1 (3.7%)	1 (4.0%)	.96	2 (5.3%)	0 (0.0%)	.38	1 (3.6%)	1 (4.2%)	.91	1 (3.6%)	1 (4.2%)	.91
Heterotopia	0 (0.0%)	1 (4.0%)	.33	1 (2.6%)	0 (0.0%)	.54	0 (0.0%)	1 (4.2%)	.28	1 (3.6%)	0 (0.0%)	.35
General atrophy	0 (0.0%)	1 (4.0%)	.33	1 (2.6%)	0 (0.0%)	.54	1 (3.6%)	0 (0.0%)	.35	0 (0.0%)	1 (4.2%)	.28
Hippocampal atrophy	1 (3.7%)	0 (0.0%)	.33	1 (2.6%)	0 (0.0%)	.54	1 (3.6%)	0 (0.0%)	.35	1 (3.6%)	0 (0.0%)	.35
Non-specific	3 (11.1%)	7 (28.0%)	.13	6 (15.8%)	4 (28.6%)	.30	6 (21.4%)	4 (16.7%)	.66	6 (21.4%)	4 (16.7%)	.66
Non-assessable	0 (0.0%)	3 (12.0%)	.08	2 (5.3%)	1 (7.1%)	.80	2 (7.1%)	1 (4.2%)	.65	2 (7.1%)	1 (4.2%)	.65
Number of AEDs[7]	2.48 ± 0.85	3.40 ± 1.12	.01	2.66 ± 0.91	3.64 ± 1.22	.01	2.89 ± 1.23	2.96 ± 0.91	.83	2.86 ± 1.18	3.00 ± 0.98	.64

Table 1 (cont.)

Characteristics	Side of seizure focus			Epilepsy type			Immediate memory competence			Delayed memory competence		
	LH (n = 27)	RH (n = 25)	*p*	TLE (n = 38)	ETLE (n = 14)	*p*	High (n =28)	Low (n =24)	*p*	High (n =28)	Low (n =24)	*p*
Type of AEDs[7]												
Levetiracetam	12 (44.4%)	14 (56.0%)	.41	15 (39.5%)	11 (78.6%)	.01	18 (64.3%)	8 (33.3%)	.03	17 (60.7%)	9 (37.5%)	.10
Lacosamide	12 (44.4%)	14 (56.0%)	.41	16 (42.1%)	10 (71.4%)	.06	15 (53.6%)	11 (45.8%)	.58	17 (60.7%)	9 (37.5%)	.10
Carbamazepine	7 (25.9%)	10 (40.0%)	.28	11 (28.9%)	6 (42.9%)	.34	11 (39.3%)	6 (25.0%)	.27	10 (35.7%)	7 (29.2%)	.62
Eslicarbazepine acetate	8 (29.6%)	6 (24.0%)	.65	11 (28.9%)	3 (21.4%)	.59	7 (25.0%)	7 (29.2%)	.74	7 (25.0%)	7 (29.2%)	.74
Valproic acid	5 (18.5%)	5 (20.0%)	.89	6 (15.8%)	4 (28.6%)	.30	4 (14.3%)	6 (25.0%)	.33	4 (14.3%)	6 (25.0%)	.33
Lamotrigine	4 (14.8%)	8 (32.0%)	.14	8 (21.1%)	4 (28.6%)	.57	9 (32.1%)	3 (12.5%)	.09	6 (21.4%)	6 (25.0%)	.76
Perampanel	4 (14.8%)	6 (24.0%)	.40	7 (18.4%)	3 (21.4%)	.81	3 (10.7%)	7 (29.2%)	.09	5 (17.9%)	5 (20.8%)	.79
Clobazam	5 (18.5%)	3 (12.0%)	.51	5 (13.2%)	3 (21.4%)	.46	3 (10.7%)	5 (20.8%)	.31	3 (10.7%)	5 (20.8%)	.31
Zonisamide	3 (11.1%)	2 (8.0%)	.70	5 (13.2%)	0 (0.0%)	.15	1 (3.6%)	4 (16.7%)	.11	1 (3.6%)	4 (16.7%)	.11
Clonazepam	1 (3.7%)	4 (16.0%)	.13	4 (10.5%)	1 (7.1%)	.71	3 (10.7%)	2 (8.3%)	.77	2 (7.1%)	3 (12.5%)	.51
Oxcarbazepine	2 (7.4%)	2 (8.0%)	.94	3 (7.9%)	1 (7.1%)	.93	0 (0.0%)	4 (16.7%)	.03	1 (3.6%)	3 (12.5%)	.23
Phenobarbital	1 (3.7%)	2 (8.0%)	.51	3 (7.9%)	0 (0.0%)	.28	1 (3.6%)	2 (8.3%)	.46	2 (7.1%)	1 (4.2%)	.65
Topiramat	1 (3.7%)	1 (4.0%)	.96	0 (0.0%)	2 (14.3%)	.12	0 (0.0%)	2 (8.3%)	.12	0 (0.0%)	2 (8.3%)	.12
Phenytoin	1 (3.7%)	1 (4.0%)	.96	2 (5.3%)	0 (0.0%)	.38	0 (0.0%)	2 (8.3%)	.12	1 (3.6%)	1 (4.2%)	.91
Lorazepam	1 (3.7%)	1 (4.0%)	.94	1 (2.6%)	1 (7.1%)	.45	1 (3.6%)	1 (4.2%)	.91	1 (3.6%)	1 (4.2%)	.91
Diazepam	1 (3.7%)	1 (4.0%)	.94	2 (5.3%)	0 (0.0%)	.38	0 (0.0%)	2 (8.3%)	.12	0 (0.0%)	2 (8.3%)	.12
Pregabalin	0 (0.0%)	2 (8.0%)	.13	2 (5.3%)	0 (0.0%)	.38	2 (7.1%)	0 (0.0%)	.18	1 (3.6%)	1 (4.2%)	.91
Alprazolam	0 (0.0%)	1 (4.0%)	.33	0 (0.0%)	1 (7.1%)	.10	1 (3.6%)	1 (4.2%)	.35	1 (3.6%)	1 (4.2%)	.35
Total DDD[8]	2.71 ± 1.16	3.45 ± 1.35	.04	2.75 ± 1.17	3.91 ± 1.27	.01	2.87 ± 1.37	3.29 ± 1.19	.24	2.84 ± 1.30	3.32 ± 1.27	.19
Seizures per month	26.88 ± 60.27	21.71 ± 38.24	.72	13.67 ± 26.53	53.50 ± 82.10	.10	28.62 ± 64.25	19.47 ± 27.47	.52	29.50 ± 64.13	18.44 ± 27.40	.44
Seizure type												
SPS[9]	3 (11.1%)	1 (4.0%)	.34	3 (7.9%)	1 (7.1%)	.93	3 (10.7%)	1 (4.2%)	.38	4 (14.3%)	0 (0.0%)	.06
CPS[10]	8 (29.6%)	13 (52.0%)	.11	16 (42.1%)	5 (35.7%)	.68	13 (46.4%)	8 (33.3%)	.34	13 (46.4%)	8 (33.3%)	.34
SPS[9] + CPS[10]	6 (22.2%)	6 (24.0%)	.88	8 (21.1%)	4 (28.6%)	.57	5 (17.9%)	7 (29.2%)	.34	5 (17.9%)	7 (29.2%)	.34
CPS[10] + GCTS[11]	8 (29.6%)	3 (12.0%)	.12	8 (21.1%)	3 (21.4%)	.98	5 (17.9%)	6 (25.0%)	.53	5 (17.9%)	6 (25.0%)	.53
SPS[9] + CPS[10] + GCTS[11]	2 (7.4%)	2 (8.0%)	.94	3 (7.9%)	1 (7.1%)	.93	2 (7.1%)	2 (8.3%)	.87	1 (3.6%)	3 (12.5%)	.23

Note. [1]TLE: temporal lobe epilepsy, [2]ETLE: extratemporal lobe epilepsy, [3]LH: left-hemisphere, [4]RH: right-hemisphere, [5]HS: hippocampal sclerosis, [6]FCD: focal cortical dysplasia, [7]AEDs: antiepileptic drugs; [8]DDD: defined daily dose; [9]SPS: simple partial seizure, [10]CPS: complex partial seizure, [11]GTCS: secondary generalized seizures.

2.2. Procedure

The procedure was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Hospital Universitario y Politécnico La Fe.

Medical history provided demographic characteristics of the patients (sex, age, and educational level) and clinical data (age at epilepsy onset, duration of epilepsy in years, frequency of seizures per month, seizure type, number of antiepileptic drugs (AEDs), type of AEDs, total defined daily dose (DDD) of all AEDs and strong enzyme inducer drugs, such as carbamazepine, phenytoin, phenobarbital, or primidone, that could modulate cortisol levels (Johannessen & Johannessen Landmark, 2010; Putignano, Kaltsas, Satta, & Grossman, 1998).

Presurgical assessment included diagnosis of the type of epilepsy and the lateralization of the epileptogenic area. Assessment was made by members of a multidisciplinary team and based on a comprehensive evaluation that included: seizure history and semiology; neurologic examination; long-term video-electroencephalography (EEG) monitoring; 3-Tesla magnetic resonance imaging (MRI), psychiatric assessment, and neuropsychological evaluation for all patients. Fluorodeoxyglucose (FDG)-positron emission tomography (PET), single photon emission computed tomography (SPECT), and intracranial EEG recording were performed selectively. Etiology of pathology was established based on MRI findings. If concerns about postsurgical memory outcome were not solved by prior evaluation, a Wada test was performed to help in the decision-making process.

The neuropsychological evaluation session was performed before the surgery. Prior to this session, participants were instructed to abstain from eating, drinking stimulants (such as tea, coffee, or alcohol), brushing their teeth, or smoking during the two-hour period before arriving at the hospital. The neuropsychological evaluation was always carried out between 4:00 pm and 8:00 pm to minimize hormonal circadian variations, and each session lasted approximately 3 h. During each neuropsychological assessment session, nine saliva samples (from C1 to C9) were collected to measure cortisol secretion and analyze accurately the cortisol decline in the late afternoon and evening — the circadian trough (Lupien et al., 2005; Kirschbaum & Hellhammer, 1989). Saliva samples were collected with a mean 20-min interval between samples, although this interval could vary depending on the duration of tests. Memory assessment was performed between C4 and C9 samples after habituation to the clinical setting. State anxiety was evaluated at the beginning and at the end of the neuropsychological evaluation, while trait anxiety and depression were evaluated at the end of the assessment session.

2.3. Salivary cortisol

Saliva samples were collected using salivettes (Sarstedt, Nümbrecht, Germany) for cortisol. Participants were instructed to keep the cotton swab in their mouths for 2 min. The samples were centrifuged at 3000 rpm for 15 min, resulting in a clear supernatant with low viscosity that was stored at − 80 °C until analyses were performed in the Laboratory of Social Cognitive Neuroscience, Faculty of Psychology (University of Valencia). Salivary cortisol concentrations were determined in duplicate with the salivary cortisol enzyme-immunoassay kit from Salimetrics (Newmarket, UK). Assay sensitivity was b 0.007 μg/dL. For each patient, all the samples were analyzed in the same trial. The criterion for measurement replication was fixed as an interduplicate variation coefficient of 8%. The intra- and interassay variation coefficients were 1.47% and 7.9%, respectively. Cortisol levels were expressed in nmol/L.

2.4. Neuropsychological assessment

The Spanish version (Pereña et al., 2004) of the Wechsler Memory Scale-Third Edition (WMS-III; Wechsler, 1997b) was used to evaluate learning, immediate, and delayed recall, as well as recognition of verbal and visual information. We used the following scales of the WMS-III: Logical Memory I and II (immediate and delayed recall, and delayed recognition for a short story); Verbal Paired Associates I and II (immediate and delayed recall, and delayed recognition for eight-word pairs); Faces I and II (immediate and delayed recognition of faces); and Family Scenes I and II (immediate and delayed recall for family scenes). These scales provide two general memory indices (immediate memory and delayed memory), material- specific memory indices (immediate auditory memory, delayed auditory memory, delayed auditory recognition, immediate visual memory, delayed visual memory), and indices related to auditory processes (single-trial auditory learning, auditory learning slope, auditory retention, and auditory retrieval), expressed in age-adjusted scalar scores. These scores were transformed to age-adjusted percentile scores, which were used in all analyses.

The Spanish version (Guillén-Riquelme, & Buela-Casal, 2011) of the State–Trait Anxiety Inventory (STAI; Spielberger, 1989) is composed by two scales: The state scale (STAI-S) evaluates the current state of anxiety, while the trait anxiety scale (STAI-T) evaluates relatively stable aspects of anxiety. Each subscale has 20 items rated on a four-point scale. Cronbach's alpha of the Spanish adaptation is 0.94 (Guillén-Riquelme, & Buela-Casal, 2011).

The Spanish version (Sanz & García-Vera, 2009) of the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) was used to assess depression by means of 21 items rated on a four-point scale. Cutting scores for different depression levels were as follows: 0–13 for minimum depression; 14–19 for mild depression; 20–28 for moderate depression; and 29–63 for severe depression (Beck et al., 1996). As variations in the cutting scores are frequent in research with this instrument and that this could complicate comparison between studies (Kendall, Hollon, Beck, Hammen, & Ingram, 1987), we used the total score as an indicator of depression level, but not the classification of depression levels. Cronbach's alpha of the Spanish adaptation is 0.89 (Sanz & García-Vera, 2009).

2.5. Statistical analyses

The Kolmogorov-Smirnov test was carried out to examine data normality. The result showed that the distribution of cortisol raw data was not normal and a logarithmic transformation was performed for this variable. In addition, of the 468 data for cortisol (nine samples x 52 individuals), 4 data were missing, due to insufficient volume of saliva sample for determinations. It supposes a percentage of less of 1% of missing data. These 4 data were estimated using the full information maximum likelihood (FIML) estimation method which retains cases that are missing in survey waves, and avoids the biased parameter estimates that can occur with pairwise or listwise deletion, according to Schafer and Graham (Schafer & Graham, 2002).

Patients were distributed into groups based on memory competence. Age-adjusted percentile scores one standard deviation below the mean (percentile scores lower than 16) were classified as ‘low competence’, while those higher than one standard deviation below the mean (percentile scores higher than 16) were classified as ‘high competence’. This criterion was in accordance with previous studies using WMS-III that suggest that a one standard deviation cut-off yields the most balanced levels of sensitivity and specificity to establish criteria for cognitive impairment (Taylor & Heaton, 2001). Patients were distributed into two groups based on immediate memory (auditory and visual) competence (p = .0001): group 1 with high immediate memory scores (mean = 49.03, SD = 25.73) (13 patients with LH focus and 15 patients with RH focus); and group 2 with low immediate memory scores (mean = 5.52, SD = 4.00) (14 patients with LH focus and 10 patients with RH focus). Patients were also distributed into two groups based on delayed memory (auditory and visual) competence (p = .0001): group 1 with

high delayed memory scores (13 patients with LH focus and 15 patients with RH focus); and group 2 with low delayed memory scores (14 patients with LH focus and 10 patients with RH focus). All but four of the patients had the same level of memory competence (low or high) in the immediate and delayed indices.

For between-group comparisons based on the side of seizure focus, epilepsy type and profiles of memory competence, the chi-square test was used to study the differences between frequencies in categorical variables. We employed *t*-tests for independent samples in descriptive variables, as well in trait anxiety, depression, and memory variables. A repeated measures ANOVA was carried out for state anxiety. When significant differences in these variables were found, they were included as covariates in further ANOVAs. These analyses were repeated in the subgroup of TLE, including the presence of HS as the between-subject factor, and anxiety, depression and memory scores as dependent variables.

The area under the curve with respect to increase (AUC_i) and the area under the curve with respect to ground (AUC_g) were used to study the cortisol fluctuations with the trapezoid formula (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). These two formulas can show different information inherent in the repeated measurements, simplifying the statistical analyses when the number of repeated measurements is high (Pruessner et al., 2003). Thus, the AUC_i is a measure of the dynamic of the cortisol changes over the evaluation, more related to the sensitivity of the system, while the AUC_g is an estimate of the total cortisol secretion over the evaluation (Pruessner et al., 2003). We also computed a cortisol percentile for each patient considering its mean value of cortisol and the normative reference values in the general population at similar hours (Miller et al., 2016a). Preliminarily, we performed *t*-tests for independent samples to analyze differences in cortisol levels, percentiles and AUCs between patients who were taking strong enzyme inducer drugs and the rest of the sample. Univariate ANOVAs were carried out to analyze differences in cortisol levels, percentiles, and AUCs among patients who were taking one enzyme inducer drug, more than one, and none.

To test the impact of the side of seizure focus, epilepsy type and memory competence on cortisol levels, we carried out repeated measures ANOVAs with 'side of seizure focus', 'epilepsy type' and 'memory competence' (immediate or delayed) as the between-subject factors; the 'moment' (C2 to C9) as the within-subject factor; and initial cortisol levels (C1) and age as covariate variables. Although no registration of seizures close to the neuropsychological assessment was available, their potential impact on cortisol levels was

controlled since C1 was used as a covariate, and C2 was measured more than 45 minutes after the beginning of the evaluation. To facilitate data interpretation, the values of cortisol in the figures and tables represent raw values and not logarithmic-transformed values. The age was covariate since various studies have found age differences in cortisol levels (Lupien et al., 2005; Pulopulos, Hidalgo, Puig-Pérez, & Salvador, 2018). Univariate ANOVAs were carried out to investigate the impact of the 'side of seizure focus', 'epilepsy type' and 'memory competence' (immediate or delayed) on the cortisol AUC_i and AUC_g, considering age as a covariate variable, and on cortisol percentiles. These ANOVAs were repeated in the subgroup of TLE, including the presence of HS as a between-subject factor. Greenhouse-Geisser adjustments of the degree of freedom were applied where appropriate. When a factor was significant in repeated measures ANOVAs, Bonferroni tests were performed.

Relationships between variables were calculated using Pearson or Spearman correlations where appropriate.

To evaluate the role of the cortisol AUC_i and the trait anxiety as predictors of memory performance, controlling seizure frequency and epilepsy type, hierarchical regressions were carried out in the total sample and in groups with LH and RH focus. Immediate and delayed memory percentile scores were included as dependent variables in the regression analyses. We sequentially entered three separate blocks of independent variables. Block 1 included the seizure frequency and epilepsy type. Block 2 was comprised of cortisol AUC_i. Block 3 included trait anxiety. After the entry of each block, we evaluated the adjusted R^2 change to determine the proportion of variance explained.

All cortisol analyses were repeated excluding two patients who suffered a seizure during neuropsychological evaluation.

Statistical analyses were carried out using SPSS 22.0 and two-tailed tests with *p* set to .05 were considered as significant.

3. Results

3.1. Preliminary analyses

The sample was composed of 52 adults with drug-resistant epilepsy (mean age = 38.98, SD = 10.25; mean epilepsy duration (years) = 23.19, SD =14.91). Demographic and clinical characteristics of groups depending on the side of seizure focus, epilepsy type, and memory competence are shown in Table 1. Patients with LH focus significantly consumed fewer AEDs and had a lower total DDD than patients with right-hemisphere (RH) focus. Patients with TLE consumed fewer AEDs and less frequently levetiracetam, had lower DDD, and had more frequently HS than those with extratemporal epilepsy (ETLE). Patients with high immediate memory consumed more frequently levetiracetam and less frequently oxcarbazepine than those with low immediate memory. These variables were controlled in further analyses. No other differences were found in demographic and clinical variables.

No differences were found in memory indices, anxiety or depression scores between patients with LH focus and RH focus neither between patients with TLE and ETLE (Table 2). In the group of TLE patients, those with HS had lower scores in most of the memory indices, including immediate and delayed memory, immediate and delayed auditory memory, immediate visual memory and single-trial auditory learning ($t(36) = -2.85$, $p = .007$; $t(36) = -2.81$, $p = .008$; $t(36) = -2.23$, $p = .03$; $t(36) = -2.81$, $p = .009$; $t(36) = -2.66$, $p = .012$; and $t(36) = -2.21$, $p = .034$, respectively) in respect to patients without HS. No differences in anxiety or depression scores were found between patients with HS and those without HS. As expected, patients with high memory competence (immediate and delayed) had better memory performance than those with low memory competence. These groups also differed in trait anxiety, patients with high memory competence having lower trait anxiety than those with low memory competence (for immediate memory groups: $p = .05$; for delayed memory groups: $p = .0001$) (Table 2), so this variable was controlled in further analyses.

In the total sample, the mean values of cortisol were compared with the normative reference values for cortisol in the general population (Miller et al., 2016a) – 9.6% of the sample having cortisol levels located in the 50-59th percentile, 7.7% in the 60-69th percentile, 15.4% in the 70-79th, 9.6% between the 80-89th percentile, and 57.7% between 90-99th percentile. In the 51.9% of the sample, cortisol levels were located above the 95th percentile of cortisol levels for the general population. Cortisol levels, percentiles and AUCs were not related to seizure frequency in the total sample, although a positive association between seizure frequency and

cortisol levels was found in patients with both partial and secondary generalized seizures ($r(15) = .54$, $p = .037$, $r(15) = .48$, $p = .07$, $r(15) = .49$, $p = .06$, $r(15) = .53$, $p = .04$, and $r(15) = .48$, $p = .07$, for C4, C5, C6, C7 and C8, respectively). Seizure frequency was also marginally related to AUC_g in these patients ($r(15) = .47$, $p = .08$). Additionally, cortisol levels, percentiles and AUCs were not related to the number of AEDs, the total DDD (for all, $p > .06$), nor the total dose of strong enzyme inducer drugs (such as carbamazepine, phenytoin, phenobarbital, or primidone) in the total sample. No differences in cortisol levels, percentiles or AUCs were found between patients who were taking strong enzyme inducer drugs (n = 19) and the rest of the sample (n = 33) neither among patients who were taking one enzyme inducer drug (n = 12), more than one (n = 7), and none (n = 33).

Considering the side of the seizure focus, cortisol AUC_g was positively related to seizure frequency in the RH group ($r(25) = .47$, $p = .018$), but not in the LH patients. No other significant relationships for the side of seizure focus, epilepsy type or memory competence groups were found between cortisol and descriptive or clinical variables.

Table 2. Memory (percentile scores), and anxiety and depression (direct scores) in groups based on the side of seizure focus, epilepsy type and memory competence (mean ± SD)

Scores	Side of seizure focus			Epilepsy type			Immediate memory competence			Delayed memory competence		
	LH (n = 27)	RH (n = 25)	*p*	TLE (n = 38)	ETLE (n = 14)	*p*	High (n =28)	Low (n =24)	*p*	High (n =28)	Low (n =24)	*p*
WMS-III												
Immediate memory	27.79 ± 29.76	30.20 ± 28.59	.77	30.24 ± 30.33	25.45 ± 25.49	.60	49.03 ± 25.73	5.52 ± 4.00	.0001	47.19 ± 27.94	7.67 ± 7.95	.0001
Immediate auditory memory	30.61 ± 30.13	41.05 ± 32.23	.23	36.27 ± 31.89	33.89 ± 30.71	.81	55.97 ± 28.15	11.89 ± 12.23	.0001	55.82 ± 28.52	12.07 ± 11.90	.0001
Immediate visual memory	31.06 ± 27.09	27.21 ± 25.98	.60	31.84 ± 28.02	22.04 ± 20.47	.18	46.21 ± 24.28	9.37 ± 9.35	.0001	42.55 ± 25.93	13.63 ± 16.81	.0001
Delayed memory	29.18 ± 28.44	33.20 ± 31.81	.50	31.67 ± 31.79	29.59 ± 24.96	.83	48.44 ± 30.27	10.90 ± 10.60	.0001	51.69 ± 26.68	7.10 ± 5.14	.0001
Delayed auditory memory	32.64 ± 30.86	40.72 ± 31.05	.09	39.63 ± 33.95	40.44 ± 27.57	.93	58.91 ± 29.24	17.61 ± 17.93	.0001	60.60 ± 28.26	15.64 ± 14.52	.0001
Delayed visual memory	34.08 ± 29.00	29.67 ± 28.75	.58	33.86 ± 29.91	26.80 ± 25.34	.44	47.40 ± 28.35	13.94 ± 15.86	.0001	49.74 ± 26.86	11.22 ± 11.96	.0001
Delayed auditory recognition	35.00 ± 30.04	40.72 ± 31.05	.50	37.13 ± 31.27	39.42 ± 28.81	.81	48.30 ± 32.39	25.44 ± 22.80	.006	52.85 ± 27.99	20.13 ± 22.88	.0001
Single-trial auditory learning	40.93 ± 27.21	42.08 ± 26.68	.88	39.63 ± 27.05	46.50 ± 26.01	.42	55.75 ± 25.19	24.83 ± 17.26	.0001	56.04 ± 25.05	24.50 ± 16.88	.0001
Auditory learning slope	48.48 ± 33.33	59.36 ± 25.84	.20	51.16 ± 32.00	60.64 ± 24.26	.38	60.46 ± 29.15	45.83 ± 30.03	.08	60.89 ± 27.51	45.33 ± 31.55	.06
Auditory retention	40.78 ± 31.95	52.80 ± 31.30	.18	46.76 ± 33.98	46.00 ± 26.61	.94	55.50 ± 31.51	36.13 ± 29.68	.03	62.82 ± 29.53	27.58 ± 23.15	.0001
Auditory retrieval	46.44 ± 31.28	40.48 ± 33.80	.51	45.50 ± 31.29	38.36 ± 35.70	.32	40.25 ± 33.39	47.46 ± 31.31	.43	46.11 ± 32.67	40.63 ± 32.38	.56
STAI												
Trait anxiety	24.81 ± 11.81	25.64 ± 11.15	.80	25.87 ± 11.83	23.43 ± 10.32	.50	22.36 ± 10.96	28.54 ± 11.20	.05	19.89 ± 10.26	31.42 ± 9.48	.0001
State anxiety pre-	19.96 ± 9.80	22.40 ± 10.41	.43	21.80 ± 10.17	19.50 ± 9.93	.49	22.63 ± 10.95	18.59 ± 8.08	.20	21.28 ± 10.76	20.79 ± 9.28	.88
State anxiety post-	20.13 ± 8.49	19.55 ± 11.86	.85	20.53 ± 10.74	18.43 ± 8.53	.52	21.07 ± 10.94	17.94 ± 8.36	.32	20.24 ± 9.43	19.37 ± 11.04	.78
State anxiety differences	0.17 ± 7.63	-2.85 ± 10.28	.27	-1.27 ± 9.30	-1.07 ± 8.47	.95	-1.56 ± 9.42	-0.65 ± 8.40	.75	-1.04 ± 9.03	-1.42 ± 9.08	.89
BDI-II												
Depression	11.74 ± 7.96	11.40 ± 6.53	.87	11.37 ± 6.74	12.14 ± 8.71	.74	12.11 ± 7.74	10.96 ± 6.73	.58	10.54 ± 7.19	12.79 ± 7.26	.27

3.2. Profiles of memory performance: cortisol, side of seizure focus and epilepsy type

A significant effect of the 'moment*side of seizure focus*immediate memory competence' interaction on cortisol levels was found (Table 3). Specifically, in the group of patients with LH focus, those with low immediate memory scores had higher cortisol levels at C4, C5, C7 and C8 (for all, $p < .05$) (Figure 1A). In the group of patients with RH focus, there were no differences in cortisol levels that depended on immediate memory scores (Figure 1B).

The interaction 'moment*side of seizure focus*delayed memory competence' on cortisol levels was also significant (Table 3). Specifically, in the group of patients with LH focus, those with low delayed memory scores had higher cortisol levels at C7 ($p = .008$) (Figure 1C). In the group of patients with RH focus, there were no differences in cortisol levels that depended on delayed memory scores (Figure 1D).

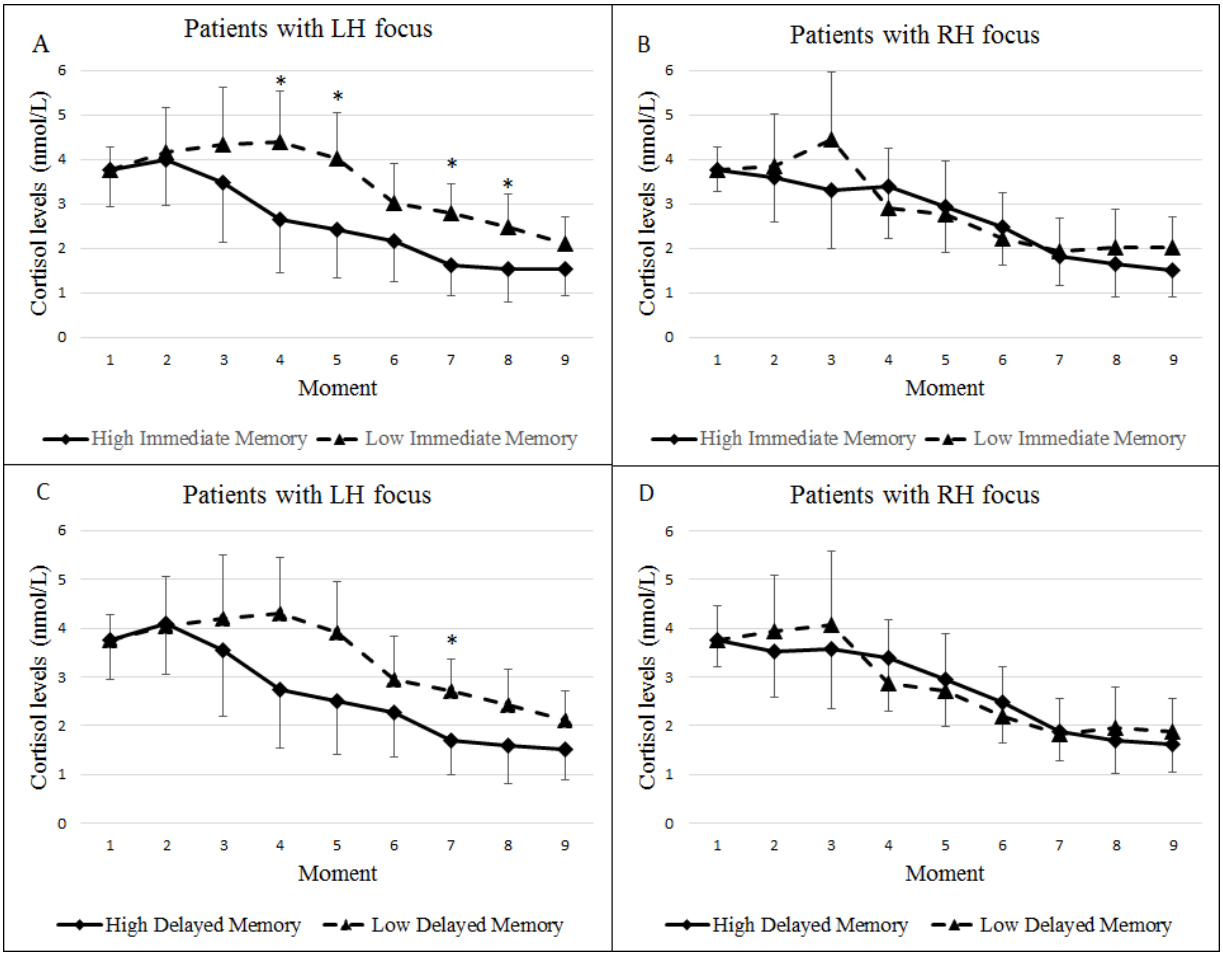

Figure 1. Cortisol levels in groups based on side of seizure focus and memory competence. (A) Cortisol levels in patients with LH focus depending on immediate memory competence.

(B) Cortisol levels in patients with RH focus depending on immediate memory competence. (C) Cortisol levels in patients with LH focus depending on delayed memory competence. (D) Cortisol levels in patients with RH focus depending on delayed memory competence. Note: errors bars represent 95% confidence intervals.

Additionally, significant effects of 'immediate memory competence' and 'delayed memory competence' on cortisol AUC_i were found (Table 3). Patients with low immediate and delayed memory scores had higher cortisol AUC_i independently of the side of seizure focus or the epilepsy type (see Figure 2).

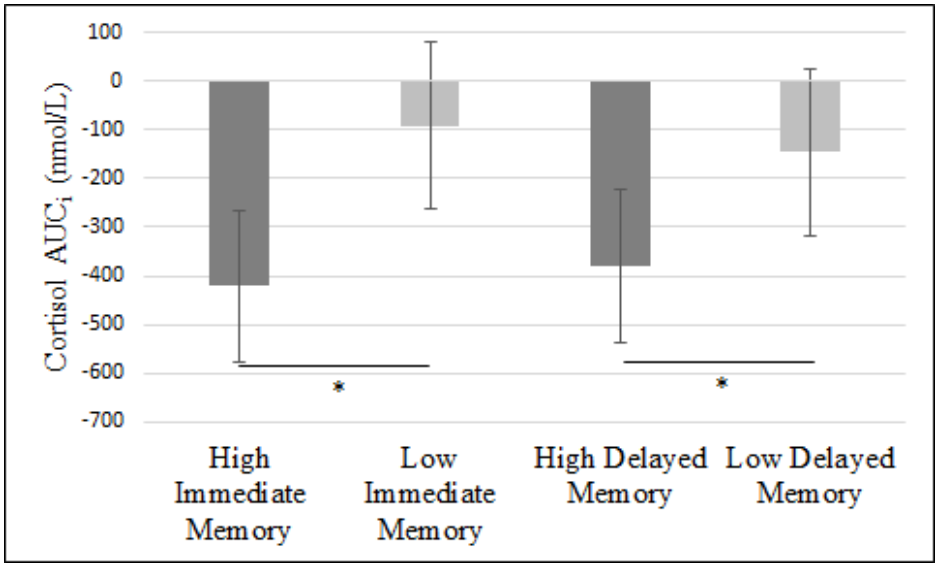

Figure 2. Cortisol AUCi in groups with high and low immediate memory, and in groups with high and low delayed memory (independently of the side of seizure focus). Note: errors bars represent 95% confidence intervals.

All these effects remained significant even when the two patients who suffered a seizure during the evaluation were excluded, and when variables in which there were significant differences between groups based on the side of seizure focus, epilepsy type and memory competence (number of AEDs, DDD, consume of levetiracetam, consume of oxcarbazepine and trait anxiety) were covariated.

Patients with LH and RH presented similar levels of cortisol and AUCs. Additionally, no significant effects of epilepsy type or HS were found in these variables. No significant effects were found on cortisol percentiles.

Table 3. Cortisol levels (nmol/l) and cortisol AUCs (arbitrary units) in groups based on side of seizure focus and memory competence (mean ± SD)

		Immediate memory competence		Delayed memory competence		Total	Statistics
Cortisol	Side[1]	High	Low	High	Low		
C1	LH[2]	4.86 ± 2.96	2.62 ± 1.88	4.84 ± 2.98	2.63 ± 1.87	3.70 ± 2.67	M[6]: $F(4.3, 42) = 1.76$, $p = .13$, $n^2_p = .04$
	RH[3]	4.37 ± 1.94	3.04 ± 2.22	3.90 ± 2.11	3.75 ± 2.24	3.84 ± 2.12	M x S[7]: $F(4.3, 42) = 0.80$, $p = .54$, $n^2_p = .02$
	Total	4.60 ± 2.43	2.78 ± 1.99	4.34 ± 2.55	3.10 ± 2.06	3.76 ± 2.40	M x IM[8]: $F(4.3, 42) = 0.53$, $p = .73$, $n^2_p = .01$
C2	LH[2]	5.18 ± 4.40	2.94 ± 2.61	5.25 ± 4.32	2.87 ± 2.66	4.01 ± 3.69	M x DM[9]: $F(4.5, 42) = 0.51$, $p = .74$, $n^2_p = .01$
	RH[3]	4.17 ± 2.24	3.11 ± 1.97	3.63 ± 2.44	3.92 ± 1.78	3.75 ± 2.16	M x S x IM[10]: $F(4.3, 42) = 3.30$, $p = .01$*, $n^2_p = .07$
	Total	4.64 ± 3.38	3.01 ± 2.32	4.38 ± 3.47	3.31 ± 2.35	3.88 ± 3.03	M x S x DM[11]: $F(4.5, 42) = 3.55$, $p = .006$*, $n^2_p = .08$
C3	LH[2]	4.45 ± 3.46	3.22 ± 3.79	4.52 ± 3.39	3.16 ± 3.82	3.81 ± 3.62	S[12]: $F(1, 42) = 0.09$, $p = .77$, $n^2_p = .01$
	RH[3]	4.00 ± 2.10	3.65 ± 2.96	3.71 ± 2.26	4.07 ± 2.77	3.86 ± 2.43	IM[13]: $F(1, 42) = 2.84$, $p = .10$, $n^2_p = .06$
	Total	4.21 ± 2.77	3.40 ± 3.40	4.09 ± 2.82	3.54 ± 3.39	3.83 ± 3.07	DM[14]: $F(1, 42) = 1.28$, $p = .26$, $n^2_p = .03$
C4	LH[2]	3.46 ± 2.62	3.51 ± 3.72	3.52 ± 2.56	3.45 ± 3.76	3.49 ± 3.18	
	RH[3]	3.87 ± 1.81	2.33 ± 1.66	3.51 ± 2.07	2.86 ± 1.57	3.25 ± 1.88	
	Total	3.68 ± 2.19	3.02 ± 3.04	3.52 ± 2.26	3.21 ± 3.01	3.37 ± 2.61	
C5	LH[2]	3.03 ± 2.17	3.33 ± 3.30	3.10 ± 2.09	3.26 ± 3.35	3.18 ± 2.76	
	RH[3]	3.35 ± 1.32	2.28 ± 1.53	3.06 ± 1.53	2.71 ± 1.44	2.92 ± 1.48	
	Total	3.20 ± 1.74	2.89 ± 2.71	3.08 ± 1.78	3.03 ± 2.69	3.06 ± 2.22	
C6	LH[2]	2.57 ± 1.70	2.59 ± 2.51	2.65 ± 1.64	2.52 ± 2.55	2.58 ± 2.12	
	RH[3]	2.73 ± 1.18	1.92 ± 1.14	2.54 ± 1.31	2.21 ± 1.07	2.41 ± 1.21	
	Total	2.66 ± 1.42	2.31 ± 2.05	2.59 ± 1.45	2.39 ± 2.04	2.50 ± 1.73	
C7	LH[2]	1.97 ± 1.41	2.38 ± 1.83	2.02 ± 1.37	2.33 ± 1.87	2.18 ± 1.62	
	RH[3]	2.11 ± 1.10	1.60 ± 0.94	1.96 ± 1.12	1.83 ± 0.98	1.91 ± 1.05	
	Total	2.04 ± 1.23	2.05 ± 1.55	1.99 ± 1.22	2.12 ± 1.55	2.05 ± 1.37	
C8	LH[2]	1.83 ± 1.00	2.15 ± 1.91	1.86 ± 0.96	2.11 ± 1.94	1.99 ± 1.52	
	RH[3]	1.87 ± 1.17	1.77 ± 1.48	1.74 ± 1.23	1.96 ± 1.40	1.83 ± 1.28	
	Total	1.85 ± 1.07	1.99 ± 1.72	1.80 ± 1.09	2.05 ± 1.70	1.91 ± 1.40	
C9	LH[2]	1.78 ± 1.06	1.78 ± 1.61	1.75 ± 1.09	1.81 ± 1.59	1.78 ± 1.35	
	RH[3]	1.79 ± 1.10	1.71 ± 0.93	1.68 ± 1.08	1.88 ± 0.96	1.76 ± 1.02	
	Total	1.79 ± 1.06	1.75 ± 1.34	1.71 ± 1.06	1.84 ± 1.34	1.77 ± 1.19	
AUC_i[4]	LH[2]	-471.34 ± 469.05	7.88 ± 488.44	-454.54 ± 477.90	-7.72 ± 496.38	-222.86 ± 529.50	S[12]: $F(1,51) = 0.20$, $p = .65$, $n^2_p = .01$
	RH[3]	-363.62 ± 287.10	-199.47 ± 292.76	-307.87 ± 272.16	-283.09 ± 340.96	-297.96 ± 294.89	IM[13]: $F(1,51) = 5.25$, $p = .027$*, $n^2_p = .11$
	Total	-413.63 ± 378.83	-78.52 ± 423.42	-375.97 ± 381.40	-122.45 ± 1.34	-258.96 ± 430.45	DM[14]: $F(1,51) = 3.85$, $p = .05$*, $n^2_p = .09$
							S x IM[15]: $F(1,51) = 1.16$, $p = .29$, $n^2_p = .03$
							S x DM[16]: $F(1,51) = 2.09$, $p = .16$, $n^2_p = .05$

Table 3 (cont.)

Cortisol	Side[1]	Immediate memory competence		Delayed memory competence		Total	Statistics
		High	Low	High	Low		
AUC_g[5]	LH[2]	739.95 ± 454.75	657.59 ± 585.74	751.00 ± 442.60	647.33 ± 592.53	697.25 ± 518.41	S[12]: F (1,51) = 0.01, p = .95, n^2_p = .01
	RH[3]	725.34 ± 300.99	557.24 ±342.40	662.73 ± 338.63	651.16 ± 313.90	658.10 ± 322.30	IM[13]: F (1,51) = 5.58, p = .45, n^2_p = .01
	Total	732.12 ± 372.74	615.78 ± 492.29	703.71 ± 385.40	648.93 ± 1.34	678.43 ± 431.60	DM[14]: F (1,51) = 0.10, p = .75, n^2_p = .01
							S x IM[15]: F (1,51) = 0.16, p = .69, n^2_p = .01
							S x DM[16]: F (1,51) = 0.02, p = .88, n^2_p = .01

Note. [1]Side: side of seizure focus, [2]LH: left-hemisphere, [3]RH: right-hemisphere, [4]AUC_i: area under the curve with respect to increase, [5]AUC_g: area under the curve with respect to ground, [6]M: moment effect, [7]M x S: moment*side of seizure focus interaction, [8]M x IM: moment*immediate memory competence interaction, [9]M x DM: moment*delayed memory competence interaction, [10]M x S x IM: moment*side of seizure focus*immediate memory competence interaction, [11]M x S x DM: moment*side of seizure focus*delayed memory competence interaction, [12]S: side of seizure focus effect, [13]IM: immediate memory competence effect, [14]DM: delayed memory competence effect, [15]S x IM: side of seizure focus*immediate memory competence interaction, [16]S x DM: side of seizure focus*delayed memory competence interaction, *: significant.

3.3. Predictors of memory performance

In the total sample, the cortisol AUC_i was negatively related to immediate and delayed memory ($r(52) = -.27$, $p = .04$ and $r(52) = -.22$, $p = .05$, respectively). The cortisol AUC_i was also negatively related to specific memory indices such as immediate and delayed auditory memory ($r(52) = -.29$, $p = .036$ and $r(52) = -.30$, $p = .031$, respectively). Cortisol percentiles were negatively associated with auditory retrieval ($r(52) = -.29$, $p = .036$). Additionally, trait anxiety was negatively related to most of the memory indices, including immediate and delayed memory, immediate and delayed auditory and visual memory, single-trial auditory learning, and auditory learning slope ($r(52) = -.48$, $p = .0001$; $r(52) = -.50$, $p = .0001$; $r(52) = -.40$, $p = .003$; $r(52) = -.40$, $p = .003$; $r(52) = -.41$, $p = .002$; $r(52) = -.48$, $p = .0001$; $r(52) = -.40$, $p = .004$; and $r(52) = -.32$, $p = .019$, respectively).

When correlations were examined in LH and RH groups, these patterns of relationships were mainly found in the LH group. In this group, immediate and delayed memory, immediate and delayed auditory memory, immediate visual memory, and auditory retention were negatively associated with the cortisol AUC_i ($r(27) = -.39$, $p = .045$; $r(27) = -.37$, $p = .05$; $r(27) = -.39$, $p = .045$; $r(27) = -.46$, $p = .016$; $r(27) = -.41$, $p = .035$; $r(27) = -.42$, $p = .03$, respectively), while immediate and delayed memory, immediate and delayed auditory and visual memory, single-trial auditory learning, and auditory learning slope were negatively related to trait anxiety ($r(27) = -.53$, $p = .003$; $r(27) = -.53$, $p = .005$; $r(27) = -.47$, $p = .014$; $r(27) = -.46$, $p = .017$; $r(27) = -.55$, $p = .003$; $r(27) = -.51$, $p = .006$; $r(27) = -.49$, $p = .01$; and $r(27) = -.42$, $p = .03$, respectively). In patients with RH focus, we only found that trait anxiety was negatively related to immediate and delayed memory, and delayed visual memory ($r(25) = -.32$, $p = .03$; $r(25) = -.49$, $p = .013$; $r(25) = -.43$, $p = .03$, respectively).

No significant associations of cortisol AUCs or percentiles with trait anxiety, state anxiety and depression were found in the total sample neither in LH and RH groups (for all, $p > .07$).

Due to the complexity of these relationships, hierarchical regressions were carried out to examine reliable predictors of memory performance in the total sample and in both groups of patients. The results of the hierarchical regressions with memory performance as dependent variables, controlling seizure frequency and epilepsy type, are shown in Table 4.

In the total sample, higher immediate memory scores were predicted by the lower cortisol AUC_i and lower trait anxiety. When groups based on the side of the seizure focus were

considered separately, this model remained significant in the group of patients with LH focus, but not in the group of patients with RH focus.

However, higher delayed memory scores were only predicted by the lower trait anxiety in the total sample. This model remained significant in the group of patients with RH focus. In the group of patients with LH focus, both lower trait anxiety and lower cortisol AUC_i predicted higher delayed memory scores.

These regression models remained significant even when the two patients who suffered a seizure during the evaluation were excluded.

Table 4. Hierarchical regression analyses investigating the effect of the cortisol AUC_i and the trait anxiety on memory performance in the total sample and in patients with LH and RH focus

			Total sample			
			Immediate memory			
	Std β	Lower limit[1]	Upper limit[1]	Δ R^2	R^2	*F*
Block 1				.01		
Seizure frequency	-.01	-0.16	0.15			
Epilepsy type	-.11	-24.27	10.15			
Block 2				.08*		
Cortisol AUC_i[1]	-.25*	-0.03	0.00			
Block 3				.22***	.31	5.25**
Trait anxiety	-.48***	-1.87	-0.58			
			Delayed memory			
	Std β	Lower limit[1]	Upper limit[1]	Δ R^2	R^2	*F*
Block 1				.01		
Seizure frequency	.17	-0.06	0.26			
Epilepsy type	-.14	-26.80	8.44			
Block 2				.05		
Cortisol AUC_i[1]	-.17	-0.03	0.01			
Block 3				.27***	.32	5.53**
Trait anxiety	-.54***	-2.07	-0.76			
			Patients with LH focus			
			Immediate memory			
	Std β	Lower limit[1]	Upper limit[1]	Δ R^2	R^2	*F*
Block 1				.04		
Seizure frequency	-.10	-0.25	0.16			
Epilepsy type	.01	-24.96	26.63			
Block 2				.19*		
Cortisol AUC_i[1]	-.42*	-0.04	-0.01			
Block 3				.22*	.45	4.54*
Trait anxiety	-.52*	-2.20	-0.40			
			Delayed memory			
	Std β	Lower limit[1]	Upper limit[1]	Δ R^2	R^2	*F*
Block 1				.03		
Seizure frequency	.20	-0.09	0.29			
Epilepsy type	.03	-22.02	26.39			
Block 2				.14		
Cortisol AUC_i[1]	-.36*	-0.04	-0.01			
Block 3				.30*	.47	4.92*
Trait anxiety	-.60*	-2.28	-0.59			
			Patients with RH focus			
			Immediate memory			
	Std β	Lower limit[1]	Upper limit[1]	Δ R^2	R^2	*F*
Block 1				.03		
Seizure frequency	.07	-0.26	0.36			
Epilepsy type	-.23	-40.58	11.85			
Block 2				.01		
Cortisol AUC_i[1]	.06	-0.04	0.05			
Block 3				.20*	.24	1.57
Trait anxiety	-.47*	-2.27	-0.12			
			Delayed memory			
	Std β	Lower limit[1]	Upper limit[1]	Δ R^2	R^2	*F*
Block 1				.01		
Seizure frequency	.03	-0.30	0.35			
Epilepsy type	-.30	-48.14	5.87			
Block 2				.01		
Cortisol AUC_i[1]	.18	-0.02	0.06			
Block 3				.29*	.35	2.66*
Trait anxiety	-.56*	-2.69	-0.48			

Note. [1]AUC_i: area under the curve with respect to increase, *, $p < .05$; **, $p < .001$; ***, $p < .0001$; (t), $p = .06$; [1]95% C.I. = confidence intervals.

4. Discussion

The results of the current study indicate that patients with low immediate and delayed memory performance have higher cortisol levels and AUC_i – and levels, therefore, decline more slowly in the afternoon (independently of the side of seizure focus). Moreover, memory performance is negatively related to AUC_i and trait anxiety in the total sample. Even after controlling for seizure frequency and epilepsy type, lower cortisol AUC_i and lower trait anxiety are reliable predictors of higher immediate memory performance in the group of patients with LH focus, although not in the patients with RH focus. Lower trait anxiety significantly predicted delayed memory performance in the total sample and in both groups of patients with LH and RH focus, while cortisol AUC_i was a significant predictor only in the group of patients with LH focus. Furthermore, no significant relationships of cortisol with anxiety and depression have been found in the sample studied.

Most demographic and clinical characteristics did not differ depending on the side of seizure focus or the epilepsy type. However, patients with RH consumed a higher number of AEDs and total DDD than those with LH focus, and ETLE patients consumed more AEDs and more frequently levetiracetam and had higher DDD and lower frequently HS than those with TLE. It is worth noting that AEDs could modulate cortisol levels, especially strong enzyme inducers drugs (Johannessen & Johannessen Landmark, 2010; Putignano et al., 1998), although the results are not homogeneous (Galimberti et al., 2005). However, in our sample, there were no differences for cortisol levels between patients with LH and RH focus neither between TLE and ETLE patients. In TLE subgroup, patients with HS had similar cortisol levels than those without HS. Additionally, cortisol levels were not related to the number of AEDs nor the total DDD or type of AED, and no differences in cortisol were found depending on the consumption of strong enzyme inducer drugs.

No differences in memory indices were found depending on the side of seizure focus neither the epilepsy type. The material-specific model establishes that the left temporal lobe sustains verbal memories, while the right temporal lobe sustains non-verbal memories (Willment & Golby, 2013). However, chronic epilepsy could imply an additional indirect impairment of functional compensation in non-epileptic areas, producing progressive cognitive deterioration in people with drug-resistant epilepsy (Elger, et al., 2004). Patients in the present study have suffered epilepsy for a mean of 23.19 years, and this could explain the scarce differences found in cognitive profile between patients with LH and RH focus or between those

with TLE and ETLE. However, in the subgroup of patients with TLE, those with HS were more likely to have lower memory scores than those without HS, according to previous studies (Miller et al., 1993). Mesial TLE with HS is a severe focal epilepsy type associated with a high degree of pharmacoresistance (Wieser, ILAE Commision on Neurosurgery of Epilepsy, 2004), more closely associated with cortical function disturbances than other focal epilepsy syndromes (Weber et al., 2006).

Patients did not differ in anxiety and depression scores depending on the side of seizure focus or the epilepsy type, in contrast to previous studies that suggested LH lesions (Altshuler, Devinsky, Post, & Theodore, 1990) and temporal focus (Altshuler et al., 1990; Piazzini, Canevini, Maggiori, & Canger, 2001) are related to higher susceptibility to anxiety and depression. Surprisingly, in the total sample, anxiety and depression scores were not significantly related to the cortisol AUC or percentiles. Previous studies found a positive association between cortisol and depression scores (Devinsky et al., 1991; Afifi et al., 2011), but also no relationship in people with epilepsy (Busch et al., 2012). It should be noted that our sample had subclinical levels of depression (mean score of 11.58), and the score of 16 has been identified as the BDI cut-off point indicating levels of depression susceptible to psychological intervention (Rohling, Green, Allen, & Iverson, 2002). This could explain the lack of significant associations between cortisol and depression scores in our study. Moreover, trait anxiety scores were not related to cortisol levels in contrast to the study of Busch et al. (2012) with a single sample of midnight cortisol. In the present study, trait anxiety was not related to cortisol levels, although it was negatively related to most of the memory indices, according to previous studies with people with epilepsy (Helmstaedter et al., 2004; Miller et al., 2016b; Paradiso et al., 2001).

Salivary cortisol levels were different depending on memory performance. Patients with low and high memory competence had similar demographic and clinical characteristics (except for the consume of levetiracetam and oxcarbazepine, that was more frequent in patients with high immediate memory). These groups differed in trait anxiety, patients with high memory competence having lower trait anxiety than those with low memory competence. Even after controlling for variables in which groups differed, patients with LH focus with low immediate and delayed memory performance showed higher rest cortisol levels, according to the results of Busch et al. (2012). Cortisol levels follow a 24-h circadian rhythm, in which cortisol concentrations present a morning circadian peak, and slowly declining levels in the late afternoon, evening and night – the circadian trough (Kirschbaum & Hellhammer, 1989; Lupien et al., 2005). Cortisol levels exhibited by over half of the sample of the present study during the

afternoon were above the 95th percentile of normative reference levels for the general population at similar hours, accordingly to the CIRCORT database (Miller et al., 2016a). It is not likely to attribute the hypercortisolism of the sample to recent seizures, since, although recent seizures can alter cortisol levels (Bazil et al., 2000), the cortisol peak in most cases appears within 30 minutes of the onset of stress in healthy people (Kirschbaum et al., 1993) and this period of potential responsiveness was covariated.

High cortisol levels in the afternoon could be interpreted as an inability of the HPA axis to inhibit itself and could be maladaptive in cognitive terms in these patients. This possible explanation is supported by the fact that people with epilepsy have high rates of non-suppression after the dexamethasone test (Robertson et al., 1986). In patients with RH focus, no differences in cortisol levels depending on memory performance were found. As far as we know, no studies have analyzed the potential role of the side of seizure focus in the relationship between cortisol and memory performance. However, patients with LH focus are at higher risk of an accelerated forgetting of declarative memory (Jokeit et al., 2001) and, although this reasoning remains speculative, this could be influenced by basal cortisol levels. Additionally, the lack of significant effects in patients with RH focus may be influenced by the lower sensitivity of the visual memory measures to the RH integrity (in respect to the verbal memory measures' sensitivity to the LH integrity), being frequently mediated by the verbalization of the information to be learned (Helmstaedter et al., Vaz, 2004).

With regards to the epilepsy type and the HS, we found no effects of these factors in the relationship between cortisol and memory performance. The relative smaller size of the ETLE group may have affected our ability to detect significant effects, so our findings should be interpreted with caution. To the best of our knowledge, the only study analyzing relationships between cortisol and memory in people with epilepsy only includes patients with TLE (Busch et al., 2012), limiting the establishment of conclusions about the impact of the epilepsy type. According to our findings, in Busch's study, patients with hippocampal atrophy performed worse in verbal memory tasks, independently of midnight cortisol (Busch et al., 2012).

Additionally, patients with low immediate and delayed memory scores had higher cortisol AUC_i, independently of the side of seizure focus and the epilepsy type. The AUC_i may be indicative of the ability of the HPA axis to descend in accordance with the daily circadian rhythm (Pruessner et al., 2003) and so patients with low memory scores had slower declining levels in the afternoon. Cortisol AUC_i is negatively related to scores in most memory indices.

Accordingly, cortisol percentiles are negatively related to memory performance, but only to auditory retrieval. This lower sensitivity of the percentiles with respect to the AUC_i on memory performance could be due to the ceiling effect produced by the accumulation of the sample in the upper cortisol percentiles. Despite these differences in the sensitivity of the measures employed, our findings are in line to previous studies that analyzed the associations between elevated cortisol and poor cognitive functions in healthy participants and predominantly found deficits in hippocampal-dependent cognitive domains (Fonda et al., 2005; Lee et al., 2007). This relationship is coherent with the considerations of the hippocampus as a region involved in episodic and declarative memory (Eichenbaum, Otto, & Cohen, 1992), rich in glucocorticoid receptors (McEwen & Sapolsky, 1995), and especially vulnerable to repeated stress (McEwen, 1998).

People with drug-resistant epilepsy deal with repetitive, uncontrollable, and unpredictable seizures together with the usual stressors in daily life, and these stressors could imply a price in terms of health. McEwen (1998) proposed the term 'allostatic load' to refer to the price a person pays for being forced to adapt to daily life stressors. The allostatic load hypothesis links repeated exposure to environmental stressors with disease through wear of the neuroendocrine systems (McEwen, 1998). In the present study, higher seizure frequency has been related to higher cortisol levels, one of the final products of the stress response in patients with both partial and secondary generalized seizures and in the LH group. This result suggests that certain characteristics of the patients could help to detect individuals with a high risk of presenting stress-related unbalanced states of health.

Controlling seizure frequency and epilepsy type, higher immediate memory performance was predicted by lower cortisol AUC_i and lower trait anxiety in the total sample. This result is mainly due to patients with LH focus, since this group replicates the pattern of predictors, not found in the patients with RH focus. Regarding delayed memory performance, lower trait anxiety was a reliable predictor in the total sample and in both groups of patients with LH and RH focus, while cortisol AUC_i was a significant predictor only in the group of patients with LH focus. Considering our results, the exposure to psychosocial stressors may facilitate cognitive impairment via elevated cortisol levels (Lee et al., 2007), especially in patients with LH focus, who more frequently have memory deficits. Additionally, cognitive impairment could affect the family, social, and work environment, and have a global impact on the life of the individual, favoring in turn, higher cortisol levels and anxiety. It is worth noting the role of trait anxiety in cognitive impairments, considering that its scores are not clinical

anxiety as evaluated in the present study. The results suggest, firstly, that cognitive and affective aspects are related and must be considered jointly from an integrative view of clinical evaluation; and, secondly, that trait anxiety could be a useful tool to early detect potential comorbidities in epilepsy.

Some limitations of our study should be considered. Firstly, although all the patients presented drug-resistant epilepsy, the group is heterogeneous in terms of the exact localization of the epileptic focus. Secondly, greater sample sizes could provide more information about groups, thereby ensuring statistical power. Thirdly, although we found no relationships between the AEDs (number, type, or total defined daily dose) and cortisol levels, patients were treated with AEDs polytherapy and the AEDs combination was individualized for each patient. Finally, it should be noted that anxiety and depression scores are not clinical measures (since we considered anxiety as a trait and depression was only measured once) and so this does not enable establishing a diagnostic criterion (Kendall et al., 1987).

In summary, the data suggest a relationship indicating that exposure to elevated levels of cortisol in people with drug-resistant epilepsy who have an LH focus is related to worse memory performance. Additionally, patients with poor memory performance have higher cortisol AUC_i and, consequently, slower declining cortisol levels in the afternoon than those with high memory performance. Considering that cortisol AUC may capture dysregulation in the HPA axis, it is possible that memory deficits in people with drug-resistant epilepsy may be influenced by exposure to chronic stress in this population. Despite the lack of a relationship between cortisol levels and anxiety and depression scores, poor memory performance is related to high trait anxiety that could contribute to individual differences in vulnerability to stress (Weger & Sandi, 2018). Further research is needed to clarify to which extent afternoon cortisol, with fewer fluctuations than morning cortisol, could be proposed as an indicator of high risk for memory deficits in people with epilepsy.

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CHAPTER 8

Study 5

Quality of life in drug-resistant epilepsy: relationships with negative affectivity, memory, somatic symptoms and social support [1]

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1. Introduction

Patients with drug-resistant epilepsy experience most of the burden of the disease (World Health Organization, 2014) as they are more likely to experience the associated disabilities, social discrimination, and side-effects of antiepileptic drugs (AEDs) (Jacoby & Baker, 2008). In these patients, chronic exposure to seizures could induce significant challenges and adaptive demands that could compromise their quality of life (QOL) (Poochikian-Sarkissian et al., 2007). Poor QOL could be an indicator of the need for surgery, considering that epilepsy treatment is directed toward seizure control, and such surgery may contribute to restoring QOL to adequate levels (Luoni et al., 2011; Taylor, Sander, Taylor, & Baker, 2011).

Baker et al. (1993) proposed the patient-based health-related QOL model for epilepsy, which is based on a global definition of health, including physical, social, and psychological (cognitive and emotional) domains. This model provides a framework for investigating the complex interactions among these variables (Baker et al., 1993). Although previous studies have found an association between QOL and the clinical history variables of the epilepsy, such as seizure frequency (Akdemir et al., 2016; Piperidou et al., 2008; Şenol et al., 2007), duration of disease (Piperidou et al., 2008), and side-effects of AEDs (Perucca, Carter, Vahle, & Gilliam, 2009), other physical, social and psychological factors non-directly related to seizures such as somatic symptoms, social support, verbal memory and negative affectivity have received less attention. Available studies show that patients with epilepsy have more somatic symptoms than the general population (Téllez-Zenteno, Matijevic, & Wiebe, 2005), although, as far as we know, the impact on QOL has not been analyzed. Social support has also been associated with QOL as a protective factor for burden (Amir, Roziner, Knoll, & Neufeld, 1999; Choi-Kwon et al., 2003; Jacoby, Snape, & Baker, 2009). Additionally, QOL has been related to cognitive performance (Giovagnoli & Avanzini, 2000; Perrine et al., 1995), especially in verbal memory, which is one of the domains most sensitive to the negative effects of epilepsy (Helmstaedter, 2004; Vingerhoets, 2006).

Negative affectivity could also influenced QOL in epilepsy patients. Previous studies have found that depression is a reliable predictor of poor QOL in patients with drug-resistant epilepsy (Boylan et al,, 2004; Scévola et al., 2017). In addition, a negative association has been found between anxiety levels and QOL in patients with different types of epilepsy (Gur-Ozmen et al., 2017) and, specifically, in TLE (Andelman, Fried, & Neufeld, 2001). When the impact of both anxiety and depression on QOL is examined, Johnson, Jones, Seidenberg, and Hermann (2004)

found that these variables were independently associated with a lower QOL in patients with TLE. Kanner, Barry, Gilliam, Hermann, & Meador, 2010) showed that although anxiety and depression when separately considered had effects on the QOL of patients with different types of epilepsy, their comorbidity favored a more negative impact.

As far as we know, no studies have analyzed the relationships between the above factors and QOL in the same sample. However, this approach may help clarify the impact of these factors in QOL and detect the contextual profiles of individuals at risk of experiencing poor QOL. The aim of this study is to investigate the relative contribution of negative affectivity, social support, somatic symptoms, and memory performance on QOL in patients with drug-resistant epilepsy.

2. Material and methods

2.1. Participants

This is a cross-sectional study. Patients were consecutively recruited from the inpatient Epilepsy Unit, Hospital Universitario y Politécnico La Fe, between April 2015 and October 2017. This center is belonging to European Reference Network for Epilepsy (EpiCARE) and approximately 50 patients are assessed every year as candidates for epilepsy surgery.

The inclusion criteria of the study comprised: 1) patients with a diagnosis of drug-resistant epilepsy; 2) candidates for epilepsy surgery; 3) chronological age of at least 18 years; 4) and a neuropsychological assessment performed prior to surgery. Excluded were patients who: 1) were older than 60 years; 2) had severe cognitive impairment that prevented a reliable neuropsychological evaluation; 3) had uncompleted primary education; 4) included a history of severe psychiatric conditions; 5) were not fluent Spanish speakers; and 6) declined to participate in the study. The sample was composed of 70 adult patients with drug-resistant epilepsy (39 women and 31 men; mean age ± *SEM* = 38.39 ± 1.30). With regard to the type of epilepsy, 48 of the patients had TLE and 22 of the patients had extratemporal epilepsy (ETLE). In addition, 38 of the patients had affected left hemisphere and 32 of the patients had affected right hemisphere. Characteristics of the sample are shown in Table 1.

Table 1. Characteristics of the total sample expressed in mean ± SEM or n (%)

Characteristics	Total (*N* = 70)
Age	38.39 ± 1.30
Sex	
Female	39 (55.7%)
Male	31 (44.3%)
Educational level	
Primary education	6 (8.6%)
Secondary education	32 (45.7%)
Lower-university education	17 (24.3%)
University education	15 (21.4%)
Handedness	
Right	60 (85.7%)
Left	10 (14.3%)
Side of seizure focus	
Right	32 (45.7%)
Left	38 (54.3%)
Age at epilepsy onset	14.66 ± 1.40
Epilepsy duration	23.73 ± 1.79
Etiology of pathology	
Hippocampal sclerosis	14 (20.0%)
Focal cortical dysplasia	17 (24.3%)
Tumor	15 (21.4%)
Gliosis	2 (2.9%)
Heterotopia	2 (2.9%)
General atrophy	1 (1.4%)
Hippocampal atrophy	1 (1.4%)
Angiomatosis	1 (1.4%)
Subcortical lesions	1 (1.4%)
Non-specific pathology	13 (18.6%)
Non-assessable	3 (4.3%)
Number of AEDs	2.90 ± 0.12
Seizures per month	25.55 ± 5.76
Seizure type	
SPS[1]	5 (7.1%)
CPS[2]	30 (42.9%)
SPS[1] + CPS[2]	13 (18.6%)
CPS[2] + GCTS[3]	17 (24.3%)
SPS[1] + CPS[2] + GCTS[3]	5 (7.1%)

[1]SPS: simple partial seizure, [2]CPS: complex partial seizure, [3]GTCS: secondary generalized seizures.

2.2. Procedure

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the Hospital Universitario y Politécnico La Fe. Informed consent was obtained from all individual participants included in the study.

Medical history provided demographic characteristics of the patients (sex, age, and educational level), and clinical data (age at epilepsy onset, duration of epilepsy in years, frequency of seizures per month, type of seizures and number of AEDs).

Pre-surgical assessment included diagnosis of the type of epilepsy and the lateralization of the epileptogenic area. Assessment was made by staff members of the multidisciplinary team and based on a comprehensive evaluation that included: seizure history and semiology; neurologic examination; long-term video-EEG monitoring; 3-Tesla magnetic resonance imaging (MRI); fluorodeoxyglucose (FDG)-positron emission tomography (PET); single photon emission computed tomography (SPECT); psychiatric assessment; and neuropsychological evaluation for all patients. If concerns about post-surgical memory outcome were not solved by prior evaluation, a Wada test was performed to help in the decision-making process.

Neuropsychological evaluation was carried out approximately 3 months before surgery. After the cognitive tasks, patients were instructed to complete psychological and QOL questionnaires described below.

2.3. Neuropsychological assessment

Handedness. We used the Edinburgh Handedness Inventory (EHI; Oldfield, 1971) to assess handedness. It consists of 10 items referring to the hand used for certain motor activities. Participants were classified as lefthanded (EHI: −100 to −61), ambidextrous (EHI: −60 to +60), or right-handed (EHI: +61 to +100) (Dragovic, 2004).

QOL. This was examined using the Quality-of-Life in Epilepsy Inventory (QOLIE-31; Cramer et al., 1998). It includes 31 items distributed in seven scales: seizure worry; overall QOL; emotional well-being; energy; cognitive self-rating; medication effects; and social functioning. Scores for each scale were computed by converting the raw precoded numeric

values of items to 0–100 scores with higher scores indicating better QOL in all cases (including seizure worry and medication effects, which were scored on an inverse scale). A QOL composite score was obtained by using a weighted average of the different scales. Cronbach's alphas of the Spanish adaptation of this inventory are: 0.92 for the composite score, 0.83 for the seizure worry scale, 0.55 for the overall QOL scale, 0.77 for the emotional well-being scale, 0.77 for the energy scale, 0.82 for the cognitive self-rating scale, 0.77 for the medication effects scale, and 0.77 for the social functioning scale (Torres, Arroyo, Araya, & Pablo, 1999).

Anxiety-trait. This was assessed using the State-Trait Anxiety Inventory (STAI; Spielberger, 1989). The trait anxiety scale (STAI-T) evaluates relatively stable aspects of anxiety and is composed of 20 items rated on a four-point scale. Cronbach's alpha of the Spanish adaptation of this inventory is 0.94 (Guillén-Riquelme & Buela-Casal, 2011).

Depression. Beck Depression Inventory – II (BDI-II; Beck et al., 1996). The inventory was used to assess depression with 21 items rated on a four-point scale. Cutting scores for different depression levels were: 0–13 for minimum depression, 14–19 for mild depression, 20–28 for moderate depression, and 29–63 for severe depression (Beck et al., 1996). Considering that variations in the cutting scores are frequent in research with this instrument, and that this could difficult the comparison between studies (Kendall et al., 1987), we used total score as indicator of depression level, but not the classification of depression levels. Cronbach's alpha of the Spanish adaptation of this inventory is 0.89 (Sanz & García-Vera, 2009).

Social support. This was examined using the Medical Outcomes Study Social Support Survey (MOS; Sherbourne & Stewart, 1991). It is composed of 20 items rated on a five-point scale, and was used to assess emotional, instrumental, and affectionate support, as well as positive social interaction. Global social support was computed as the sum of the scores in these four subscales. The Cronbach's alphas are: 0.97 for global social support, 0.96 for emotional support, 0.92 for instrumental support, 0.91 for affectionate support, and 0.94 for positive social interaction (Sherbourne & Stewart, 1991).

Somatic symptoms. The Somatic Symptoms Scale-Revised (ESS-R; Sandín & Chorot, 1995) was used to assess health status in terms of physical complaints. It is composed of 90 items rated on a five-point scale, and distributed in eight subscales: immunological; respiratory; cardiovascular; neurosensory; gastrointestinal; dermatological; genital-urinary; and muscular (reliability coefficients from 0.79 to 0.84) (Sandín & Chorot, 1995).

Verbal memory. The Spanish Complutense Verbal Learning Test (TAVEC; Benedet & Alejandre, 1998) was used to assess episodic verbal memory. It is a Spanish version of the California Verbal Learning Test (CVLT; Delis et al., 1987). TAVEC consists of three shopping lists: a learning list (list A); an interference list (list B); and a recognition list (list C). Immediate verbal memory, short-term verbal memory, short-term verbal with semantic cues, long-term verbal memory, long-term verbal memory with semantic cues, long-term verbal recognition, number of semantic learning strategies, number of serial learning strategies, total number of intrusions and total number of perseverations were computed.

Immediate visual memory. It was examined using the immediate visual subtest of the Revised-Barcelona Test – a neuropsychological battery validated in the Spanish population (BCN-R; Peña-Casanova, 2005). The immediate visual memory subtest consists of the presentation of ten figures during ten seconds each and participants had to recognize each from among four options. The total score was computed as the sum of correct answers and therefore the maximum score was ten points.

2.4. Statistical analyses

The Kolmogorov-Smirnov test was carried out to examine data normality and the relationships between patient characteristics and QOL, and between patient characteristics and cognitive and affective scores proposed as possible predictors of QOL were then examined. *t*-tests for independent samples were performed for between-group comparisons based on gender, handedness, type of epilepsy (TLE or ETLE), the side of seizure focus, and the type of seizures in the QOL composite score and subscales, and in affective and cognitive variables (according to Levene's tests for equality of variance). In addition, Pearson correlations were performed to establish the association among quantitative variables (frequency of seizures, number of AEDs, age at epilepsy onset, and epilepsy duration) and QOL, cognitive and affective variables.

Linear regression analysis was conducted to analyze the predictive role of each independent variable from four domains (negative affectivity, social support, somatic symptoms, and memory) on QOL composite score. Once we detected factors strongly related to QOL composite score, we analyzed which of the QOL subscales were more sensitive to these factors using separate linear regression analyses. Stepwise multiple regression analyses were then performed – including significant predictors resulting from the separate linear regression

analyses as independent variables and QOL composite and subscales scores as dependent variables. Block 1 included negative affectivity; block 2 was comprised of neurosensory symptoms; and block 3 included long-term verbal memory.

Statistical analysis was carried out using SPSS 22.0 and two-tailed tests with p set to 0.05 considered as significant.

3. Results

3.1. Patient characteristics and QOL

QOL composite score did not differ between groups based on sex, handedness, and type of epilepsy (TLE or ETLE), and was not associated with epilepsy-related variables in the total sample (frequency of seizures, number of AEDs, age at epilepsy onset, nor epilepsy duration). For that, these variables were not included in posterior regression analysis. However, although total frequency of seizures was not related to QOL composite score in the total sample, a negative relationship between both variables was found in patients suffering exclusively partial seizures (simple and complex) ($r = -0.31$, $p = .03$). No significant association was found in patients with both partial and tonic-clonic seizures.

In QOL subscales, patients with left hemisphere (LH) epilepsy had more seizure worry than patients with right hemisphere (RH) epilepsy ($t(68) = -2.10$, $p = .04$). Additionally, higher scores in medication effects were related to age at epilepsy onset ($r = -0.31$, $p = .009$). No other relationships were found.

Scores in variables proposed as possible factors related to QOL (anxiety, depression, social support, somatic symptoms, and memory) did not differ between groups based on sex, handedness, type of epilepsy (TLE or ETLE), and side of seizure focus (LH or RH). Most characteristics of patients were not related to these factors. However, positive social interactions were negatively related to epilepsy duration ($r = 0.28$, $p = .017$). Additionally, patients with both partial and tonic-clonic seizures had higher depression scores that patients suffering exclusively partial seizures ($t(68) = -2.62$, $p = .01$).

3.2. Factors related to QOL composite score

To estimate the predictive strength of each independent variable from four separate domains (negative affectivity, social support, somatic symptoms, and memory) in terms of QOL, we conducted a separate analysis for each domain (Table 2). The results showed that QOL composite score was significantly predicted by anxiety-trait and depression of the negative affectivity domain, positive social interaction of the social support measures, neurosensory symptoms of the somatic domain, and long-term verbal memory with semantic cues for the memory scores.

Table 2. Separate regression analyses investigating the effect of negative affectivity, social support, somatic symptoms and memory on QOL composite score and subscales

	QOLIE-31 composite score					
	Std β	*p*	R^2	Adj. R^2	*F*	*p*
Anxiety-trait	-0.51	.0001	0.56	0.55	43.31	.0001
Depression	-0.32	.002				
Positive social interaction	0.32	.008	0.10	0.09	7.55	.008
Neurosensory symptoms	-0.35	.003	0.12	0.11	9.34	.003
Long-term verbal memory	0.31	.009	0.10	0.08	7.28	.009
	Seizure worry					
	Std β	*p*	R^2	Adj. R^2	*F*	*p*
Anxiety-trait	-0.16	.29	0.02	-0.01	0.60	.55
Depression	0.13	.40				
Positive social interaction	-0.07	.56	0.01	-0.01	0.34	.56
Neurosensory symptoms	0.02	.88	0.01	-0.01	0.02	.88
Long-term verbal memory	0.21	.08	0.05	0.03	3.27	.08
	Overall QOL					
	Std β	*p*	R^2	Adj. R^2	*F*	*p*
Anxiety-trait	-0.32	.02	0.26	0.25	8.90	.0001
Depression	-0.19	.18				
Positive social interaction	0.38	.001	0.14	0.13	11.11	.001
Neurosensory symptoms	-0.28	.02	0.08	0.07	5.92	.02
Long-term verbal memory	0.25	.03	0.07	0.05	4.84	.03

Table 2. (Cont.)

	Emotional well-being					
	Std β	*p*	R^2	Adj. R^2	*F*	*p*
Anxiety-trait Depression	-0.50 -0.27	.0001 .02	0.49	0.47	31.49	.0001
Positive social interaction	0.33	.005	0.11	0.10	8.37	.005
Neurosensory symptoms	-0.26	.03	0.07	0.05	4.75	.03
Long-term verbal memory	0.26	.03	0.07	0.05	4.84	.03
	Energy					
	Std β	*p*	R^2	Adj. R^2	*F*	*p*
Anxiety-trait Depression	-0.37 -0.38	.001 .001	0.46	0.44	28.42	.0001
Positive social interaction	0.36	.002	0.13	0.12	10.20	.002
Neurosensory symptoms	-0.38	.001	0.14	0.13	11.44	.001
Long-term verbal memory	0.21	.09	0.04	0.03	3.00	.09
	Cognitive self-rating					
	Std β	*p*	R^2	Adj. R^2	*F*	*p*
Anxiety-trait Depression	-0.37 -0.34	.002 .005	0.41	0.39	22.97	.0001
Positive social interaction	0.33	.006	0.11	0.09	8.08	.006
Neurosensory symptoms	-0.35	.003	0.12	0.11	9.38	.003
Long-term verbal memory	0.17	.17	0.03	0.01	1.97	.17
	Medication effects					
	Std β	*p*	R^2	Adj. R^2	*F*	*p*
Anxiety-trait Depression	-0.04 -0.34	.79 .02	0.13	0.11	5.19	.008
Positive social interaction	0.07	.55	0.01	-0.01	0.36	.55
Neurosensory symptoms	-0.21	.09	0.04	0.03	2.97	.09
Long-term verbal memory	0.13	.27	0.02	0.01	1.22	.27
	Social functioning					
	Std β	*p*	R^2	Adj. R^2	*F*	*p*
Anxiety-trait Depression	-0.14 -0.32	.32 .03	0.17	0.15	6.94	.002
Positive social interaction	0.21	.08	0.04	0.03	3.11	.08
Neurosensory symptoms	-0.11	.37	0.01	-0.01	0.80	.37
Long-term verbal memory	0.25	.03	0.06	0.05	4.69	.03

The selected variables of each dimension were included in a stepwise multiple regression analysis for the QOL composite score. Four variables were included in the regression model, which accounted for 58% of the accumulated variance (Table 3). In this model, the QOL composite score was predicted by the lowest trait-anxiety, lowest depression, lowest neurosensory symptoms, and highest long-term verbal memory with semantic cues (see Figure 1). Negative affectivity (anxiety-trait and depression) was the strongest predictor of QOL composite score.

Table 3. Stepwise multiple regression analyses investigating the role of anxiety-trait, depression, neurosensory symptoms and long-term verbal memory with semantic cues on QOL composite score

	QOLIE-31 composite score						
	Std β	*p*	R^2	Adj. R^2	*p*	*F*	*p*
Step 1							
Anxiety-trait	-0.43	.0001	0.56	0.55	.0001	43.31	.0001
Depression	-0.30	.004					
Step 2							
Neurosensory symptoms	-0.17	.045	0.58	0.56	.10	30.54	.0001
Step 3							
Long-term verbal memory	0.18	.045	0.61	0.58	.045	25.05	.0001

3.3. Factors related to QOL subscales

To analyze which of the QOL subscales were more sensitive to the factors related to QOL composite score, we also conducted separate regressions for each domain in each subscale (Table 2). Emotional well-being was significantly predicted by anxiety-trait, depression, positive social interaction, neurosensory symptoms, and long-term verbal memory. All these factors except depression were also significant predictors of overall QOL. Energy and cognitive self-rating were significantly predicted by anxiety-trait, depression, positive social interaction and neurosensory symptoms. Medication effects were predicted by depression and neurosensory symptoms, while social functioning was predicted by depression and long-term verbal memory. No predictors were found for seizure worry.

Significant predictors of each subscale were included in stepwise multiple regressions, and significant models are summarized in Figure 1. The subscales with the highest percentage of explained variance were emotional well-being (47%), energy (47%), and cognitive self-rating (39%), mainly because of lower anxiety-trait and depression. Additionally, neurosensory symptoms were involved in the energy scores. To a lesser degree, overall QOL (25%) was predicted by anxiety-trait. Finally, lower social functioning (15%) and higher medication effects (11%) were explained by depression. Lower long-term verbal memory tended to predict lower social functioning (p = .06).

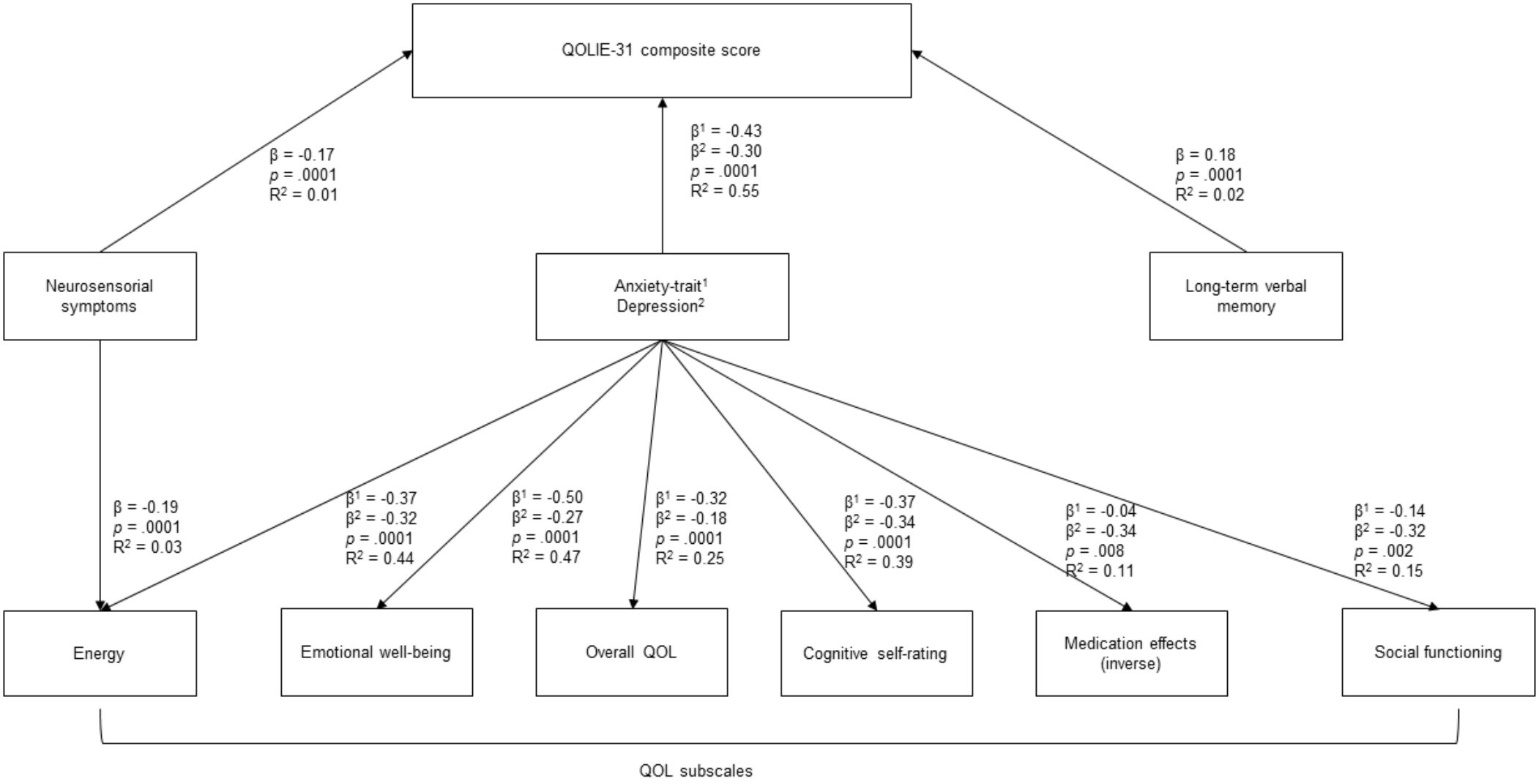

Figure 1. Summary of the stepwise regression models for QOL composite score and subscales

4. Discussion

The results of the current study indicate that lower negative affectivity (including anxiety-trait and depression), higher social support, lower perceived neurosensory symptoms, and higher verbal memory performance are significantly related to higher QOL. Even after controlling for negative affectivity, neurosensory symptoms and long-term verbal memory significantly contribute to QOL.

QOL composite score did not vary depending on epilepsy-related variables, although we found that the side of seizure focus and the age at epilepsy onset could influence some aspects of QOL (such as seizure worry and perception of medication effects). Although total frequency of seizures was not related to QOL composite scores in the total sample, higher frequency of seizures was significantly related to worse QOL in patients suffering exclusively partial seizures (simple and complex). In the systematic review carried out by Taylor et al. (2011), seizure frequency appeared to be a consistent predictor of QOL in patients with epilepsy, while the association between seizure severity and QOL was less consistent. Contrarily, Luoni et al. (2011) found that any epilepsy-related variable had significant predictive value on QOL composite scores, suggesting the important role of non-epilepsy-related variables in QOL in patients with drug-resistant epilepsy.

When we analyzed the role of these variables we found that, separately, anxiety-trait, depression, positive social interaction, neurosensory symptoms, and long-term verbal memory were significantly related to QOL composite score. However, the relationship between positive social interaction and QOL could be mediated by its association with epilepsy duration. In fact, when we analyzed the predictive strength of these variables jointly in a stepwise multiple regression, positive social interaction did not have a significant effect on QOL composite score, so it was excluded from the model. After the exclusion of positive social interaction, we obtain a model in which low anxiety-trait, low depression, low neurosensory symptoms and high long-term verbal memory accounted for 58% of the variance of QOL.

The factor most strongly related to QOL composite score was negative affectivity (anxiety and depression), that accounted for 56% of the variance. It should be noted that in our sample patients with both partial and tonic-clonic seizures had higher depression scores that patients suffering exclusively partial seizures, so depression scores could be influenced by seizures. Boylan et al. (2004) also found depression as a reliable predictor of poor QOL in patients with

drug-resistant epilepsy, without considering other variables such as memory performance or neurosensory symptoms. Johnson et al. (2004) also found that anxiety and depression explained a higher percentage of variance of poor QOL than other clinical variables in patients with TLE. Nevertheless, it should be underlined that QOL composite score includes energy and emotional well-being subscales, and low energy (fatigue) and low emotional well-being are fundamental aspects of depression (American Psychiatric Association, 2013). Taking into account this and the high percentage of variance of the QOL composite score explained by the negative affectivity in our study, a conceptual overlap between the constructs of negative affectivity and QOL may be plausible. In this line, Tracy, Dechant, Sperling, Cho, and Glosser (2007b) also found that QOL composite score could strongly reflect psychological state, especially with regard to depression, in patients with different types of epilepsy (not all with drug-resistant epilepsy). According to our results and those of Tracy et al. (2007b), any intervention focused on the QOL improvement that considered QOL scores as a target should at least consider the possibility that the outcome is closely related to negative affectivity, which is highly prevalent in patients with epilepsy. In fact, more than 60% of patients have psychiatric comorbidity (Gur-Ozmen et al., 2017; Kanner, 2016), with a high prevalence of anxiety and depression (Kwon & Park, 2014; Mensah et al., 2007; Park, 2016). These affective disorders could be the consequence of epilepsy or its treatment, sharing the same pathophysiology underlying epilepsy (Helmstaedter et al., 2014), and so the study of the impact of negative affectivity in this population is especially relevant. However, there are difficulties in the recognition and treatment of these symptoms (Kanner et al., 2010), probably due to the use of clinical anxiety and depression instruments that only detect negative affectivity in a clinical range. A possible solution could be the complementary use of non-clinical scales such as the anxiety-trait questionnaire employed in our study for detecting certain susceptibilities to clinical disorders.

After accounting for the effect of negative affectivity, due to its potential overlap with the QOL construct, we found that neurosensory symptoms and long-term verbal memory remained significantly related to QOL composite score. As far as we know, no previous studies have analyzed the impact of somatic symptoms on QOL in this population. However, Téllez-Zenteno et al. (2005) found that patients with epilepsy had a higher prevalence of somatic symptoms than people without epilepsy, indicating the need for a more integrated approach to health complaints in these patients. With regards to memory performance, various studies have found that both recurrent epileptic seizures and epilepsy treatments may involve memory impairment (Cano-López et al., 2017; Miller et al., 2016b). In fact, verbal memory disruption is one of the

most frequently reported complaints by patients with epilepsy (Helmstaedter, 2004; Thompson et al., 2016; Vingerhoets, 2006), and could be a major contributor to the burden of this disease, disrupting not only QOL, but also other aspects of the patient's life such as employment, school and family life. In respect to QOL, Giovagnoli and Avanzini (2000) found that perceived mnemonic functioning, but not objective memory performance, had a significant impact on QOL in patients with TLE. Perrine et al. (1995) showed that verbal memory was a significant predictor of QOL in a mixed sample of patients with drug-resistant epilepsy and medically-controlled epilepsy. In these studies, mood was also a significant predictor of QOL, although the role of social support or somatic symptoms on QOL was not analyzed (Giovagnoli & Avanzini, 2000; Perrine et al., 1995). Although this reasoning remains speculative, the fact that verbal memory performance is associated with QOL may suggest that memory improvement by specific rehabilitation could be also effective in improving QOL in patients with drug-resistant epilepsy.

The subscales of QOL showed different sensitivities to negative affectivity, neurosensory symptoms, and memory performance, as previously reported by Andelman et al. (2001) considering only the anxiety-trait. As expected, energy and emotional well-being were the subscales most strongly related to negative affectivity, but also to positive social interaction and neurosensory symptoms. Emotional well-being was also associated with long-term verbal memory. However, after controlling for negative affectivity, only the relationship between low neurosensory symptoms and higher energy remained significant. Negative affectivity was also the factor most strongly related to the rest of subscales (excluding seizure worry), with whom this strong relationship was not to be expected. Although these subscales were also related to other factors such as positive social interaction, neurosensory symptoms and long-term verbal memory, only long-term verbal memory tended to be positively related to social functioning after controlling for negative affectivity.

Interestingly, different analytic techniques, including one that considered the overlapping variance of different factors related to QOL, and another that captured only the unique variance of these factors, showed high agreement and highlight that negative affectivity is strongly related to the QOL composite score and most of the subscales. Additionally, these approaches showed that verbal memory performance and somatic symptoms had a significant association with QOL composite score, even controlling negative affectivity, which might have an overlap with the QOL construct. Taken together, our results suggest that clinical management should consider the treatment of verbal memory in order to improve the QOL of patients with drug-

resistant epilepsy. These patients are at high risk of an accelerated forgetting of declarative memory (Jokeit et al., 2001), so it is necessary to identify and treat memory impairments at an early stage. Additionally, recognition of poor social support and high somatic symptoms would lead health professionals to develop different strategies to improve the QOL of patients with drug-resistant epilepsy.

Some limitations should be considered. Firstly, larger sample sizes could provide more information, thereby ensuring greater statistical power. In this regard, the number of variables to be included in the regression analysis as potential predictors is reduced to maintain an acceptable statistical power (Wilson Van Voorhis & Morgan, 2007). Secondly, given the cross-sectional design of our study, it is not possible to describe factors related to QOL as predictors; longitudinal studies are necessary for this purpose. Thirdly, considering that QOLIE-31 includes energy and emotional well-being as subscales, the potential overlap between the constructs of negative affectivity and QOL is an important limitation of our study. Finally, it is necessary to consider that although QOL instruments can provide a comprehensive assessment of the effects of an illness and its therapy (Wagner & Wickrey, 1995) these instruments are based on the perceptions of patients. For this reason, although they contribute to understanding patient satisfaction with their daily performances, the results may or may not coincide with their functionality and autonomy in daily life. Future studies should consider functionality and autonomy measurements. In addition, it would be interesting to analyze these relationships after epilepsy surgery in this population.

Despite these limitations, this study emphasizes the relevance of memory performance, somatic symptoms and social support in the QOL of patients with drug-resistant epilepsy. These results fit the patient based health-related QOL model for epilepsy proposed by Baker et al. (1993), so somatic symptoms could be considered the physical component, social support would correspond to the social component, and negative affectivity and verbal memory performance would be part of the psychological component. Our results could have clinical implications from a preventive approach considering that understanding relationships among these components will lead to design protocols for optimal care in patients with epilepsy.

CAPÍTULO 9

Discusión general, limitaciones y direcciones futuras

1. Discusión general

Los principales resultados de cada estudio han sido discutidos separadamente. En este capítulo se presenta una discusión general de los principales resultados de esta Tesis, sus implicaciones clínicas y sus limitaciones, sugiriendo algunas direcciones futuras basadas en los resultados de los diferentes estudios.

Los estudios empíricos de la presente Tesis doctoral exploran los factores intervinientes en el funcionamiento mnésico en personas con epilepsia farmacorresistente, así como el impacto de esta función cognitiva en la calidad de vida de esta población. Así, los primeros cuatro estudios analizaron el papel de factores escasamente examinados en la literatura sobre la memoria, considerando la influencia de otros factores moduladores identificados en estudios previos. Por su parte, el quinto estudio se centró en determinar la influencia del funcionamiento de la memoria sobre la calidad de vida, considerando el papel de otros factores psicobiológicos y sociales.

1.1. Factores intervinientes en el funcionamiento mnésico

Son numerosos los estudios que han explorado el papel de las variables, en su mayoría directamente relacionadas con las crisis epilépticas, sobre la memoria en personas con epilepsia, a saber: la localización y la lateralización del área epileptógena (Aikia et al., 2001; Baxendale et al., 2008; Delaney et al., 1980; Gleissner et al., 2004; Golby et al., 2001; Helmstaedter y Kockelmann, 2006; Hermann et al., 2007), la frecuencia y el tipo de crisis (Dodrill, 1986; Helmstaedter et al., 2003; Hermann et al., 2006; Thompson y Duncan, 2005; Seidenberg et al., 2007), la edad de inicio y la duración de la epilepsia (Dennis, 2000; Elger et al., 2004; Hermann et al., 2006; Vingerhoets, 2006), la presencia de esclerosis hipocampal (Alessio et al., 2004; Baxendale et al., 1998a; Kilpatrick et al., 1997) y las características de los diferentes tratamientos (Clusmann et al., 2002; Elger et al., 2004; Javed et al., 2015; Kwan y Brodie, 2001). Sin embargo, apenas se ha examinado el papel de otros factores relacionados con el sustrato neural de la memoria como la morfología del hipocampo a lo largo de su eje anterior-posterior (Pauli et al., 2006), la activación funcional durante el procesamiento cognitivo (Berl et al., 2005), y la edad en el momento de la cirugía del lóbulo temporal (Thompson et al., 2015), cuyo estudio puede ser crucial en estos pacientes que frecuentemente presentan déficits de memoria (Thompson et al., 2016). Otros factores que apenas se han explorado en la literatura

son los niveles de cortisol (Busch et al., 2012) y la afectividad negativa (Helmstaedter et al., 2004; Miller et al., 2016b), que podrían considerarse indicadores del bienestar del individuo. En cuanto al cortisol, la epilepsia es una condición potencialmente estresante, por lo que el estudio de los niveles de cortisol en esta población es especialmente relevante. Esto nos llevó a realizar una revisión sistemática sobre los niveles de cortisol en personas con epilepsia, incluida en el capítulo 2 de esta Tesis, en la que se encontraron mayores niveles basales de cortisol en personas con epilepsia respecto a personas sanas, así como una asociación entre las crisis epilépticas y el aumento en los niveles de cortisol. Por su parte, los resultados de los estudios empíricos presentados en esta Tesis muestran que los factores nombrados anteriormente son relevantes en el funcionamiento mnésico de personas con epilepsia farmacorresistente. Dependiendo del factor considerado, el sentido de su relación con el funcionamiento mnésico es diferente.

Respecto a los factores neurales, cabe destacar que, en pacientes con epilepsia y concretamente en aquellos con ELT, se ha descrito de forma consistente una reorganización del funcionamiento mnésico al lóbulo temporal medial contralesional (Bonelli et al., 2010; Powell et al., 2007; Richardson et al., 2003, 2004; Sidhu et al., 2013). Dado que la reorganización funcional de la memoria podría ser un mecanismo compensatorio que se produce como consecuencia de alteraciones estructurales mesiotemporales (Powell et al., 2007; Richardson et al., 2004) y que la esclerosis hipocampal no afecta al hipocampo uniformemente (Blümcke et al., 2013), en el primer estudio abordamos los objetivos específicos 1.1. y 1.2. de la Tesis. Así, nos centramos en determinar las relaciones entre la morfología del hipocampo a lo largo de su eje anterior-posterior, el patrón de activación funcional durante la codificación mnésica y el rendimiento en tareas de memoria. Los resultados encontrados son parcialmente congruentes con las hipótesis planteadas. Así, el patrón de atrofia hipocampal no se asoció significativamente al rendimiento mnésico en pacientes con ELT derecha, mientras que, en los pacientes con ELT izquierda, mayor atrofia en la cabeza del hipocampo (respecto al hipocampo posterior) se asoció a una peor memoria visual. A su vez, en ambos grupos de pacientes, una mayor atrofia en la cabeza del hipocampo se asoció a una menor activación en los lóbulos temporales mediales ipsilaterales y contralaterales durante la codificación mnésica. Este perfil de activación funcional parece modular el aprendizaje verbal y visual a través de un patrón de asociaciones dependiente de la lateralización del área epileptógena. Así, en pacientes con ELT derecha, menor activación temporal medial derecha se asoció con peor aprendizaje verbal, mientras que menor activación temporal medial izquierda se relacionó con peor aprendizaje

visual, sugiriendo mecanismos compensatorios interhemisféricos. Estos resultados apuntan a que la representación bilateral de la codificación mnésica de información verbal y visual podría ser adaptativa en pacientes con ELT derecha (Sidhu et al., 2013). Por su parte, en pacientes con ELT izquierda, los resultados fueron más intrigantes, pues el perfil de activación funcional asociado al patrón de atrofia anterior-posterior del hipocampo no se tradujo en un determinado rendimiento en tareas de memoria. Nuestros hallazgos sugieren que la alteración en la integridad estructural predominantemente en la cabeza del hipocampo interfiere con la red funcional de codificación mnésica en los lóbulos temporales mediales ipsilaterales y contralaterales en pacientes con ELT. Considerando que la región anterior del hipocampo habitualmente se incluye en la resección estándar del lóbulo temporal, mientras que no ocurre lo mismo con la región posterior (Baxendale et al., 2000), estos resultados podrían explicar por qué son habituales los déficits de memoria tras la cirugía del lóbulo temporal.

Es preciso destacar que no sólo se ha descrito una reorganización funcional de la memoria en pacientes con epilepsia, sino que también se ha encontrado una reorganización del lenguaje, cuyos efectos sobre el funcionamiento mnésico permanecen sin esclarecer. Concretamente, la exposición crónica a crisis epilépticas en pacientes con foco epileptógeno izquierdo puede favorecer la reorganización del lenguaje al hemisferio contralateral (Adcock et al., 2003; Brázdil et al., 2003; Janszky et al., 2006). Por ello, en el segundo estudio de la Tesis abordamos el objetivo específico 1.3., analizando la influencia del patrón de asimetría hemisférica en un paradigma de RMf de comprensión verbal sobre el rendimiento en memoria y otros dominios cognitivos, considerando el papel de factores moduladores (i.e., lateralización del área epileptógena y dominancia manual). Los resultados mostraron que el foco epileptógeno izquierdo y la dominancia manual izquierda fueron predictores significativos de la asimetría atípica durante el procesamiento del lenguaje, en línea con estudios previos (Adcock et al., 2003; Corballis et al., 2012; Janszky et al., 2006; Stewart et al., 2014). De acuerdo con nuestras hipótesis, los pacientes con asimetría hemisférica atípica durante el procesamiento del lenguaje obtuvieron puntuaciones más bajas en cociente intelectual (CI) manipulativo y en aprendizaje verbal respecto a aquellos con asimetría hemisférica típica. En esta línea, los pacientes con foco epileptógeno izquierdo presentaron más frecuentemente asimetría atípica que aquellos con foco epileptógeno derecho, y este patrón de asimetría atípica se asoció a peor rendimiento en dominios verbales y no verbales. Estos resultados sugieren que el aumento de la activación de áreas homólogas implicadas en la comprensión verbal del hemisferio derecho podría favorecer una competición de recursos cognitivos de ambos hemisferios implicados en una misma tarea,

desestabilizando el rendimiento cognitivo, de acuerdo con el fenómeno conocido como *crowding* (Jokeit y Ebner, 2002).

Los estudios anteriores se centraron en analizar la morfología del hipocampo a lo largo de su eje anterior-posterior y el patrón de activación funcional en el lóbulo temporal, factores relacionados con el sustrato neural de la memoria, en pacientes con epilepsia farmacorresistente no sometidos a cirugía. En estos pacientes, dicho sustrato neural puede modificarse mediante la cirugía. A pesar de que la cirugía del lóbulo temporal es un tratamiento seguro y efectivo (Clusmann et al., 2002), puede conllevar efectos cognitivos colaterales (Helmstaedter, 2013). Por ello, en el tercer estudio nos planteamos analizar qué factores predecían una mejor evolución en memoria tras la cirugía en estos pacientes, abordando el objetivo 2 de la Tesis. En concreto, nos centramos en examinar si la edad en el momento de la cirugía era un predictor fiable de la evolución mnésica postquirúrgica, considerando otras variables clínicas relevantes y la asociación entre la memoria y otros dominios cognitivos. Los resultados mostraron que la cirugía fue eficaz en el control de las crisis, de manera que el 86.9% de los pacientes quedó libre de crisis un año después de la cirugía. Los pacientes con ELT derecho presentaron mejor evolución en memoria verbal a corto y largo plazo y en denominación respecto a aquellos con ELT izquierdo, de acuerdo con estudios previos (Ives-Deliperi y Butler, 2012; Witt et al., 2015). No se encontraron efectos del sexo o del tipo de cirugía sobre la evolución cognitiva. Dado que se halló una asociación positiva entre la evolución en diferentes dominios cognitivos, se identificaron dos perfiles de evolución en competencia verbal considerando varios procesos (i.e., fluidez, memoria y denominación): un grupo con mejorías tras la cirugía y otro con empeoramientos tras la cirugía. En línea con nuestras hipótesis, los pacientes que presentaron mejorías en su competencia verbal tras la cirugía habían sido intervenidos quirúrgicamente a edades más tempranas y habían sufrido crisis epilépticas durante un período más corto que aquellos que no mejoraron. De acuerdo con lo esperado, controlando la lateralización del área epileptógena, una menor edad en el momento de la cirugía fue un predictor significativo de una mejor evolución en memoria verbal a largo plazo tras la cirugía, aunque la menor frecuencia de crisis focales antes de la cirugía también explicó, al menos parcialmente, esta mejoría. Además, la frecuencia de crisis focales prequirúrgicas predijo significativamente los cambios en memoria verbal a corto plazo. Estos resultados ponen de manifiesto la necesidad de intervención temprana, en un contexto en el que estos pacientes habitualmente sufren crisis epilépticas aproximadamente durante 20 años antes de ser referidos a una unidad especializada en cirugía para su evaluación prequirúrgica (Haneef et al., 2010).

Además de los factores neurales considerados en los estudios anteriores, otros factores como los niveles de cortisol y la afectividad negativa podrían influenciar el funcionamiento de la memoria. De hecho, las personas con epilepsia farmacorresistente están expuestas a crisis repetidas, impredecibles e incontrolables, lo que podría considerarse una condición de estrés crónico. Además, estos pacientes suelen presentar déficits de memoria (Helmstaedter, 2013; Hoppe et al., 2007; Lee et al., 2002; Thompson et al., 2016) y elevada prevalencia de depresión y ansiedad (Kwon y Park, 2014; Mensah et al., 2007; Park, 2016). El cortisol, la principal hormona implicada en la respuesta de estrés, tiene un papel modulador de la memoria en personas sanas (Fonda et al., 2005; Lee et al., 2007) y en pacientes con trastornos emocionales (Hinkelmann et al., 2009; Rubinow et al., 1984). Por ello, el cuarto estudio de la Tesis se centró en el objetivo 3, analizando las diferencias en los niveles de cortisol en personas con epilepsia farmacorresistente con alto y bajo rendimiento en memoria, y las relaciones entre los niveles de cortisol, las variables relacionadas con las crisis epilépticas, la memoria, la ansiedad y la depresión. De acuerdo con nuestras hipótesis, los pacientes con bajo rendimiento en memoria inmediata y demorada y epilepsia del hemisferio izquierdo presentaron mayores niveles de cortisol. En esta línea, los pacientes con bajo rendimiento en memoria presentaron una mayor área bajo la curva de cortisol con respecto al incremento (AUC_i) y, por tanto, descensos más lentos de los niveles de cortisol durante la tarde. Además, en línea con nuestras hipótesis, el rendimiento en memoria se asoció negativamente al AUC_i de cortisol y al nivel de ansiedad rasgo, siendo ambos factores predictores significativos del funcionamiento mnésico, especialmente en pacientes con epilepsia del hemisferio izquierdo. En contra de nuestras hipótesis, los niveles de depresión no se asociaron significativamente al rendimiento mnésico, posiblemente debido a que nuestra muestra presentaba niveles subclínicos de depresión. Nuestros resultados sugieren que los déficits en memoria en personas con epilepsia farmacorresistente pueden estar influenciados por la exposición a los niveles de cortisol en el contexto de una condición de estrés crónico. A su vez, la ansiedad rasgo podría contribuir a aumentar la vulnerabilidad al estrés (Weger y Sandi, 2018). Estos hallazgos son congruentes con estudios previos con personas sanas y pacientes con trastornos emocionales (Fonda et al., 2005; Hinkelmann et al., 2009; Lee et al., 2007; Rubinow et al., 1984) y con la consideración del hipocampo como una región relevante en la memoria declarativa (McEwen & Sapolsky, 1995) y especialmente vulnerable al estrés crónico (McEwen, 1998).

1.2. Deterioro mnésico y calidad de vida

Una vez abordados los factores intervinientes en el funcionamiento de la memoria en personas con epilepsia farmacorresistente, nos planteamos analizar cómo repercuten los déficits de memoria sobre la calidad de vida, que es el objetivo terapéutico final en estos pacientes. Así, el quinto estudio se centró en el objetivo 4 de la Tesis, consistente en determinar el papel del funcionamiento mnésico sobre la calidad de vida de pacientes con epilepsia farmacorresistente, considerando la influencia de otros factores psicológicos, sociales y físicos, siguiendo el modelo propuesto por Baker et al. (1993). Los resultados mostraron que una mayor frecuencia de crisis no se asoció significativamente con peor calidad de vida en la muestra total. En línea con nuestras hipótesis, encontramos una asociación positiva y significativa entre el rendimiento en memoria verbal a largo plazo y la calidad de vida global. Otros factores asociados significativamente con mejor calidad de vida global fueron: menor afectividad negativa (incluyendo ansiedad-rasgo y depresión), mayor apoyo social percibido y menores síntomas neurosensoriales.

Estos resultados encajarían con el modelo de calidad de vida en epilepsia propuesto por Baker et al. (1993), de manera que el rendimiento en memoria y la afectividad negativa formarían parte de su componente psicológico, el apoyo social correspondería al componente social, y los síntomas neurosensoriales podrían ser considerados el componente físico. Incluso controlando la influencia de la afectividad negativa, que fue el factor que explicó mayor porcentaje de la varianza de la calidad de vida, el rendimiento en memoria verbal y los síntomas neurosensoriales contribuyeron significativamente a explicar la calidad de vida global. Las subescalas de calidad de vida tuvieron diferente sensibilidad a estos factores, siendo las de bienestar emocional, calidad de vida general y funcionamiento social las subescalas más sensibles al funcionamiento mnésico. Nuestros hallazgos sugieren que el manejo clínico de estos pacientes debería considerar el tratamiento de las alteraciones de memoria de forma temprana.

Como se ha expuesto anteriormente, el modelo de calidad de vida en epilepsia propuesto por Baker et al. (1993) contemplaba tres dominios: psicológico, social y físico. Considerados globalmente, los resultados de la presente Tesis permiten especificar un poco más estos dominios, ampliando el modelo de Baker et al. (1993). Con este objetivo, en la Figura 3 se representa un modelo de calidad de vida en pacientes con epilepsia farmacorresistente basado en los resultados globales de la Tesis. Siguiendo dicho modelo, una calidad de vida óptima

dependería de una adecuada salud percibida, un nivel alto de apoyo social percibido, una baja afectividad negativa y un funcionamiento adecuado de la memoria. Al mismo tiempo, los factores asociados a un funcionamiento mnésico adecuado son los siguientes: una baja alteración de la integridad estructural de la cabeza del hipocampo, la asimetría hemisférica típica durante el procesamiento del lenguaje, la realización de la cirugía del lóbulo temporal (en su caso) a una edad temprana, unos niveles bajos de cortisol durante la tarde (indicativos de una adecuada capacidad del eje HPA para descender de acuerdo a su ritmo circadiano), y una baja afectividad negativa.

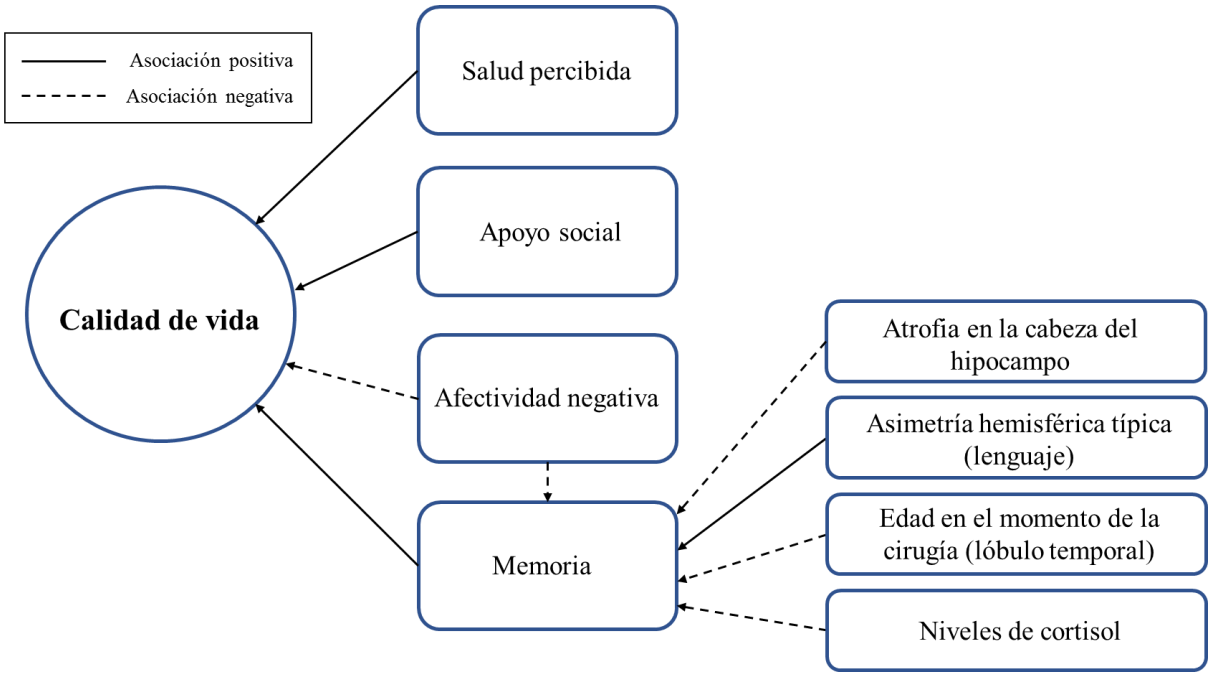

Figura 3. Modelo de calidad de vida en pacientes con epilepsia farmacorresistente basado en los resultados globales de la Tesis.

1.3. Implicaciones clínicas

Los resultados de la presente Tesis tienen implicaciones clínicas, pues la comprensión de los factores intervinientes en el funcionamiento mnésico y de las implicaciones de esta función cognitiva sobre la calidad de vida puede favorecer el diseño de protocolos para la evaluación y el tratamiento óptimo de personas con epilepsia farmacorresistente. En cuanto a la evaluación clínica, en primer lugar, se corrobora el papel de la neuroimagen en la identificación de perfiles

de alto riesgo de declive mnésico, planteándose como una alternativa que podría reemplazar al test de Wada en lo que respecta a la valoración del riesgo postquirúrgico. En segundo lugar, se enfatiza la relevancia de considerar las funciones cognitivas como procesos relacionados desde una perspectiva integral. En tercer lugar, se pone de manifiesto que los niveles de cortisol podrían ser un indicador relevante del funcionamiento cognitivo, así como la asociación entre los aspectos cognitivos y afectivos y la necesidad de considerarlos de forma integrada. En lo que respecta al tratamiento, los resultados de esta Tesis ponen de manifiesto la necesidad de una intervención precoz en personas con epilepsia, a fin de minimizar los efectos cognitivos colaterales de la exposición prolongada a crisis epilépticas, de los FAEs y de la cirugía. Además, el hecho de que las alteraciones de memoria se asocien con una calidad de vida pobre sugiere que la inclusión de técnicas específicas de rehabilitación neuropsicológica como parte del tratamiento de estos pacientes podría tener implicaciones en la mejora de su calidad de vida.

2. Limitaciones generales

Las limitaciones de cada estudio han sido descritas en la discusión de cada uno de ellos. En esta sección se presentan algunas limitaciones generales que deben ser consideradas para interpretar y generalizar adecuadamente los resultados de esta Tesis.

En primer lugar, los estudios de la presente Tesis, a excepción del estudio 3, fueron transversales. La realización de estudios longitudinales permitiría obtener un conocimiento más profundo de los aspectos explorados, especialmente en la investigación sobre la activación funcional y el funcionamiento mnésico. Con estudios longitudinales, podríamos clarificar si determinados perfiles de activación funcional son consecuencia de la reorganización funcional de la memoria y del lenguaje, respectivamente. En segundo lugar, aunque todos los estudios incluyeron únicamente pacientes con epilepsia farmacorresistente, en algunos de ellos la muestra era diversa en lo que respecta a la localización del área epileptógena, siendo la ELT el tipo de epilepsia más frecuente, en línea con la literatura (Téllez-Zenteno y Hernández-Ronquillo, 2012). El tamaño relativamente reducido de la muestra en estos estudios dificultó la obtención de información de diferentes subgrupos basados en el tipo de epilepsia (e.g., ELF), clasificando a los pacientes en dos grupos generales: ELT y epilepsia extratemporal. Un mayor tamaño de la muestra permitiría obtener información sobre estos subgrupos, asegurando la potencia estadística. Finalmente, aunque la posible influencia de los FAEs (i.e., número, tipo o

dosis diaria definida total) ha sido considerada en todos los estudios de esta Tesis, es preciso tener en cuenta que los pacientes siguieron un tratamiento de politerapia que fue individualizado en cada caso, lo que podría haber influenciado ligeramente los resultados.

3. Direcciones futuras

A partir de los diferentes estudios presentados en esta Tesis, se plantean nuevas cuestiones de interés.

En primer lugar, en relación las limitaciones planteadas en el apartado anterior, sería interesante realizar estudios longitudinales que permitan analizar los procesos de reorganización funcional de la memoria y del lenguaje y su relación con el funcionamiento cognitivo a lo largo del tiempo en estos pacientes. Además, sería conveniente examinar las relaciones entre el funcionamiento mnésico y los factores explorados en esta Tesis doctoral en subgrupos de pacientes con diferentes tipos de epilepsia, estableciendo comparaciones entre ellos.

En segundo lugar, nuestros resultados muestran que los pacientes con epilepsia farmacorresistente presentan hipercortisolismo en comparación con datos normativos de la población general (Miller et al., 2016a) y que los pacientes con niveles altos de cortisol durante la tarde tienen mayor vulnerabilidad a presentar alteraciones de memoria. Si consideramos las crisis epilépticas como estresores agudos en el contexto de la epilepsia como una condición de estrés crónico, futuros estudios deberían explorar las diferencias en la respuesta de estrés ante un estresor agudo en personas con epilepsia farmacorresistente en comparación con un grupo control de personas sanas, así como las relaciones entre la respuesta de cortisol al estrés y el rendimiento cognitivo.

En tercer lugar, hemos encontrado que las alteraciones de memoria se asocian con una pobre calidad de vida en esta población, por lo que sería interesante determinar la eficacia de programas de rehabilitación cognitiva basados en la evidencia en el funcionamiento mnésico y la calidad de vida de estos pacientes, especialmente en pacientes sometidos a cirugía.

Finalmente, cabe considerar que, aunque los instrumentos que evalúan la calidad de vida contribuyen a comprender la satisfacción del individuo con su funcionamiento diario, sus resultados están basados en las percepciones del paciente, pudiendo o no coincidir con su

funcionalidad y autonomía en la vida diaria. Por ese motivo, futuros estudios deberían centrarse en el desarrollo e implementación de medidas de funcionalidad y autonomía específicos para estos pacientes.

CHAPTER 10

Main conclusions

1. Main conclusions

The following main conclusions can be drawn from the studies included in this thesis:

1. The hippocampal atrophy pattern is not associated with memory performance in right TLE patients, while left TLE patients with more atrophy in the hippocampal head are more likely to have poor visual memory.
2. More atrophy of the hippocampal head is related to less activation within the ipsilateral and contralateral medial temporal structures during memory encoding, and this activation seems to modulate verbal and visual learning in right TLE patients.
3. Patients with left-hemisphere focus are more likely to have atypical hemispheric asymmetry during an fMRI verbal comprehension paradigm, and this is related to poor cognitive performance in verbal and non-verbal tasks.
4. TLE patients with postsurgical improvements in verbal competence underwent surgery at earlier ages and suffered epilepsy for less time.
5. Low age at surgery and low pre-surgical frequency of seizures are relevant predictors of verbal memory improvements after surgery.
6. Patients with left-hemisphere focus and poor memory have higher cortisol levels.
7. Patients with low memory scores have higher cortisol AUC, and therefore slower declining levels in the afternoon.
8. Lower cortisol AUC and lower trait anxiety are reliable predictors of higher memory performance.
9. Higher long-term verbal memory significantly contributes to a better quality of life, especially to better emotional well-being, overall quality of life, and social functioning.
10. Lower negative affectivity, higher social support, and lower perceived neurosensory symptoms are also related to a better quality of life.

CHAPTER 11

General summary

1. Introduction

Epilepsy is a neurological disease affecting more than 70 million people worldwide (Thijs et al., 2019). It is characterized by a predisposition to experience seizures and the associated neurobiological, cognitive, psychological, and social consequences (Fisher et al., 2005). Approximately 30% of patients have drug-resistant epilepsy (Barr & Morrison, 2014; de Tisi et al., 2011; Kwan et al., 2011). This epilepsy type is defined by the failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapy or polytherapy) to achieve sustained seizure freedom (Kwan et al., 2010). Patients with drug-resistant epilepsy may be candidates for surgical procedures, which, in the case of focal seizures, usually consist of a resection of the epileptogenic area, with proven efficacy in seizure control (Helmstaedter, 2013).

Both repeated exposure to uncontrollable seizures and different treatments used for its control can lead to relatively variable cognitive deficits (Aldenkamp et al., 2004; Helmstaedter, 2013) with memory deficits being one of the most frequent complaints (Helmstaedter, 2013; Hoppe et al., 2007; Lee et al., 2002; Thompson et al., 2016) and referred to by more than 70% of patients (Thompson & Corcoran, 1992). Memory is defined as a cognitive process that enables the encoding, consolidation, and retrieval of learned information.

Different factors, mostly directly related to seizures, have been proposed as possible modulators of memory performance in patients with drug-resistant epilepsy. Among them, it is worth highlighting: the location and lateralization of seizure area; the frequency and type of seizures; the age at epilepsy onset and epilepsy duration; the presence of hippocampal sclerosis; and the characteristics of different treatments – AEDs and surgery.

With respect to the location of seizure area, the epilepsy type most frequently associated with memory deficits is temporal lobe epilepsy (TLE) (Helmstaedter & Kockelmann, 2006; Tramoni-Negre et al., 2017). Regarding the lateralization of seizure area, greater verbal memory deficits have been consistently found in patients with affectation within the dominant hemisphere for language (typically left) (Aikia et al., 2001; Gleissner et al., 2004; Golby et al., 2001; Rausch et al., 2003), although the relationship between visuospatial memory impairment and the affectation of the non-dominant hemisphere is inconsistent (Alessio et al., 2004; Giovagnoli et al., 1995).

A significant association has been found between a higher frequency of seizures and greater memory deficits in some studies (Helmstaedter et al., 2003; Hermann et al., 2006; Thompson

& Duncan, 2005), as well as greater cognitive deficits in people who suffer different seizure types as opposed to those with only one type (Seidenberg et al., 2007). Most studies focusing on age at epilepsy onset and epilepsy duration suggest that early onset and longer duration of illness are associated with greater cognitive impairment (Dennis, 2000; Elger et al., 2004; Hermann et al., 2006). Considering the structural alterations of the hippocampus, an association has been found between the loss of hippocampal volume and poor memory functioning (Alessio et al., 2004; Baxendale et al., 1998a; Kilpatrick et al., 1997). Greater memory deficits have been found in patients treated with polytherapy and high doses of AEDs compared to those treated with monotherapy and low doses (Javed et al., 2015; Kwan & Brodie, 2001). Factors such as the resection of the left hemisphere (Sherman et al., 2011) and a large resection size in the temporal lobe (Clusmann et al., 2002) have consistently been associated with an increased risk of post-surgical memory deficits.

Although the influence of the above factors on memory has been studied in depth, other factors, mostly not directly related to seizures, have been understudied. These factors include those related to the neural substrate of memory such as the morphology of the hippocampus along its anterior-posterior axis, the functional activation during cognitive processing, and the age at temporal lobe surgery. Other relevant factors could be considered as indicators of the individual's well-being such as cortisol levels and negative affectivity.

Regarding neural factors, it should be noted that a reorganization of memory functions to the contralesional medial temporal lobe has been consistently described in patients with epilepsy, especially in those with TLE (Bonelli et al., 2010; Powell et al., 2007; Richardson et al., 2003, 2004; Sidhu et al., 2013). Memory functional reorganization could be a compensatory mechanism elicited by mesiotemporal structural deficits (Powell et al., 2007; Richardson et al., 2004). However, hippocampal sclerosis does not affect the hippocampus uniformly (Blümcke et al., 2013). It is unknown whether selective damage in anterior or posterior regions of the hippocampus is related to a different pattern of functional memory activation and memory performance. A more-detailed understanding of hippocampal structural-functional interactions may help to better classify TLE phenotypes (Coras & Blümcke, 2015) and understand why some people with TLE are more likely to have memory deficits compared to others.

In addition to a functional memory reorganization, an inter-hemispheric language reorganization has been found in patients with drug-resistant epilepsy because of repeated exposure to uncontrollable seizures that can induce brain injury around eloquent language areas (Tzourio-Mazoyer et al., 2017). Thus, patients with epilepsy more frequently have right-

hemispheric or bilateral language lateralization than the general population (Hamberger & Cole, 2011). This pattern of language lateralization was defined as atypical, considering left-hemispheric lateralization as the typical pattern (Mateer & Dodrill, 1983). Although a certain consensus exists about language reorganization in patients with left hemisphere focus, the cognitive implications of this remain unclear.

In patients with drug-resistant epilepsy, the memory neural substrate can be modified by surgery. Since epilepsy surgery is a common treatment in these patients, it is crucial to determine the appropriate ages for performing epilepsy surgery to optimize seizure control and minimize cognitive sequelae. However, few studies have analyzed the importance of age at surgery in postsurgical memory changes and the results are inconsistent (Chapin et al., 2013; Grivas et al., 2006; Thompson et al., 2015). It is possible that factors not considered in previous studies such as the seizure frequency and the inclusion of patients with atypical language dominance could explain, at least in part, the discrepancy in results. In addition, the approach in most studies mainly consists in analyzing the role of age at surgery on memory and other cognitive domains such as independent processes, without examining the possible association among them. However, the identification of profiles of postsurgical cognitive evolution that consider the possible association among different cognitive processes should provide ecological validity to the neuropsychological evaluation – and could contribute to making clinical decisions for patients with drug-resistant epilepsy.

In addition to the neural factors discussed above, other factors may influence memory performance. One of these factors is cortisol (one of the final products of the stress response) which has been proposed as an indicator of health status (Hellhammer et al., 2007) and the cognitive processing in other populations (Adam & Kumari, 2009). Increased cortisol levels have been linked to poor memory in healthy people (Fonda et al., 2005; Lee et al., 2007) and people with emotional disorders (Hinkelmann et al., 2009; Rubinow et al., 1984). The study of cortisol levels and their relationship to memory in people with epilepsy acquires special relevance as people with drug-resistant epilepsy deal with repetitive, unpredictable, and uncontrollable seizures, and this condition could be considered as potentially stressful.

Another factor whose influence on memory functioning in this population has been understudied is negative affectivity. In contexts in which the individual's homeostasis is threatened by chronic stressors, such as repeated exposure to uncontrollable and unpredictable seizures, it is also common to find increases in negative affectivity (Lazarus, 2006). In fact, more than 60% of people with epilepsy have psychiatric comorbidity (Gur-Ozmen et al., 2017;

Kanner, 2016), which a high prevalence of anxiety and depression (Kwon & Park, 2014; Mensah et al., 2007; Park, 2016). These affective disorders could be the result of epilepsy or its treatment and share the same physiopathology underlying epilepsy (Helmstaedter et al., 2014). Therefore, the study of negative affectivity in this population is especially interesting.

The study of the above factors (i.e., the morphology of the hippocampus along its anterior-posterior axis, the pattern of functional activation during cognitive processing, the age at temporal lobe surgery, the cortisol levels, and negative affectivity) could contribute to identify profiles at higher risk of memory decline. In addition, as memory impairment is one of the most frequent complaints in people with epilepsy, this could be one of the main factors contributing to the burden of this disease and disrupting their quality of life. The analysis of the impact of memory on quality of life would facilitate clinical decision-making with these patients, and justify where appropriate the implementation of specific rehabilitation programs. However, only a few studies with inconsistent findings have focused on the predictive role of memory on the quality of life of these patients (Giovagnoli & Avanzini, 2000; Perrine et al., 1995).

As far as we know, the relative contribution of psychobiological and social factors, including cognitive variables such as memory, on quality of life has not been comprehensively analyzed in a sample formed exclusively of patients with drug-resistant epilepsy. This approach would make it possible to clarify the impact of these factors on quality of life and detect profiles associated with a high risk of experiencing poor quality of life. Additionally, the study of the factors presented above, whose relationship with memory remains unclear, could be relevant in this population, insofar as they are potentially associated with quality of life, which is the ultimate therapeutic objective in these patients.

2. Objectives and hypotheses

We conducted five studies to clarify the factors involved in memory functioning in people with drug-resistant epilepsy, and the impact of this cognitive function on the quality of life of this population. The objectives and hypotheses of this thesis are presented below.

Objective 1. The first general objective was to clarify the role of hippocampal alterations along the anterior-posterior axis and the functional activation pattern during memory encoding and language processing in regions-of-interest (ROIs) on memory performance in patients with drug-resistant epilepsy. Considering the previous literature (Pauli et al., 2006), we hypothesized that patients with greater anterior atrophy in the hippocampus (versus posterior) would have

worse memory performance, either directly or through low functional activation in the medial temporal lobe during memory encoding. Regarding the functional activation pattern during language processing, patients with atypical asymmetry were expected to perform worse on verbal and non-verbal tasks (Jokeit & Ebner, 2002).

Objective 2. This objective focused on determining whether age at surgery was a reliable predictor of memory evolution of patients undergoing temporal lobe surgery from a multivariate and comprehensive view, considering the association among memory and other cognitive domains. Considering the previous literature (Jambaqué et al., 2007; Thompson et al., 2015), it was hypothesized that patients with a profile of verbal competence improvement would be younger at surgery than those with verbal competence decline, and that age at surgery would be a significant predictor of improvement in verbal memory after surgery, even controlling for the influence of other factors not considered in previous studies along with the age at surgery.

Objective 3. The third objective was to determine the influence of cortisol levels and negative affectivity (trait anxiety and depression) on memory functioning in patients with drug-resistant epilepsy, considering other potential modulating factors. We hypothesized that patients with low memory performance would have higher cortisol levels than those with high memory performance (Busch et al., 2012), especially those with left hemisphere focus who are at higher risk of memory deterioration (Jokeit et al., 2001). Based on previous findings in healthy people (Fonda et al., 2005; Lee et al., 2007) and other clinical populations (Hinkelmann et al., 2009; Rubinow et al., 1984), we expect to find a negative association between cortisol levels and memory performance. Regarding negative affectivity, we hypothesized that high scores in trait anxiety (Miller et al., 2016b) and depression (Helmstaedter et al., 2004; Paradiso et al., 2001) would be associated with poorer memory performance.

Objective 4. The fourth objective was to clarify the role of memory performance on quality of life in patients with drug-resistant epilepsy, considering the influence of seizures-related variables and other psychobiological and social factors not directly related to seizures. It was hypothesized that patients with poorer memory performance would perceive a poorer quality of life than those with high memory performance (Perrine et al., 1995) and that this relationship would remain significant even after controlling for the relative contribution of other factors. However, given the lack of previous studies, we did not have any specific hypotheses regarding the different sensitivity of quality of life subscales to memory performance and other influencing factors.

3. Studies conducted

3.1. Study 1

The aim of this study was to determine whether relative damage of the anterior or posterior hippocampus was linked to memory performance and to diverging functional activation during memory encoding. Thus, we assessed hippocampal surface-shape patterns along the anterior-posterior axis with high-resolution magnetic resonance imaging and related them to functional magnetic resonance imaging (fMRI) encoding activation and memory performance in 58 patients with drug-resistant TLE (27 right and 31 left). The hippocampal patterns were not associated with memory performance in right TLE patients, while left TLE patients with more atrophy in the hippocampal head (versus posterior hippocampus) were more likely to have poor visual memory. Additionally, in both groups, more atrophy of the hippocampal head was related to less activation within the ipsilateral and contralateral medial temporal structures during memory encoding. This functional activation seems to modulate verbal and visual learning through a pattern of association dependent on the side of seizure focus. Thus, in right TLE patients, lower right temporal medial activation was associated with worse verbal learning, while lower left temporal medial activation was related to worse visual learning, suggesting interhemispheric compensation mechanisms. In left TLE patients, this activation pattern did not translate in memory performance. Our results suggest that a disturbed structural integrity predominantly of the hippocampal head interferes with the functional memory encoding network in the ipsilateral and contralateral medial temporal lobes in TLE patients. This emphasizes that neuroimaging can be used to classify TLE phenotypes, identifying the functional implications of different hippocampal atrophy patterns, and their association with higher risk of memory deficits.

3.2. Study 2

This study assessed the relationship between asymmetry in hemispheric activation during an fMRI language paradigm on memory and other cognitive domains. Whereas prior studies primarily used fMRI paradigms that favor frontal lobe activation and less prominent activation of the medial or superior temporal lobes, we used a verbal comprehension paradigm previously demonstrated to reliably activate receptive language areas. Forty-seven patients with drug-resistant epilepsy candidates for surgery underwent a multidisciplinary assessment, including a

comprehensive neuropsychological evaluation and an fMRI verbal comprehension paradigm. Patients were distributed in two groups depending on laterality indexes (LI): typical hemispheric asymmetry (unilateral left activation preponderance; n = 23); and atypical hemispheric asymmetry (bilateral or unilateral right preponderance; n = 24). Right-handedness and right hemisphere focus were significant predictors of typical asymmetry. Patients with atypical activation pattern presented worse performance intelligence quotient (IQ) and verbal learning than patients with typical hemispheric asymmetry. Patients with left hemisphere focus had more frequently atypical hemispheric asymmetry than patients with right hemisphere focus. Specifically, they showed lower LI and this was related to worse performance in verbal and non-verbal tasks. These findings suggest that an increased activation of homologous right hemisphere areas for verbal comprehension processing could imply a competition for cognitive resources in the performance of the same task that disrupts cognitive performance.

3.3. Study 3

The aim of this study was to establish if age at surgery was a reliable predictor of post-surgical memory evolution considering factors such as: resected hemisphere; type of surgery; pre-surgical seizure frequency; and epilepsy duration. Sixty-one typically dominant patients with drug-resistant TLE (34 with left TLE and 27 with right TLE) underwent a neuropsychological assessment before and a year after surgery. Right TLE patients had better evolution in short- and long-term verbal memory and naming than left TLE patients. No effects for sex or type of surgery on cognitive evolution were found. Since a positive relationship was found in the evolution of different cognitive domains, we identified two profiles of verbal competence evolution considering various processes (i.e., fluency, memory and naming): one group with improvements after surgery; and the other with impairments after surgery. Patients with improvements in verbal competence underwent surgery at earlier ages and suffered epilepsy for less time. Controlling the side of seizure focus, a younger age at surgery was a significant predictor of better post-surgical evolution in long-term verbal memory, although the lower frequency of partial seizures also explains, at least partially, these improvements. In addition, the frequency of partial seizures significantly explained short-term verbal memory changes. These results emphasize the importance of early intervention, independently of the resected hemisphere, to minimize the cognitive side-effects of epilepsy treatment, as well the need to consider cognitive functions as related processes and network dependent.

3.4. Study 4

This study analyzed the differences in cortisol levels in people with epilepsy with high and low memory performance, and the relationships among cortisol levels, epilepsy-related factors, memory, anxiety, and depression. Fifty-two adults with drug-resistant epilepsy underwent a neuropsychological evaluation, in which nine saliva samples were collected to analyze the ability of the hypothalamic-pituitary-adrenal (HPA) axis to descend in accordance with the circadian rhythm. Cortisol area under the curve (AUC) was computed to study the global cortisol changes. Patients with low immediate and delayed memory performance and left hemisphere focus showed higher cortisol levels. In this line, patients with low memory scores had higher cortisol AUC, and therefore slower declining levels in the afternoon. Memory performance was negatively related to the cortisol AUC and trait anxiety, being both reliable predictors of memory performance, especially in patients with left hemisphere focus. These results suggest that memory deficits in people with drug-resistant epilepsy may be influenced by exposure to cortisol derived from chronic stress. Additionally, trait anxiety could contribute to increasing the vulnerability to stress.

3.5. Study 5

The aim of this study was to analyze the role of memory functioning on quality of life of patients with drug-resistant epilepsy, considering the relative contribution of other psychobiological and social factors. For this purpose, 70 patients with drug-resistant epilepsy underwent a multidisciplinary pre-surgical assessment, which included diagnosis of the type of epilepsy and the lateralization of the epileptogenic area. All the patients underwent a neuropsychological assessment in which quality of life (QOLIE-31), memory, negative affectivity, social support, and somatic symptoms were evaluated. Medical history provided demographic characteristics of the patients (sex, age, and educational level), and clinical data (age at epilepsy onset, duration of epilepsy in years, frequency of seizures per month, type of seizures and number of AEDs). Results showed that long-term verbal memory, negative affectivity, social support, and neurosensory symptoms were significantly related to quality of life composite score, with subscales of quality of life showing different sensitivities to them. Verbal memory performance and neurosensory symptoms significantly contribute to quality of life composite score even after controlling for negative affectivity, which was the factor that

explained the greatest percentage of the variance of quality of life. These findings suggest that the clinical management of patients with drug-resistant epilepsy should consider the treatment of verbal memory impairments at an early stage. Recognition of negative affectivity, poor social support, and high somatic symptoms would also lead health professionals to develop different strategies to improve the quality of life of patients with drug-resistant epilepsy.

4. Main conclusions

The following main conclusions can be drawn from the studies included in this thesis:

1. The hippocampal atrophy pattern is not associated with memory performance in right TLE patients, while left TLE patients with more atrophy in the hippocampal head are more likely to have poor visual memory.
2. More atrophy of the hippocampal head is related to less activation within the ipsilateral and contralateral medial temporal structures during memory encoding, and this activation seems to modulate verbal and visual learning in right TLE patients.
3. Patients with left-hemisphere focus are more likely to have atypical hemispheric asymmetry during an fMRI verbal comprehension paradigm, and this is related to poor cognitive performance in verbal and non-verbal tasks.
4. TLE patients with postsurgical improvements in verbal competence underwent surgery at earlier ages and suffered epilepsy for less time.
5. Low age at surgery and low pre-surgical frequency of seizures are relevant predictors of verbal memory improvements after surgery.
6. Patients with left-hemisphere focus and poor memory have higher cortisol levels.
7. Patients with low memory scores have higher cortisol AUC, and therefore slower declining levels in the afternoon.
8. Lower cortisol AUC and lower trait anxiety are reliable predictors of higher memory performance.
9. Higher long-term verbal memory significantly contributes to a better quality of life, especially to better emotional well-being, overall quality of life, and social functioning.
10. Lower negative affectivity, higher social support, and lower perceived neurosensory symptoms are also related to a better quality of life.

5. Clinical implications

The results of this thesis have clinical implications, since the understanding of the factors involved in memory functioning and the impact of this cognitive function on quality of life may favor the design of optimal evaluation and treatment protocols for people with drug-resistant epilepsy. Regarding clinical evaluation, first, the role of neuroimaging in the identification of profiles at high risk of memory decline is corroborated, considering it as an alternative that could replace Wada test in the post-surgical risk assessment. Second, the relevance of considering cognitive functions as related processes from an integrative view is emphasized. Third, the relevance of cortisol levels as an indicator of cognitive functioning is underlined, as well as the association between cognitive and affective aspects and the need to consider them from an integral perspective. In terms of treatment, the results of this thesis highlight the need for early intervention in people with epilepsy in order to minimize the cognitive side-effects of prolonged exposure to seizures, AEDs, and surgery. In addition, the fact that memory impairments are associated with poor quality of life suggests that the inclusion of specific neuropsychological rehabilitation techniques as part of the treatment of these patients could have implications for improving their quality of life.

CAPÍTULO 12

Resumen general

1. Introducción

La epilepsia es una afectación neurológica que afecta a más de 70 millones de personas en el mundo (Thijs et al., 2019). Se caracteriza por una predisposición a presentar crisis epilépticas, y por las consecuencias neurobiológicas, cognitivas, psicológicas y sociales asociadas (Fisher et al., 2005). Aproximadamente el 30% de los pacientes presentan una epilepsia farmacorresistente o refractaria a fármacos (Barr y Morrison, 2014; de Tisi et al., 2011; Kwan et al., 2011). Este tipo de epilepsia se define por el fracaso de dos fármacos antiepilépticos (FAEs), adecuadamente tolerados y elegidos (en monoterapia o politerapia), en el control de las crisis de forma prolongada (Kwan et al., 2010). Los pacientes con epilepsia refractaria pueden ser candidatos a cirugía de epilepsia, que, en el caso de presentar crisis focales, habitualmente consistirá en la resección de la zona epileptógena, siendo este procedimiento frecuentemente eficaz en el control de las crisis (Helmstaedter, 2013).

Tanto la exposición repetida a crisis incontrolables como los diferentes tratamientos que se han empleado para el control de éstas suelen conllevar cuadros relativamente variables de déficits cognitivos (Aldenkamp et al., 2004; Helmstaedter, 2013), siendo el deterioro de la memoria una de las quejas más frecuentes (Helmstaedter, 2013; Hoppe et al., 2007; Lee et al., 2002; Thompson et al., 2016), referida por más del 70% de pacientes (Thompson y Corcoran, 1992). La memoria se define como un proceso cognitivo que permite la codificación, el almacenamiento y la recuperación de la información aprendida.

Se han propuesto diferentes factores, en su mayoría directamente relacionados con las crisis epilépticas, que podrían modular el rendimiento en memoria en pacientes con epilepsia farmacorresistente. Entre ellos, destacan: la localización y lateralización del área epileptógena, la frecuencia y el tipo de crisis, la edad de inicio y la duración de la epilepsia, la presencia de esclerosis hipocampal, y las características de los diferentes tratamientos – FAEs y cirugía.

Atendiendo a la localización del área epileptógena, el tipo de epilepsia más frecuentemente asociada a déficits de memoria es la epilepsia del lóbulo temporal (ELT) (Helmstaedter y Kockelmann, 2006; Tramoni-Negre et al., 2017). En cuanto a la lateralización del área epileptógena, se han hallado consistentemente mayores déficits en memoria verbal en pacientes con afectación del hemisferio dominante para el lenguaje (típicamente izquierdo) (Aikia et al., 2001; Gleissner et al., 2004; Golby et al., 2001; Rausch et al., 2003), aunque la relación entre el deterioro en memoria visoespacial y la afectación del hemisferio no dominante es poco consistente (Alessio et al., 2004; Giovagnoli et al., 1995). Respecto a las crisis, se ha encontrado

en algunos estudios una asociación significativa entre mayor frecuencia de crisis y mayor deterioro mnésico (Helmstaedter et al., 2003; Hermann et al., 2006; Thompson y Duncan, 2005), así como mayor deterioro cognitivo en personas que sufren diferentes tipos de crisis frente a aquellos con un solo tipo (Seidenberg et al., 2007). Por su parte, la mayoría de los estudios centrados en la edad de inicio y la duración de la epilepsia sugieren que un inicio temprano y una mayor duración de la enfermedad se asocian con mayor deterioro cognitivo (Dennis, 2000; Elger et al., 2004; Hermann et al., 2006). Atendiendo a las alteraciones estructurales del hipocampo, se ha encontrado una asociación entre la pérdida de volumen hipocampal y el funcionamiento mnésico pobre (Alessio et al., 2004; Baxendale et al., 1998a; Kilpatrick et al., 1997). En cuanto a las características de los tratamientos, se han hallado mayores déficits mnésicos en pacientes tratados con politerapia y altas dosis de fármacos antiepilépticos respecto a aquellos tratados con monoterapia y dosis bajas (Javed et al., 2015; Kwan y Brodie, 2001). En lo que respecta a la cirugía, factores como la resección del hemisferio izquierdo (Sherman et al., 2011) y la realización de resecciones más extensas en el lóbulo temporal (Clusmann et al., 2002) se han asociado consistentemente con mayor riesgo de deterioro mnésico postquirúrgico.

A pesar de que la influencia de los factores anteriores sobre la memoria ha sido estudiada en profundidad, otros factores, en su mayoría no directamente relacionados con las crisis epilépticas, apenas han sido explorados. Por una parte, entre ellos, destacan los relacionados con el sustrato neural de la memoria como la morfología del hipocampo a lo largo de su eje anterior-posterior, la activación funcional durante el procesamiento cognitivo, y la edad en el momento de la cirugía del lóbulo temporal. Por otra parte, encontramos factores que podrían considerarse indicadores del bienestar del individuo como los niveles de cortisol y la afectividad negativa.

Respecto a los factores neurales, cabe destacar que, en pacientes con epilepsia, concretamente en aquellos con ELT, se ha descrito de forma consistente una reorganización del funcionamiento mnésico al lóbulo temporal medial contralesional (Bonelli et al., 2010; Powell et al., 2007; Richardson et al., 2003, 2004; Sidhu et al., 2013). La reorganización funcional de la memoria podría ser un mecanismo compensatorio que se produce como consecuencia de alteraciones estructurales mesiotemporales (Powell et al., 2007; Richardson et al., 2004). Sin embargo, la esclerosis hipocampal no afecta al hipocampo uniformemente (Blümcke et al., 2013). Se desconoce si el daño selectivo en regiones anteriores o posteriores del hipocampo se relaciona con un patrón diferente de activación funcional de la memoria y con un rendimiento

mnésico diferente. Una comprensión más detallada de las interacciones estructurales y funcionales del hipocampo podría ayudar a clasificar los fenotipos de la ELT (Coras y Blümcke, 2015) y a comprender por qué algunas personas con ELT son más propensas a presentar déficits de memoria respecto a otras.

No sólo se ha descrito una reorganización funcional de la memoria en pacientes con epilepsia farmacorresistente, sino que también se ha encontrado que la exposición repetida a crisis incontrolables puede producir daño cerebral alrededor de áreas elocuentes para el lenguaje, dando lugar a una reorganización inter-hemisférica del lenguaje (Tzourio-Mazoyer et al., 2017). Por ello, las personas con epilepsia presentan con mayor frecuencia que la población general una lateralización derecha o bilateral del lenguaje (Hamberger y Cole, 2011). Este patrón de lateralización del lenguaje fue definido como lateralización atípica, considerando la lateralización izquierda como el patrón típico (Mateer y Dodrill, 1983). Aunque existe cierto consenso sobre la reorganización del lenguaje en pacientes con epilepsia del hemisferio izquierdo, las implicaciones cognitivas de presentar una lateralización atípica del lenguaje permanecen sin esclarecer.

En pacientes con epilepsia farmacorresistente, el sustrato neural de la memoria puede modificarse mediante la cirugía. Dado que la cirugía de epilepsia es un tratamiento habitual en estos pacientes, es especialmente relevante analizar cuál es el momento más apropiado a lo largo de la vida para someterse a un procedimiento quirúrgico que permita lograr el control de las crisis epilépticas, minimizando los efectos cognitivos colaterales. No obstante, son escasos los estudios que han abordado el papel de la edad en el momento de la cirugía en la evolución mnésica postquirúrgica, encontrando, además, resultados inconsistentes (Chapin et al., 2013; Grivas et al., 2006; Thompson et al., 2015). Es posible que factores no considerados en estos estudios como la frecuencia de crisis o la inclusión de pacientes con dominancia atípica del lenguaje pudieran explicar, al menos parcialmente, la inconsistencia de los resultados encontrados. Además, en la mayoría de los casos, se ha estudiado el papel predictivo de la edad en el momento de la cirugía sobre la memoria y otros dominios cognitivos, considerándolos como procesos independientes, sin examinar la posible asociación entre ellos. Sin embargo, la identificación de diferentes patrones de evolución cognitiva tras la cirugía, considerando la posible asociación entre diferentes procesos cognitivos, podría proveer de mayor validez ecológica a la evaluación neuropsicológica y contribuir al proceso de toma de decisiones clínicas con pacientes con epilepsia farmacorresistente.

Además de los factores neurales expuestos anteriormente, otros factores podrían influenciar el funcionamiento de la memoria. Uno de estos factores es el cortisol, uno de los productos finales de la respuesta de estrés, que se ha propuesto como un indicador del estado de salud (Hellhammer et al., 2007) y del procesamiento cognitivo en otras poblaciones (Adam y Kumari, 2009). De hecho, los niveles elevados de cortisol se han asociado a un rendimiento pobre en memoria en personas sanas (Fonda et al., 2005; Lee et al., 2007) y en personas con trastornos emocionales (Hinkelmann et al., 2009; Rubinow et al., 1984). Dado que las personas con epilepsia farmacorresistente sufren crisis epilépticas repetidas, impredecibles e incontrolables, y esta condición podría considerarse potencialmente estresante, el estudio de los niveles de cortisol y de su relación con la memoria en personas con epilepsia adquiere especial relevancia.

Otro factor cuya influencia sobre el funcionamiento mnésico en esta población apenas ha sido estudiada es la afectividad negativa. En contextos en los que la homeostasis del individuo se ve amenazada por estresores crónicos, como puede ser la exposición repetida a crisis incontrolables e impredecibles, también es frecuente encontrar aumentos en la afectividad negativa (Lazarus, 2006). De hecho, más del 60% de personas con epilepsia presentan comorbilidad psiquiátrica (Gur-Ozmen et al., 2017; Kanner, 2016), con una alta prevalencia de ansiedad y depresión (Kwon y Park, 2014; Mensah et al., 2007; Park, 2016). Estas alteraciones afectivas podrían ser el resultado de la epilepsia o de su tratamiento, compartiendo la misma fisiopatología subyacente a la epilepsia (Helmstaedter et al., 2014), por lo que el estudio de la afectividad negativa en esta población es especialmente interesante.

El estudio de los factores expuestos anteriormente (i.e., la morfología del hipocampo a lo largo de su eje anterior-posterior, el patrón de activación funcional durante el procesamiento cognitivo, la edad en el momento de la cirugía del lóbulo temporal, los niveles de cortisol y la afectividad negativa) podría contribuir a identificar perfiles con mayor riesgo de deterioro mnésico. Además, las alteraciones de memoria, al ser una de las quejas más frecuentes de las personas con epilepsia, podrían ser uno de los principales factores que contribuyen a la carga de esta enfermedad, perturbando su calidad de vida. El análisis del impacto del rendimiento en memoria sobre la calidad de vida facilitaría la toma de decisiones clínicas con estos pacientes, justificando, en su caso, la realización de programas de rehabilitación específicos. Sin embargo, son escasos los estudios centrados en el papel predictivo de la memoria sobre la calidad de vida de estos pacientes, mostrando resultados inconsistentes (Giovagnoli y Avanzini, 2000; Perrine et al., 1995).

Hasta donde sabemos, no se ha analizado de forma global la contribución relativa de factores psicobiológicos y sociales, incluyendo variables cognitivas como la memoria, sobre la calidad de vida en una misma muestra formada exclusivamente por pacientes con epilepsia farmacorresistente. Este enfoque permitiría clarificar el impacto de estos factores en la calidad de vida y detectar perfiles asociados a alto riesgo de experimentar una calidad de vida pobre. A su vez, el estudio de los factores presentados anteriormente, cuya relación con la memoria permanece sin esclarecer, podría ser muy relevante en esta población, en la medida en que estarían potencialmente asociados con la calidad de vida, que es el objetivo terapéutico final en estos pacientes.

2. Objetivos e hipótesis

En la presente Tesis, realizamos cinco estudios con el fin de clarificar los factores intervinientes en el funcionamiento mnésico en personas con epilepsia farmacorresistente y el impacto de esta función cognitiva en la calidad de vida de esta población. Los objetivos y las hipótesis de esta Tesis se presentan a continuación.

Objetivo 1. El primer objetivo general fue clarificar el papel de las alteraciones hipocampales a lo largo de su eje anterior-posterior y del patrón de activación funcional durante la codificación mnésica y el procesamiento del lenguaje en regiones de interés sobre el rendimiento mnésico en pacientes con epilepsia farmacorresistente. Considerando la literatura previa (Pauli et al., 2006), hipotetizamos que los pacientes con mayor atrofia anterior en el hipocampo (versus posterior) presentarían peor rendimiento mnésico, ya sea de forma directa o a través de una baja activación funcional en el lóbulo temporal medial durante la codificación mnésica. Respecto al patrón de activación funcional durante el procesamiento del lenguaje, se esperó que los pacientes con asimetría atípica presentaran peor rendimiento en tareas verbales y no verbales (Jokeit y Ebner, 2002).

Objetivo 2. Este objetivo se centró en determinar si la edad en el momento de la cirugía era un predictor fiable de la evolución mnésica de pacientes sometidos a cirugía del lóbulo temporal desde una perspectiva multivariada e integral, considerando la asociación entre la memoria y otros dominios cognitivos. Considerando la literatura previa (Jambaqué et al., 2007; Thompson et al., 2015), se hipotetizó que los pacientes con un perfil de mejoría en su competencia verbal tras la cirugía tendrían menor edad que aquellos que presentaban empeoramientos en los dominios verbales tras la cirugía, y que la edad en el momento de la cirugía sería un predictor

significativo de mejoría en memoria verbal tras la cirugía, aun controlando la influencia de otros factores no considerados en estudios previos juntamente con la edad de la cirugía.

Objetivo 3. El tercer objetivo fue determinar la influencia de los niveles de cortisol y de la afectividad negativa (ansiedad rasgo y depresión) en el funcionamiento mnésico de pacientes con epilepsia farmacorresistente, considerando el papel de otros factores potencialmente influyentes. Hipotetizamos que los pacientes con bajo rendimiento mnésico presentarían mayores niveles de cortisol respecto a pacientes con alto rendimiento mnésico (Busch et al., 2012), especialmente aquellos con foco epileptógeno temporal izquierdo, que tienen mayor riesgo de deterioro mnésico (Jokeit et al., 2001). En base a los hallazgos previos en personas sanas (Fonda et al., 2005; Lee et al., 2007) y en otras poblaciones clínicas (Hinkelmann et al., 2009; Rubinow et al., 1984), esperamos encontrar una asociación negativa entre los niveles de cortisol y la ejecución en tareas de memoria. En lo que respecta a la afectividad negativa, hipotetizamos que las altas puntuaciones en ansiedad rasgo (Miller et al., 2016b) y en depresión (Helmstaedter et al., 2004; Paradiso et al., 2001) se asociarían con peor rendimiento en memoria.

Objetivo 4. El cuarto objetivo fue clarificar el papel del rendimiento mnésico sobre la calidad de vida de pacientes con epilepsia farmacorresistente, considerando la influencia de variables relacionadas con las crisis epilépticas y de otros factores psicobiológicos y sociales no directamente relacionados con las crisis. Se hipotetizó que los pacientes con peor rendimiento mnésico percibirían una calidad de vida más pobre respecto a aquellos con alto rendimiento mnésico (Perrine et al., 1995), y que esta relación se mantendría aun controlando la relativa contribución de otros factores influyentes. No obstante, debido a la escasez de estudios previos no se establecieron hipótesis respecto a la diferente sensibilidad de las subescalas de calidad de vida al rendimiento mnésico y otros factores influyentes.

3. Estudios desarrollados

3.1. Estudio 1

El objetivo de este estudio fue determinar si el daño relativo del hipocampo anterior o posterior se asociaba con el rendimiento en tareas de memoria y con la activación funcional durante la codificación mnésica. Para ello, se evaluaron los patrones de la forma de la superficie del hipocampo a lo largo de su eje anterior-posterior con imágenes por resonancia magnética

de alta resolución y se relacionaron con la activación en un paradigma de codificación mnésica de resonancia magnética funcional (RMf) y el rendimiento en memoria en 58 pacientes con ELT farmacorresistente (27 con ELT derecha y 31 con ELT izquierda). El patrón de atrofia hipocampal no se asoció significativamente con el rendimiento mnésico en pacientes con ELT derecha, mientras que, en los pacientes con ELT izquierda, mayor atrofia en la cabeza del hipocampo (respecto al hipocampo posterior) se asoció con peor memoria visual. A su vez, en ambos grupos de pacientes, una mayor atrofia en la cabeza del hipocampo se asoció con menor activación en los lóbulos temporales mediales ipsilaterales y contralaterales durante la codificación mnésica. Este patrón de activación funcional parece modular el aprendizaje verbal y visual a través de un patrón de asociaciones dependiente de la lateralización del foco epileptógeno. Así, en pacientes con ELT derecha, menor activación temporal medial derecha se asoció con peor aprendizaje verbal, mientras que menor activación temporal medial izquierda se relacionó con peor aprendizaje visual, sugiriendo mecanismos compensatorios interhemisféricos. Por su parte, en pacientes con ELT izquierda, el perfil de activación funcional asociado al patrón de atrofia anterior-posterior del hipocampo no se tradujo en un determinado rendimiento en tareas de memoria. Nuestros hallazgos sugieren que la alteración en la integridad estructural predominantemente en la cabeza del hipocampo interfiere con la red funcional de codificación mnésica en los lóbulos temporales mediales ipsilaterales y contralaterales en pacientes con ELT. Estos resultados enfatizan que la neuroimagen puede ser utilizada para clasificar los fenotipos de ELT, identificando las implicaciones funcionales de los diferentes patrones de atrofia hipocampal, y su asociación con mayor deterioro de la memoria.

3.2. Estudio 2

En este estudio nos planteamos analizar la influencia del patrón de asimetría hemisférica durante el procesamiento del lenguaje sobre la memoria y otros dominios cognitivos. Mientras que estudios previos utilizaron paradigmas que favorecían principalmente la activación del lóbulo frontal, con una menor activación del lóbulo temporal medial y superior, en nuestro estudio utilizamos un paradigma de comprensión verbal que previamente ha demostrado activar de forma fiable las áreas del lenguaje receptivo. Cuarenta y siete pacientes con epilepsia farmacorresistente que eran candidatos a cirugía de la epilepsia fueron sometidos a una evaluación multidisciplinar, incluyendo una evaluación neuropsicológica extensa y un

paradigma de comprensión verbal de RMf. Los pacientes se distribuyeron en dos grupos dependiendo de sus índices de lateralidad (LI): asimetría hemisférica típica (activación predominante unilateral izquierda; n = 23) y asimetría hemisférica atípica (activación predominante unilateral derecha o bilateral; n = 24). El foco epileptógeno izquierdo y la dominancia manual izquierda fueron predictores significativos de la asimetría atípica durante el procesamiento del lenguaje. Los pacientes con asimetría hemisférica atípica durante el procesamiento del lenguaje obtuvieron puntuaciones más bajas en cociente intelectual (CI) manipulativo y en aprendizaje verbal respecto a aquellos con asimetría hemisférica típica. En esta línea, los pacientes con foco epileptógeno izquierdo presentaron más frecuentemente asimetría atípica que aquellos con foco epileptógeno derecho. Específicamente, presentaron menor LI y esto se asoció con peor rendimiento en dominios verbales y no verbales. Estos resultados sugieren que el aumento de la activación de áreas homólogas implicadas en la comprensión verbal del hemisferio derecho podría favorecer una competición de recursos cognitivos implicados en una misma tarea, desestabilizando el rendimiento cognitivo.

3.3. Estudio 3

Este estudio se centró en examinar si la edad en el momento de la cirugía era un predictor fiable de la evolución mnésica postquirúrgica, considerando otros factores relevantes como el hemisferio intervenido, el tipo de cirugía, la frecuencia prequirúrgica de crisis y la duración de la epilepsia. Para ello, se realizó una evaluación neuropsicológica antes y un año después de la cirugía a 61 pacientes con ELT farmacorresistente y dominancia típica para el lenguaje (34 con ELT izquierda y 27 con ELT derecha). Los pacientes con ELT derecha presentaron mejor evolución en memoria verbal a corto y a largo plazo y en denominación respecto a aquellos con ELT izquierda. No se encontraron efectos del sexo o del tipo de cirugía sobre la evolución cognitiva. Dado que se halló una asociación positiva entre la evolución en diferentes dominios cognitivos, se identificaron dos perfiles de evolución en competencia verbal considerando varios procesos (i.e., fluidez, memoria y denominación): un grupo con mejorías tras la cirugía y otro con empeoramientos tras la cirugía. Los pacientes que presentaron mejorías en su competencia verbal tras la cirugía habían sido intervenidos quirúrgicamente a edades más tempranas y habían sufrido crisis epilépticas durante un período más corto. Controlando la lateralización de la epilepsia, menor edad en el momento de la cirugía fue un predictor significativo de mejor evolución en memoria verbal a largo plazo tras la cirugía, aunque la

menor frecuencia de crisis focales antes de la cirugía también explicó, al menos parcialmente, esta mejoría. Además, la frecuencia de crisis focales prequirúrgicas predijo significativamente los cambios en memoria verbal a corto plazo. Estos resultados ponen de manifiesto la necesidad de intervención temprana, independientemente del hemisferio intervenido, para minimizar los efectos cognitivos colaterales del tratamiento de la epilepsia, así como la necesidad de considerar las funciones cognitivas como procesos relacionados y dependientes de una misma red.

3.4. Estudio 4

Este estudio se centró en analizar las diferencias en los niveles de cortisol en personas con epilepsia farmacorresistente con alto y bajo rendimiento en memoria, y las relaciones entre los niveles de cortisol, las variables relacionadas con las crisis epilépticas, la memoria, la ansiedad y la depresión. Para ello, 52 adultos con epilepsia farmacorresistente fueron sometidos a una evaluación neuropsicológica, en la que se recogieron nueve muestras de saliva, a fin de analizar la capacidad del eje hipotálamo-hipofisiario-adrenal (HPA) para descender de acuerdo con su ritmo circadiano. Se calculó el área bajo la curva de cortisol (AUC) para estudiar los cambios globales de cortisol. Los pacientes con bajo rendimiento en memoria inmediata y demorada y foco epileptógeno izquierdo presentaron mayores niveles de cortisol. En esta línea, los pacientes con bajo rendimiento en memoria presentaron una mayor AUC y, por tanto, descensos más lentos de los niveles de cortisol durante la tarde. Además, el rendimiento en memoria se asoció negativamente al AUC de cortisol y al nivel de ansiedad rasgo, siendo ambos factores predictores significativos del funcionamiento mnésico, especialmente en pacientes con foco epileptógeno izquierdo. Nuestros resultados sugieren que los déficits en memoria en personas con epilepsia farmacorresistente pueden estar influenciados por la exposición a cortisol en el contexto de una condición de estrés crónico. A su vez, la ansiedad rasgo podría contribuir a aumentar la vulnerabilidad al estrés.

3.5. Estudio 5

El objetivo de este estudio fue analizar el papel del funcionamiento mnésico sobre la calidad de vida de pacientes con epilepsia farmacorresistente, considerando la relativa contribución de otros factores psicobiológicos y sociales. Para ello, 70 pacientes con epilepsia farmacorresistente fueron sometidos a una evaluación prequirúrgica multidisciplinar, en la que

se determinó el tipo de epilepsia y la lateralización de la misma. A todos ellos se les realizó una valoración neuropsicológica en la que se evaluó la calidad de vida (QOLIE-31), la memoria, la afectividad negativa, el apoyo social y los síntomas somáticos. La revisión de la historia clínica permitió obtener datos demográficos (edad, sexo y nivel educativo) y clínicos (edad de inicio de la epilepsia, duración de la epilepsia en años, frecuencia de crisis por mes, tipo de crisis y número de FAEs). Los resultados mostraron que la memoria verbal a largo plazo, la afectividad negativa, el apoyo social y los síntomas neurosensoriales se asociaron significativamente a la calidad de vida global, mostrando las subescalas de calidad de vida diferente sensibilidad a estos factores. Incluso controlando la influencia de la afectividad negativa, que fue el factor que explicó mayor porcentaje de la varianza de la calidad de vida, el rendimiento en memoria verbal y los síntomas neurosensoriales contribuyeron significativamente a explicar la calidad de vida global. Estos resultados sugieren que el manejo clínico de los pacientes con epilepsia farmacorresistente debería considerar el tratamiento de las alteraciones de memoria de forma temprana. El reconocimiento de la afectividad negativa, del apoyo social deficiente y de elevados síntomas somáticos también podrían favorecer el desarrollo de diferentes estrategias para mejorar la calidad de vida de estos pacientes por parte de los profesionales de la salud.

4. Conclusiones principales

Las principales conclusiones derivadas de los estudios incluidos en la presente tesis doctoral son las siguientes:

1. El patrón de atrofia del hipocampo no se asocia con el rendimiento en memoria en pacientes con ELT derecha, mientras que los pacientes con ELT izquierda con mayor atrofia en la cabeza del hipocampo tienen una mayor predisposición a tener una memoria visual deteriorada.
2. Una mayor atrofia de la cabeza del hipocampo se asocia con menor activación en las estructuras temporales mediales ipsilaterales y contralaterales durante la codificación de la memoria, y esta activación parece modular el aprendizaje verbal y visual en pacientes con ELT derecha.
3. Los pacientes con epilepsia del hemisferio izquierdo son más propensos a presentar asimetría hemisférica atípica durante un paradigma de comprensión verbal de RMf, y esto está relacionado con un pobre desempeño cognitivo en tareas verbales y no verbales.

4. Los pacientes con ELT con mejorías en su competencia verbal tras la cirugía fueron sometidos a cirugía a edades más tempranas y sufrieron crisis epilépticas durante menos tiempo.
5. Una menor edad en el momento de la cirugía y una baja frecuencia prequirúrgica de crisis son predictores relevantes de mejorías en memoria verbal tras la cirugía.
6. Los pacientes con epilepsia del hemisferio izquierdo y memoria pobre presentan niveles más altos de cortisol.
7. Los pacientes con bajas puntuaciones de memoria presentan una mayor AUC de cortisol y, por lo tanto, una disminución más lenta de los niveles de cortisol durante la tarde.
8. Menor AUC de cortisol y menor ansiedad rasgo son predictores fiables de mayor rendimiento en memoria.
9. Un mayor rendimiento en memoria verbal a largo plazo contribuye significativamente a una mejor calidad de vida, especialmente a un mayor bienestar emocional, una mejor calidad de vida general y un mejor funcionamiento social.
10. Menor afectividad negativa, mayor apoyo social y menores síntomas neurosensoriales también son factores asociados a una mejor calidad de vida.

5. Implicaciones clínicas

Los resultados de la presente Tesis tienen implicaciones clínicas, pues la comprensión de los factores intervinientes en el funcionamiento mnésico y de las implicaciones de esta función cognitiva sobre la calidad de vida puede favorecer el diseño de protocolos para la evaluación y el tratamiento óptimo de personas con epilepsia farmacorresistente. En cuanto a la evaluación clínica, en primer lugar, se corrobora el papel de la neuroimagen en la identificación de perfiles de alto riesgo de declive mnésico, planteándose como una alternativa que podría reemplazar al test de Wada en lo que respecta a la valoración del riesgo postquirúrgico. En segundo lugar, se enfatiza la relevancia de considerar las funciones cognitivas como procesos relacionados desde una perspectiva integral. En tercer lugar, se pone de manifiesto que los niveles de cortisol podrían ser un indicador relevante del funcionamiento cognitivo, así como la asociación entre los aspectos cognitivos y afectivos y la necesidad de considerarlos de forma integrada. En lo que respecta al tratamiento, los resultados de esta tesis doctoral ponen de manifiesto la necesidad de una intervención precoz en personas con epilepsia, a fin de minimizar los efectos cognitivos colaterales de la exposición prolongada a crisis epilépticas, de los FAEs y de la

cirugía. Además, el hecho de que las alteraciones de memoria se asocien con una calidad de vida pobre sugiere que la inclusión de técnicas específicas de rehabilitación neuropsicológica como parte del tratamiento de estos pacientes podría tener implicaciones en la mejora de su calidad de vida.

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