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COMPARAÇÃO PROSPECTIVA ENTRE O TRATAMENTO CLÍNICO E O TRATAMENTO CIRÚRGICO PARA EPILEPSIA DE LOBO TEMPORAL MESIAL

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Tese de doutorado apresentado à Pós-graduação da Faculdade de Ciências Médicas da Universidade Estadual de Campinas para obtenção do título de Doutor em Ciências Médicas, área de concentração em Neurologia.

Orientador: Prof. Dr. Fernando Cendes

Co-orientador: Prof. Dr. Helder Tedeschi

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RESUMO

Objetivo: A cirurgia para pacientes com epilepsia de lobo temporal mesial refratária oferece um controle de crises para aproximadamente 70% dos pacientes. Neste estudo comparamos a eficácia entre o tratamento clínico e cirúrgico e investigamos a relação entre as alterações estruturais (atrofia de substância branca, SB e cinzenta, SC) nas imagens de ressonância magnética (RM) pré-operatórias e o resultado cirúrgico; bem como evidências estruturais de neuroplasticidade nas imagens de RM pós-operatórias.

Métodos: Realizamos uma curva de sobrevivência de Kaplan-Meier para comparar a eficácia entre os dois tipos de tratamento, para o *grupo clínico* (85 pacientes, 30 mulheres) e *grupo cirúrgico* (46 pacientes, 16 mulheres). Avaliamos as imagens de RM através da técnica de Morfometria Baseada em Voxel com o software SPM2 (Statistical Parametric Mapping)/MATLAB 7.0, comparando pacientes com indivíduos normais através de um Teste-T. Para essa análise dividimos os pacientes operados em grupos de acordo com o controle de crises obtido. Para investigar as alterações plásticas pós-operatórias realizamos um teste-T pareado entre as imagens pré e pós-operatórias.

Resultados: A análise de sobrevivência confirmou a superioridade do tratamento cirúrgico (84% de pacientes controlados) em longo prazo em comparação ao tratamento medicamentoso (7% de pacientes controlados), $p < 0{,}001$. Os pacientes com melhor resultado cirúrgico apresentavam um padrão restrito de atrofia de SC em comparação aos

pacientes com crises após a cirurgia. Apenas os pacientes controlados tiveram evidências de recuperação de SB e SC após a cirurgia.

Conclusão: A cirurgia oferece um melhor controle de crises que o tratamento medicamentoso e a chance de recuperar áreas com atrofia de SB e SC.

ABSTRACT

Objective: Surgery for refractory mesial temporal lobe epilepsy (MTLE) generally offers good seizure control for approximately 70% of patients. In this study we compared the efficacy between surgical and clinical treatments and investigated the relationship between pre-operative structural abnormalities (white matter and grey matter atrophy) and surgical outcome. We also investigated the structural evidences of brain plasticity on post-operative MRI scans.

Methods: We performed Kaplan-Meier survival analysis to compare the efficacy between surgical and medical groups. Clinical group included 85 patients (30 women) and the surgical group included 46 patients (16 women).

We applied Voxel Based Morphometry technique on SPM2 (Statistical Parametric Mapping)/MATLAB 7.0 and compared patients with normal individuals with T-Test. For this analysis we separated patients according to post-operative surgical control. In order to investigate plastic changes after surgery we performed paired T-Test between pre and post-operative MR scans.

Results: Survival analysis confirmed the superiority of surgical treatment for long-term seizure control (seizure control in 84% of patients) compared to medical treatment (seizure control in 7% of patients), $p<0.001$. Patients with better seizure control presented a restricted pattern of Grey matter atrophy, compared to patients with poorer seizure control which presented a widespread pattern of Grey matter atrophy. Our analysis showed that

only patients with good seizure control presented structural evidences of white matter and grey matter recovery after surgery.

Conclusion: Surgical treatment offers better chances of seizure control for refractory MTLE as well as the opportunity of relative white matter and grey matter recovery.

CONTEÚDO

LISTA DE ABREVIATURAS

AH	Atrofia hipocampal
CPC	Crise parcial complexa
CPS	Crise parcial simples
CTCG	Crise tônico-clônica generalizada
DAE	Droga antiepiléptica
EEG	Eletroencefalograma
EH	Esclerose hipocampal
ELT	Epilepsia de Lobo Temporal
ELTM	Epilepsia de Lobo Temporal Mesial
RM	Ressonância Magnética
ROI	Região de interesse
SB	Substância Branca
SC	Substância Cinzenta
VBM	Morfometria baseada em voxel

INTRODUÇÃO

EPIDEMIOLOGIA

A epilepsia é uma das patologias cerebrais mais comuns(1) e de acordo com pesquisas da Organização Mundial de Saúde é responsável por cerca de 1% do ônus global gerado por doenças, em posição equivalente ao câncer de mama em mulheres e ao câncer de pulmão nos homens (2). As estimativas do Banco Mundial mostram que a epilepsia é responsável por 9% do ônus total gerado por doenças mentais e neurológicas (3). No Reino Unido, a epilepsia é a segunda maior causa de procura por neurologista (4) (atrás somente das cefaléias) e a terceira maior causa (atrás apenas do prolapso de disco lombar e doenças cerebrovasculares) entre as condições neurológicas que necessitam hospitalização (5).

A incidência em países desenvolvidos é de aproximadamente 24 a 53 casos novos /100.000 pessoas – ano com uma incidência acumulada de aproximadamente 3% (6). Estudos realizados em países em desenvolvimento identificaram uma incidência que pode alcançar o dobro ou triplo da incidência observada nos países desenvolvidos, como por exemplo, no Chile (114/100.000) (7) e na Tanzânia (77/100.000) (8).A epilepsia apresenta uma prevalência de casos ativos que varia entre 3,6 a 41,3/1000 indivíduos, levando-se em conta diferenças metodológicas e locais estudados (9-12). No Brasil, um estudo realizado no interior do estado de São Paulo mostrou uma prevalência estimada de 18,6 /1000 pessoas (10).

A proporção de crises parciais nos estudos de incidência contemporâneos tem sido de aproximadamente 50-70%(13;14), de acordo com pesquisas realizadas em Minnesota (15), Chile (7) e sudoeste da França (16). Essa proporção parece ser constante desde a infância até os 65 anos, quando então se observa um grande aumento na ocorrência de crises parciais com alteração da consciência (15). Quanto à origem das crises parciais em adolescentes e adultos, estudos mostraram que aproximadamente dois terços têm origem no lobo temporal (13;17), ou seja, a prevalência da epilepsia do lobo temporal entre todas as formas de epilepsia é de aproximadamente 30-35% (18), com uma refratariedade às medicações ao redor de 30-40% (17).

De acordo com estudos populacionais, o prognóstico geral dos casos tratados clinicamente em longo prazo é de que a remissão acumulada (durante 5 anos) atinja 58 a 65% dos indivíduos num período de 10 anos (19;20), podendo alcançar 70% com 20 anos de seguimento. Em relação aos indivíduos com crises parciais, um estudo mostrou que aproximadamente 30% destes indivíduos não conseguem permanecer em remissão por 5 anos quando seguidos por 9 anos (21). Estima-se que 10% dos pacientes recém diagnosticados com epilepsia focal permaneçam com crises freqüentes e se tornem realmente refratários apesar do uso adequado de drogas antiepilépticas (22;23). Desta forma, uma população com um milhão de indivíduos gera a cada ano aproximadamente 35 novos casos de epilepsia parcial crônica, que resultarão em 15-20 indivíduos com epilepsia refratária, até mesmo às drogas antiepilépticas modernas; ou seja, nos Estados Unidos cerca de 10.000 a 15.000 novos casos refratários são identificados anualmente. Além disso, a prevalência de casos com crises parciais associadas à alteração da consciência ou generalização secundária que não entram em remissão em longo prazo tem sido estimada em aproximadamente 265 indivíduos para cada milhão de pessoas (23).

Aproximadamente 60% dos pacientes com epilepsia refratária apresentam crises parciais e embora todos estes devessem ser referidos para centros que realizam investigação para tratamento cirúrgico, apenas uma pequena porcentagem (cerca de 3000 a cada ano nos Estados Unidos) torna-se candidata a procedimentos cirúrgicos padrão como corticectomias, lesionectomias e amigdalohipocampectomia (22). Alguns se tornam candidatos a procedimentos como calosotomia, e ainda assim devemos ressaltar que a cada ano acumulam-se pacientes que podem ser candidatos a novos procedimentos como estimulação vagal, bem como aos testes de novos medicamentos.

EPILEPSIA DE LOBO TEMPORAL (ELT)

Em 1888, Hughlings Jackson descreveu as crises de lobo temporal como “estado onírico” e em 1899 fez a descrição dos “ataques uncinados”, correlacionando os dados clínicos com os resultados de uma autópsia (24); posteriormente, outros investigadores mostraram interesse em estudar e descrever as crises que não correspondiam aos conceitos existentes na época de “*grand mal”* e “*petit mal”* (25). Denominações como “*petit* e *grand mal* intelectual” e “epilepsia mental larval” foram criadas em 1860 por Falret (26) e Morel (27) respectivamente.

Crises epilépticas com origem no lobo temporal compõem a maior parte das crises parciais (17) e podem ser divididas em crises que se originam na região mesial do lobo temporal (2/3 dos indivíduos) e crises que se originam na região neocortical lobo temporal (1/3 dos indivíduos), determinando duas síndromes distintas, a epilepsia de lobo temporal mesial (ELTM) e a epilepsia de lobo temporal neocortical, respectivamente (18). Entre os casos de pacientes epilépticos referidos aos centros terciários para investigação cirúrgica, aproximadamente 70% apresentam crises que se originam no sistema límbico do lobo temporal e a esclerose hipocampal constitui o substrato patológico mais comumente associado a essas crises (25;28).A ELTM está associada à esclerose hipocampal em aproximadamente 65% dos casos (29), enquanto que para o restante dos indivíduos (incluindo os indivíduos com ELT neocortical), outras etiologias podem estar associadas, tais como tumores (astrocitoma, gangliogliomas, tumor neuroepitelial disembrioblástico), lesões vasculares (angioma cavernoso, malformação arteriovenosa) e malformações do desenvolvimento cortical (30-32). Devemos ressaltar que alguns indivíduos apresentam dupla patologia, ou seja, esclerose hipocampal associada a outras patologias tais como microdisgenesia cortical, displasia cortical, pequenos tumores ou cavernomas (33;34).

Além de apresentar a maior freqüência entre todas as epilepsias parciais, a ELTM associada à esclerose hipocampal (ELTM-EH) apresenta uma alta refratariedade às drogas

antiepilépticas, com um controle de crises em apenas 11% em pacientes acompanhados num centro terciário (35) e 42% em um centro de atendimento primário (36). Apesar da alta refratariedade às DAEs, caracteristicamente a síndrome ELTM-EH apresenta uma boa resposta ao tratamento cirúrgico, que oferece um bom controle de crises para aproximadamente 60-80% (37-40).

APRESENTAÇÃO CLÍNICA

As crises se iniciam ao redor dos 10 anos, podendo se manifestar como crises parciais complexas com ou sem generalização secundária. Apresentam uma boa resposta ao tratamento com drogas antiepilépticas no início do tratamento, embora muitas vezes apresentem recorrência no fim da juventude ou início da idade adulta, com uma maior tendência a refratariedade às DAEs (32;41). A persistência de crises gera conseqüências relacionadas à alta freqüência de eventos, tais como maior morbidade (queimaduras (42), traumatismos cranianos (43), fraturas ósseas (44) e afogamentos (45)) e mortalidade (46;47). Não podemos deixar de ressaltar que a alta freqüência de crises durante um tempo prolongado na vida do indivíduo tem sido freqüentemente associada a uma maior incidência de distúrbios psiquiátricos, entre eles ansiedade, depressão, distúrbios de personalidade (41;48-51), bem como a déficits cognitivos (52;53) e de memória (54;55) .

PATOGÊNESE DA ESCLEROSE HIPOCAMPAL

ASPECTOS GENÉTICOS

A associação entre convulsão febril e o desenvolvimento de ELTM-HE foi descrita inicialmente por (56), e apesar de algumas controvérsias (57), estudos mais recentes confirmaram a associação entre antecedente de crises febris e esclerose hipocampal através de volumetria hipocampal (58;59) e análise histopatológica (60). A ocorrência de crises febris é variável podendo acometer até 66% dos indivíduos (41;61), enquanto que estudos prospectivos de crianças que tiveram convulsões febris mostraram um risco entre 2 e 7% de desenvolverem epilepsia (62). Apesar das evidências sobre a associação entre crise febril – esclerose hipocampal, sabemos que a interpretação sobre tais achados ainda é motivo de questionamentos. Uma possível explicação seria que as crises febris precoces causam danos ao hipocampo, levando à esclerose hipocampal (63;64). A outra explicação seria a de que crianças com danos no hipocampo (secundários a insultos perinatais e ou fatores genéticos) estariam mais predispostas a apresentar crises febris (65-67). A prevalência de história familiar de crises febris é elevada tanto para pacientes com recorrência tardia de crises, quanto para pacientes com ELTM submetidos à cirurgia, indicando que a susceptibilidade para crises febris apresente uma forte determinação genética, e que a associação entre as CF e esclerose hipocampal resulte de uma complexa interação entre fatores genéticos e ambientais (32;59).

O antecedente familiar positivo para crises epilépticas e ou epilepsia é freqüente entre os pacientes com ELTM (68;69), e diversas síndromes já foram descritas, tais como Epilepsia de Lobo Temporal Mesial Familiar (67;70), Epilepsia Familiar com auras auditivas (71;72), epilepsia familiar parcial com foco variável (FPEVF) (73). Diante das várias síndromes, é importante ressaltar a importância da história detalhada sobre os antecedentes familiares a fim de definir corretamente a síndrome de epilepsia familiar (69). Em relação à ELTM, destacamos a síndrome de ELTM familiar, caracterizada por apresentar uma melhor resposta ao tratamento medicamentoso para a maioria dos

indivíduos (67), um padrão de herança autossômica dominante com penetração incompleta, achado de atrofia hipocampal em indivíduos sintomáticos e assintomáticos (74;75), bem como déficits de memória até mesmo nos indivíduos assintomáticos com atrofia hipocampal (76). Apesar da evolução benigna para maioria dos pacientes com ELTM familiar, alguns indivíduos evoluem com refratariedade ao tratamento clínico e acabam necessitando de intervenção cirúrgica; para estes, a cirurgia tem oferecido um controle de crises com resultados semelhantes aos dos pacientes esporádicos quando conseguimos identificar atrofia hipocampal unilateral ou evidências claras de assimetria hipocampal (77).

A observação de que alguns indivíduos apresentam associação entre EH e microdisgenesia ou outras lesões displásicas (tais como hamartomas e heterotopia) (28;78) sugere também uma predisposição genética ou congênita para o desenvolvimento de epilepsia, reforçando o componente genético no desenvolvimento da ELTM.

Além da predisposição genética associada à ELTM e crises febris, os estudos epidemiológicos mostraram que outros fatores precipitantes também estavam relacionados com o desenvolvimento de ELTM, entre eles insulto isquêmico perinatal, traumatismo craniano e infecções do sistema nervoso central (17;28;41;79).

A etiopatogenia da esclerose hipocampal ainda é motivo de debates apesar das inúmeras pesquisas realizadas nas últimas décadas. A questão principal está em se determinar se a perda neuronal é causa ou conseqüência de crises repetitivas. Apesar de as observações clinicopatológicas de (80) e (81) darem suporte a hipótese de que a esclerose hipocampal representava uma área de gliose capaz de gerar crises, outros estudos mostraram evidências de que a lesão hipocampal poderia ser uma conseqüência das crises repetitivas (82;83). O mais provável é que a esclerose hipocampal resulte da interação complexa entre predisposição genética individual, idade e tipo de insultos cerebrais precoces (84), vulnerabilidade hipocampal a apoptose (85;86), bem como perda neuronal progressiva secundária às crises repetitivas.

A epileptogenicidade da ELTM deriva da perda neuronal em regiões específicas do hipocampo associada à reorganização sináptica dos neurônios remanescentes, de forma a permitir uma hipersincronização associada à hiperexcitabilidade regional (41).

A identificação macroscópica de um hipocampo atrófico e endurecido em um indivíduo com epilepsia crônica foi primeiramente descrita por (87), e a avaliação microscópica da esclerose hipocampal foi realizada inicialmente por (88). Além de identificar a destruição neuronal dos neurônios piramidais do corno de Ammon, mais especificamente no setor CA1 (setor de Sommer) e no prosubiculum, Sommer descreveu também o dano das células granulares e dos neurônios do hilo da fascia dentada e sugeriu que deveria existir uma relação entre o dano hipocampal e a clínica das crises apresentadas pelos indivíduos. Ainda no final do século 19, (81) realizou estudos minuciosos sobre a esclerose hipocampal, determinando critérios utilizados ainda nos dias de hoje. Ele notou que a depleção neuronal no hipocampo se concentrava principalmente no setor de Sommer (CA1) e na região que mais tarde seria denominada *end folium* (CA3 e CA4) por (89), com uma relativa preservação dos neurônios do subiculum e na porção de CA2 (setor "resistente") (28). A correlação entre os sintomas de ELT e os achados histopatológicos da esclerose hipocampal foi avaliada primeiramente por (90) e posteriormente por (89). Apesar das limitações do estudo realizado por Margerison e Corsellis (pacientes institucionalizados, portadores de distúrbios psiquiátricos graves ou deficiências físicas), os autores comprovaram estatisticamente que a esclerose hipocampal estava mais associada aos indivíduos que preenchiam critérios clínicos ou eletroencefalográficos de ELT. Eles ainda expuseram que além do dano hipocampal, os pacientes com EH apresentavam também dano adicional na amígdala, tálamo e neocortex; mostraram também que 10% dos pacientes com ELT (por critérios eletroencefalográficos) apresentavam esclerose hipocampal bilateral.

De forma resumida, a EH é caracterizada por uma intensa perda neuronal no setor CA1 e região hilar, uma perda menos intensa na região de CA3 e CA4, associada a uma preservação relativa dos neurônios de CA2. O complexo subicular, o córtex entorrinal, outros setores de córtex transicional bem como os giros temporais são relativamente resistente à perda neuronal. Devemos ressaltar também outras características da EH: o aumento das fibras dendríticas das células granulares do giro denteado, as fibras musgosas (*mossy fiber sprouting*) (91) bem como a depleção seletiva de neurônios que contêm somatostatina e neuropeptídeo Y (92).

Os estudos de exploração invasiva pré-operatória em um grande número de indivíduos permitiram analisar em detalhes os achados dos eletrodos profundos juntamente com a clínica desses indivíduos (41). Estes estudos comprovaram que a atividade ictal confinada ao hipocampo e giro parahipocampal não apresenta correlação clínica (93), e que os sinais e sintomas clássicos da ELTM estão relacionados à propagação ipsilateral e contralateral da atividade epileptiforme, para o neocortex frontal e temporal, ínsula, hipotálamo, gânglios da base e outras estruturas subcorticais (41;94;95).

As características da semiologia ictal podem ser separadas em subjetivas ou objetivas. As crises típicas da síndrome de ELTM caracterizam-se principalmente pelas auras (componente subjetivo) que se originam das estruturas mesiais do lobo temporal e ocorrem em aproximadamente 90% dos pacientes (41;61). Essas crises podem ocorrer tanto como manifestação inicial da crise parcial complexa, bem como eventos isolados (crises parciais simples). O sintoma mais típico da síndrome é uma sensação visceral, descrita como um mal estar epigástrico ascendente (96) (61;97). A sensação de medo aparece em segundo lugar, mas outros fenômenos também podem ocorrer, tais como *déjà vu, jamais vu*, alucinações olfatórias, micropsia, macropsia, sintomas e sinais neurovegetativos (palidez, sudorese, taquicardia, náusea, vômitos) e sensação de despersonificação. É importante ressaltar que em algumas situações os pacientes experimentam situações e sensações que não são capazes de descrever ou detalhar (41), mas garantem que a sensação, apesar de indescritível, se repete de forma inalterada a cada crise.

O componente objetivo da crise da ELTM tem sido estudado extensivamente com base nos dados obtidos durante as monitorizações de vídeo-EEG pré-operatórias e em geral tem início com a alteração do nível de consciência, portanto o paciente não se lembra dos fatos ocorridos durante o período. Em geral o paciente interrompe sua ação, apresenta um olhar distante associado a uma dilatação pupilar; o evento ictal pode terminar nesse período ou evoluir com a associação de movimentos repetitivos ou automatismos, também típicos da ELTM. Os automatismos oro-alimentares são os mais freqüentes e podem envolver movimentos mastigatórios, de deglutição, sucção e ranger de dentes; outros automatismos estereotipados ou não tais como gesticulação sem sentido e agarrar objetos também são descritos, enquanto que outros (cuspir (98), vocalizar (99) e pedalar (100)) são menos freqüentes e também podem ser encontrados em outras síndromes.

Um aspecto importante da semiologia das crises de ELTM refere-se ao valor lateralizatório que os sinais apresentam, incluindo algumas manifestações motoras, de linguagem e eventos pós-ictais (41). O desvio cefálico e do olhar que ocorrem tardiamente na crise são geralmente contralaterais ao início da crise (101;102), assim como a postura distônica ou tônica unilateral que ocorre em 15% a 70% dos indivíduos (102;103) e está associada a um aumento da atividade nos gânglios da base ipsilaterais ao foco epiléptico de acordo com estudos realizados com SPECT (104). A paresia ictal contralateral também apresenta valor lateralizatório (105) assim como a afasia ictal e a interrupção da fala durante a crise que estão associadas a crises com origem no hemisfério dominante para linguagem (106;107). Outros estudos mostraram que a afasia pós-ictal também está associada a crises que se originam no hemisfério dominante (106) e que o déficit motor pós-ictal em geral é contralateral ao foco epileptogênico e está associado à postura distônica (41).

Apesar de todo o avanço tecnológico, o EEG continua tendo grande importância na investigação pré-cirúrgica da ELTM (108). A realização de EEGs interictais prolongados nos permite identificar algumas anormalidades características como lentificação na região temporal anterior que pode ter caráter lateralizatório quando são encontrados “trens de ondas lentas” unilateralmente. Os elementos típicos são as ondas agudas e espículas, com máxima atividade localizada predominantemente nas derivações basais, como os eletrodos esfenoidais, fronto-temporais e “temporais verdadeiros”. Podemos encontrar também complexos onda aguda-onda lenta como atividade paroxística localizada nas regiões temporais anteriores (68;109;110). É importante observar que esses paroxismos podem ser encontrados bilateralmente em aproximadamente 30% dos indivíduos (110;110);

Os achados ictais são obtidos mais comumente durante vídeo-monitorização e mostram que as auras em geral não estão associadas com alterações eletroencefalográficas específica, mas podem coincidir com uma atenuação regional ou generalizada da atividade de base associada ao desaparecimento das espículas (41). Os estudos com eletrodos profundos demonstraram que o início das crises parciais simples está associado a descargas hipersíncronas do hipocampo com transição para um ritmo recrutante rápido e de baixa voltagem, imediatamente antes da propagação contralateral, que por sua vez dá início a crise parcial complexa caracterizada pela alteração do nível de consciência, atividade rítmica do tipo teta com aproximadamente 5-7 Hz e amplitude crescente, paralela a uma lentificação do ritmo de descargas (68;110;111). Devemos ressaltar também que ocasionalmente as alterações ictais típicas são observadas no lobo temporal contralateral ao hipocampo atrófico, fenômeno que foi estudado com eletrodos intracranianos que por sua vez revelaram que as crises de fato se originam no hipocampo atrófico, porém a atividade epileptiforme propaga rapidamente para o lobo temporal contralateral ao invés de se propagar para o neocortex ipsilateral, caracterizando o “burned out hippocampus” (112).

Quando os achados de EEG interictal são inconclusivos quanto à lateralização do foco ictal, pode ser realizada investigação com eletrodos profundos temporais ou de forame oval, que aumentam as chances de se identificar o local de início da crise (110;113;114).

O uso da RM de alta resolução para a identificação de atrofia hipocampal tem sido eficaz para grande proporção de pacientes com ELTM refratária (115). A utilização de protocolos adequados é essencial para o diagnóstico adequado da atrofia e deve incluir cortes coronais obtidos a partir de um plano perpendicular ao eixo longo do hipocampo, guiado pela imagem sagital inicial. Os cortes devem ser finos para que os detalhes possam ser avaliados com precisão nas diferentes porções do hipocampo. Em geral incluem seqüências ponderadas em T1, T2, T1-IR (inversion recovery) e FLAIR (fluid attenuation inversion recovery) que permitem a análise do volume, forma, orientação e estrutura interna do hipocampo (116). A análise visual qualitativa das seqüências descritas apresenta uma boa sensibilidade para identificar a atrofia hipocampal (115;117) para aplicações clínicas, tornando desnecessária a realização de volumetria manual dos hipocampos para todos os pacientes.

O diagnóstico de atrofia hipocampal é baseado na identificação de uma diminuição do volume hipocampal (característica mais importante), perda do formato oval (o hipocampo atrófico em geral se torna achatado e inclinado), sinal hipointenso em T1, hipersinal em T2 e FLAIR (118). Além dessas alterações podemos encontrar também atrofia do pólo temporal (associada a uma redução da substância branca subjacente)(119;120), assimetria dos cornos temporais dos ventrículos laterais (o corno ipsilateral aparece aumentado pela atrofia do hipocampo) e perda da estrutura interna do hipocampo como conseqüência da morte neuronal e gliose. A identificação da atrofia hipocampal unilateral através da discriminação visual em geral não apresenta dificuldades quando um dos hipocampos é normal e o outro apresenta alterações evidentes (116). Por outro lado, quando os dois hipocampos apresentam anormalidades estruturais, a identificação do hipocampo mais atrófico pode ser necessária já que a cirurgia pode ser benéfica para os indivíduos que apresentam início ictal ipsilateral ao hipocampo de menor volume (121). Nessa situação a investigação pré-operatória pode exigir a realização de

volumetria manual, vídeo-EEG bem como outras modalidades de imagem funcional tais como PET e SPECT.

O SPECT ictal (^{99m}Tc-HMPAO) é o melhor método para localização da origem das crises na epilepsia de lobo temporal, com uma sensibilidade de até 97% (122;123). É um exame empregado rotineiramente na avaliação dos casos em que há suspeita de envolvimento bilateral sugerido pelos EEGs ou pela RM. A subtração ictal-interictal (SISCOM) com o co-registro na RM melhora a sensibilidade do exame e facilita a interpretação dos resultados (124) quanto à localização da zona de início ictal. Um estudo recente mostrou que o SPECT ictal foi o melhor método para predizer o prognóstico cirúrgico (125).

O PET-FDG na epilepsia de lobo temporal também tem sido importante na lateralização do foco ictal já que é realizado no período interictal e caracteristicamente mostra um hipometabolismo no lobo temporal que dá origem às crises epilépticas (126;127), podendo dispensar a investigação invasiva para alguns indivíduos. Para os casos em que a RM não evidencia atrofia hipocampal apesar da clínica sugestiva, é possível ainda utilizar o [^{11}C] FMZ PET que evidencia uma redução da ligação do [^{11}C] FMZ aos receptores GABA-A, restrita ao hipocampo atrófico. Quando comparado ao PET-FDG, o [^{11}C] FMZ PET mostra uma área de redução de ligação aos receptores que é mais restrita que a área de hipometabolismo evidenciada pelo PET-FDG (128), sugerindo que a área de ligação anormal do [^{11}C] FMZ esteja relacionada à zona epileptogênica, enquanto que a extensa área de hipometabolismo do PET-FDG tenha menor implicação cirúrgica (129) e esteja relacionada à zona de déficit funcional (130;131).

O tratamento cirúrgico com a remoção das estruturas mesiais do lobo temporal é a proposta terapêutica que oferece maior chance de controle de crises em comparação ao tratamento medicamentoso tradicional (38-40). Para indivíduos com diagnóstico de atrofia hipocampal unilateral a cirurgia proporciona o controle de crises para aproximadamente 60-80%, (132;133), bem como melhora da qualidade de vida (134;135), reabilitação psicossocial (136-138) e melhora cognitiva (139). A diminuição da mortalidade também tem sido relacionada ao bom resultado cirúrgico (140;141) e um estudo recente com modelo computacional de análise de decisão mostrou que para esses pacientes a cirurgia propicia um ganho substancial na expectativa de vida bem como na qualidade de vida ajustada à expectativa de vida (142).

A seleção dos candidatos deve ser sempre cuidadosa e estudos mais recentes (39;143) mostraram que a monitorização com vídeo-EEG não é obrigatória para os pacientes que apresentam concordância entre os achados de RM (atrofia hipocampal unilateral sem dupla patologia), EEG (exames seriados com lateralização inequívoca ipsilateral à atrofia hipocampal) e déficit neuropsicológico (déficit de memória visual para atrofia hipocampal em hemisfério não dominante para linguagem e déficit de memória verbal para atrofia hipocampal no hemisfério dominante para linguagem). Por outro lado, quando a investigação apresenta resultados discordantes, a monitorização com vídeo-EEG é necessária, podendo ser associada ao exame de SPECT ictal (144) a fim de se obter a clara lateralização da origem das crises.

Os acessos cirúrgicos incluem a ressecção combinada da porção neocortical anterior com as estruturas mesiais do lobo temporal (145), amigdalohipocampectomia transsilviana (146;147), amigdalohipocampectomia transventricular transcortical (148;149), e amigdalohipocampectomia subtemporal (150). Os estudos comparativos entre a ressecção temporal anterior com a amigdalohipocampectomia seletiva (151;152) mostraram que as duas técnicas são igualmente eficazes no controle de crises. O melhor prognóstico cirúrgico

tem sido associado à extensão da ressecção (153;154), bem como à inclusão de estruturas como giro parahipocampal (154) e córtex entorrinal (155). Fatores não relacionados com a cirurgia incluem evidência de atrofia exclusivamente unilateral (152), ausência de crises generalizadas no pré-operatório, idade de início das crises e duração da epilepsia até a cirurgia (156;157) e antecedente de convulsão febril (158;159). Para os casos de falha terapêutica a reoperação tem oferecido bons resultados para um melhor controle das crises (160-162).

JUSTIFICATIVA

A relevância deste estudo foi baseada na necessidade de se confirmar a eficácia e segurança do tratamento cirúrgico para ELT refratária, em contraposição ao tratamento com múltiplas DAEs durante um seguimento prolongado. Além disso, a possibilidade de se identificar fatores prognósticos através da avaliação pré-operatória utilizando parâmetros clínicos e de RM é de grande aplicabilidade clínica uma vez que permite a identificação mais rápida dos candidatos que efetivamente podem ou não se beneficiar do tratamento cirúrgico.

OBJETIVOS

O presente estudo teve como objetivo principal acompanhar por um tempo prolongado os dois grupos (grupo clínico e grupo cirúrgico) a fim de se obter resultados robustos confirmando a superioridade do tratamento cirúrgico no controle das crises em pacientes com ELTM que não apresentaram controle adequado de crises com pelo menos dois esquemas terapêuticos com DAEs de primeira linha e posologia adequada, durante o intervalo de pelo menos um ano.

OBJETIVOS ESPECÍFICOS

1. Comparar a eficácia no controle de crises entre o tratamento clínico e o tratamento cirúrgico de pacientes com ELTM refratária;

2. Comparar o efeito sobre a morbidade e mortalidade entre o tratamento clínico e o tratamento cirúrgico para ELTM refratária;

3. Investigar a relação entre volume de ressecção e prognóstico;

4. Investigar a relação entre diferentes padrões de atrofia de SB e SC e o resultado cirúrgico.
5. Investigar possíveis evidências estruturas de plasticidade cerebral (aumento de SB e SC) após a cirurgia nos pacientes com ELTM refratária.

MATERIAIS E MÉTODOS

O estudo realizado foi do tipo prospectivo, comparando as formas de tratamento clínico e cirúrgico para ELTM associada à esclerose hipocampal. Como continuação do estudo de mestrado iniciado em agosto de 2002, a data de entrada dos pacientes no estudo coincide com esse período e se estende até março de 2009.

IDENTIFICAÇÃO DO GRUPO DE ESTUDO

CRITÉRIOS DE INCLUSÃO

- Idade acima de 12 anos;
- Diagnóstico clínico e eletroencefalográfico de ELTM;
- Refratariedade às DAEs, ou seja, uso em dose máxima tolerada de no mínimo duas DAEs, adequadas ao tipo de crise, por um período mínimo de um ano e manutenção de crises na freqüência mínima de um episódio por mês;
- RM com evidências de atrofia hipocampal unilateral.

CRITÉRIOS DE EXCLUSÃO

- Doença neurológica progressiva;
- Cirurgia prévia para epilepsia;
- Lesões cerebrais que requerem cirurgia de urgência;
- Evidência de patologia dupla, lesões expansivas e ou sinais de atrofia hipocampal bilateral;

- Contra-indicações para o exame de RM; como por exemplo: próteses metálicas, marca-passo cardíaco, clipes metálicos intracranianos (para aneurisma), claustrofobia severa;
- Co-existência de outra doença afetando o SNC;
- Gravidez;
- Não consentimento para a participação no estudo.

- EEGs interictais;
- Vídeo – EEG conforme rotina em nosso serviço;
- SPECT ictal e interictal quando indicados;
- Avaliação neuropsicológica;
- Exame neurológico detalhado.
- Ressonância magnética:
    - (1) *sagital* T_1 spin echo; 6 mm espessura; flip angle, 180°; Tempo de repetição (TR), 400; tempo de eco (TE), 12; matriz, 320X320; e "field of view" (FOV), 25X25cm;
    - (2) *imagens coronais*, perpendicular ao eixo longo do hipocampo, definido a partir da imagem sagita: (a) imagem ponderada em T_2 e densidade de protóns "fast spin echo"; 3mm de espessura; "flip angle", 160°; TR, 4600; TE, 108/18; matrix, 256X256; FOV, 22X22 cm; (b) Imagem do tipo "inversion recovery"ponderadas em T. 3mm de espessura; "flip angle", 180°; TR 2700; TE, 14; tempo de inversão, 860; matriz, 155X256; e FOV 18X18 cm;
    - (3) *imagens axiais* paralelas ao eixo longo do hipocampo: (a) imagem ponderada em T_1 e gradiente eco; 3mm de espessura; "flip angle",70°; TR, 200; TE, 5.27; matriz, 230X230; e FOV, 22X22 cm; (b) FLAIR (fluid

attenuation inversion recovery); 5 mm de espessura; “flip angle”,110°;TR, 10099; TE, 90; matriz, 250x250; e FOV, 24X24 cm;

- (4) *Imagem volumétrica ponderadas em T1:* imagem ponderada em T_1 e gradiente eco com voxels isotrópicos de 1mm, adquiridos no plano sagital (1mm de espessura; flip angle, 35°; TR, 22; TE, 9; matriz, 256x220; e FOV, 25x22cm) (163)

FORMAÇÃO DOS GRUPOS DE ESTUDO

GRUPO1- *Tratamento clínico:* constituído por pacientes que preencheram os critérios de inclusão e estavam em investigação ou aguardando a convocação para cirurgia, assim como por pacientes que não desejavam a cirurgia por razões pessoais (preconceito, medo, aspectos religiosos);

GRUPO2- *Tratamento cirúrgico:* constituído por pacientes submetidos ao tratamento cirúrgico para ELTM a partir da data de início do estudo.

Os pacientes que pertenciam ao grupo clínico e foram convocados para a cirurgia entraram no grupo cirúrgico, mas preservamos seu histórico de tratamento clínico junto ao grupo-1 durante período de seguimento clínico.

SEGUIMENTO DOS PACIENTES

Todos os pacientes do estudo foram acompanhados por epileptologistas e orientados quanto à realização de um diário de crises mensais, para a descrição detalhada das crises, auras e eventos relacionados. Para um preenchimento adequado do diário solicitamos ajuda dos familiares próximos.

Os pacientes do grupo clínico foram seguidos a partir da data de entrada no estudo com consultas a cada 4 a 6 meses ou em intervalos menores quando necessário. Os pacientes receberam monoterapia com DAE de primeira linha diferente das usadas antes do início do estudo ou então uma combinação de DAEs (politerapia). Para esses pacientes os epileptologistas fizeram os ajustes e combinações necessárias de acordo com a tolerância individual. Quando da perda das consultas os pacientes foram contatados por telefone.

Os pacientes submetidos à cirurgia retornaram mensalmente nos 3 primeiros meses, a cada 2 meses nos 6 meses seguintes e a cada 4 ou 6 meses posteriormente. Estes pacientes foram orientados a não alterar as DAE após a cirurgia sem orientação médica, mesmo que estivessem com controle total das crises. Durante o seguimento, os pacientes foram avaliados por epileptologistas que fizeram os ajustes individuais das DAEs a fim de se controlarem os efeitos colaterais e distúrbios hidroeletrolíticos, como hiponatremia. O contato telefônico foi realizado quando necessário.

Conforme protocolo do serviço, os pacientes realizaram exames de ressonância magnética de controle pós–operatório nos primeiros quatro dias e depois de 6 meses da cirurgia para controle da ressecção. Quando necessário, realizam novos exames a critério dos epileptologistas responsáveis.

CLASSIFICAÇÃO PÓS-OPERATÓRIA DE ENGEL

I. Livre de crises incapacitantes:

IA. Completamente livre de crises desde a cirurgia;

IB. Presença de CPS desde a cirurgia;

IC. Algumas crises incapacitantes após a cirurgia, mas totalmente livre de crises nos últimos dois anos;

ID. Crise convulsiva generalizada decorrente de abstinência de DAE.

II. Crises incapacitantes raras ("quase totalmente livre de crises"):

IIA. Inicialmente livre de crises, mas atualmente com crises raras;

IIB.Crises incapacitantes raras desde a cirurgia;

IIC. Crises incapacitantes desde a cirurgia, mas que se tornaram raras durante o período mínimo de dois anos;

IID. Somente crises noturnas.

III Melhora (crises, funções cognitivas, qualidade de vida):

IIIA. Redução das crises;

IIIB. Períodos prolongados sem crises até maiores do que a metade do tempo de seguimento, mas não inferiores há dois anos.

IV. Sem melhora:

IVA. Redução significativa das crises;

IVB. Nenhuma mudança;

IVC. Piora das crises.

SEGMENTAÇÃO MANUAL DOS HIPOCAMPOS

A segmentação manual das imagens de RM pré-operatórias foi realizada com o software interativo DISPLAY, desenvolvido no "Brain Imaging Center" do "Montreal Neurological Institute", Canadá. Este programa permite a visualização simultânea das imagens de RM nos planos coronal, sagital e axial (164;165). Neste programa, a delineação dos limites anatômicos é facilitada pelo ajuste de contraste entre a substância cinzenta e a branca bem como é possível navegar por voxels isotrópicos de 1mm em diferentes orientações com a mesma resolução. O volume resultante das estruturas delineadas é calculado automaticamente pelo software.

Etapas da segmentação:

- Conversão para o formato eletrônico "MINC", com o programa DICOM to MINC (script do MNI);

- Registro das imagens para o espaço estereotáxico de TALAIRACH através de uma transformação linear automática a fim minimizar a interferência de diferenças de volume cerebral entre os diferentes indivíduos e permitir comparações entre eles. Além disso, este procedimento minimiza também a variabilidade na orientação das imagens (166).

- Correção da falta de homogeneidade de campo com o software N3: "Non-parametric Non-uniform intensity Normalization" (167).

SEGMENTAÇÃO DO MÚSCULO TEMPORAL

Para a análise das alterações do músculo temporal após a cirurgia realizamos a segmentação manual nas imagens pré e pós-operatórias com o software para imagens médicas: ITK/SNAP (http://www.itksnap.org/download/snap/). Este *software* foi desenvolvido para a reconstrução tridimensional de estruturas do corpo humano a partir de regiões segmentadas em séries (chamadas de fatias ou slices) O ITK/SNAP permite segmentação manual ou automática, delineando a estrutura anatômica escolhida em um dos três planos mostrados em sua tela (sagital, coronal e axial) atualizando a estrutura nos planos subseqüentes, que combinados, produzem a imagem em três dimensões. O programa ainda possui ferramentas para colorir as estruturas desejadas e calcular seu volume, transposição dessa estrutura em qualquer ângulo desejado e eliminação de elementos ao seu redor. O volume é dado em número de voxels por milímetro cúbico.

Realizamos a volumetria do músculo temporal bilateralmente nas imagens 3D pré e pós-operatórias a fim de detectarmos a atrofia e a assimetria do mesmo após a intervenção. Os detalhes do procedimento, da análise estatística e do protocolo clínico estão descritos detalhadamente no artigo “POST-CRANIOTOMY TEMPORAL MUSCLE ATROPHY: MRI VOLUMETRY AND EMG INVESTIGATION”.

TÉCNICA DE MORFOMETRIA BASEADA EM VOXEL

A técnica de VBM permite identificar diferenças sutis na composição local de volume de tecido cerebral em imagens, baseada em comparações realizadas voxel a voxel. Ela apresenta duas etapas essenciais: inicialmente as imagens passam por uma série de transformações espaciais, em que são realizados processos de normalização espacial, segmentação, modulação e suavização, e após todo o processamento é possível realizar comparações entre grupos através de modelos estatísticos (168-170) .

Etapas do VBM:

Pré-processamento: As imagens adquiridas no formato DICOM foram transformadas para o formato ANALYSE com o software MRIcro (www.mricro.com) (171). Com o mesmo software nós invertemos para a esquerda as imagens com atrofia hipocampal direita a fim de estudarmos simultaneamente todos os indivíduos, evitando cancelamentos do tipo direito-esquerdo. Com a ferramenta de desenho de ROIs (Region of interest) nós segmentamos manualmente a lacuna cirúrgica de cada paciente na imagem 3D.

Nós utilizamos o software SPM2 (www.fil.ion.ucl.ac.uk) junto ao MATLAB 7.0 para obter mapas probabilísticos da substância branca.

Normalização: transformações espaciais são aplicadas nas imagens a fim de aproximá-las a um cérebro padrão (*template*), que pertence a um determinado espaço estereotáxico. Este *template* é uma média de um conjunto de cérebros de indivíduos sem patologia, previamente alinhados. Para isso, são estimados parâmetros de transformações lineares (para um ajuste global: rotação, translação, *zooms* e *shears*), e não lineares (para um ajuste fino: transformada de cossenos discreta), de tal forma a minimizar uma função de custo, baseada no quadrado da diferença de intensidade dos voxels entre a imagem processada e o *template*. Uma vez encontrado os melhores parâmetros com o menor valor

possível para a função de custo, estes são aplicados às imagens originais, normalizando-as para um espaço padrão.

Segmentação: ocorre a separação da imagem cerebral em seus diferentes tecidos: substância cinzenta, substância branca e líquor. Nesta etapa o algoritmo combina duas fontes de informação: um mapa de probabilidades baseado em uma distribuição espacial conhecida dos diferentes tecidos, obtida a partir de imagens de sujeitos normais, e um modelo de análise que identifica a distribuição da intensidade dos voxels dos tipos de tecidos de uma imagem em particular. Assim, a classificação de tecidos realizada é baseada na probabilidade de determinado voxel pertencer a uma determinada região. As imagens a serem segmentadas devem ter alta resolução (voxels de $1mm^3$-$1,5mm^3$), para minimizar a interferência de efeitos de volume parcial.

Modulação: Após a segmentação, as imagens são "moduladas", ou seja, os voxels são multiplicados pelo valor de deformidade de campo obtidos durante o processo de normalização, a fim de se compensar as deformidades decorrentes durante a normalização e preservar o volume de SB e SC. As imagens moduladas após a segmentação permitem análise de diferenças de volume e não apenas de concentração de SB e SC em determinada área do cérebro.

Morfometria Baseada em Voxel:

VBM otimizado e lacunas cirúrgicas

A presença de uma lacuna cirúrgica na imagem gera um grande problema durante as etapas de normalização e segmentação, uma vez que tais processos levam em conta informações globais do encéfalo. O algoritmo para segmentação, assim como para

normalização espacial, é totalmente dependente da intensidade dos voxels das imagens processadas. Assim, quando a imagem a ser normalizada possui uma região que se distorce demasiadamente da normalidade (tal como uma lacuna cirúrgica), ocorre um efeito de distorção nessa região durante a comparação com o *template* na tentativa de aproximar os cérebros no espaço padrão. A distorção ocorre porque o local da lesão influencia na procura dos melhores parâmetros de transformação: como a região apresenta um nível de cinza muito diferente, a função de custo acaba tendo um valor que, mesmo minimizado, não é capaz de conferir os parâmetros corretos às transformações espaciais a serem aplicadas para a normalização. Devido à distorção local, a segmentação é prejudicada, já que o valor de intensidade de cada voxel se relaciona com sua probabilidade de pertencer a um tecido em particular (Figura 1).

Além da classificação inadequada dos tecidos, os erros na normalização no local da lacuna cirúrgica podem se propagar para outras regiões cerebrais, já que a suavização (etapa posterior) também envolve operações com baseadas intensidades dos voxels da imagem.

O problema principal da utilização da técnica de VBM em imagens pós-operatórias surge na etapa de normalização espacial, que compromete toda a seqüência de processamento de forma adequada. O uso de máscaras para a função de custo é a proposta mais adequada para corrigir o problema uma vez que a máscara "exclui" a lesão durante a procura dos parâmetros de transformação, restringindo o cálculo da função de custo às áreas do cérebro que não possuem sinais anormais. Dessa forma, as transformações

espaciais aplicadas para a normalização não sofrem influência da lesão, e as etapas subseqüentes da técnica de VBM podem ser processadas rotineiramente (Figura 2).

Nós desenvolvemos uma versão modificada da segmentação com o SPM que aceita uma máscara (Figura 3) como parâmetro e ignora, para efeito global, todos os voxels dentro da região da máscara correspondente.

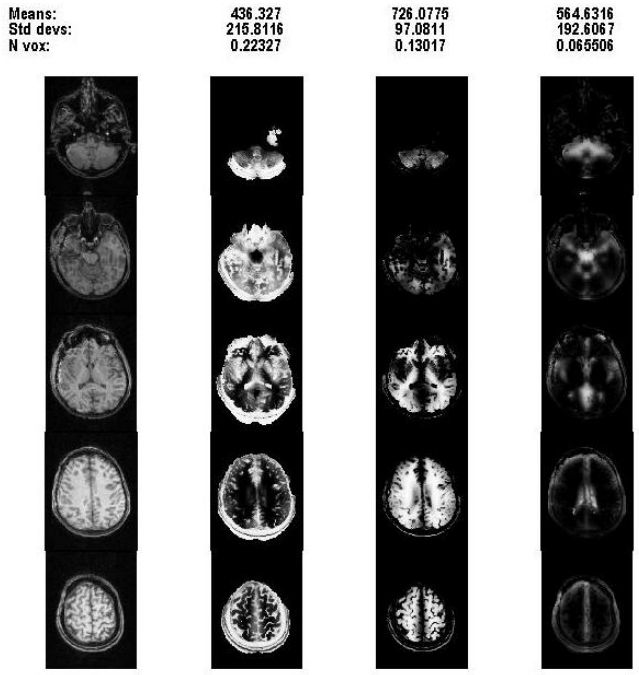


Figura 1. Resultado da segmentação do cérebro em diferentes tecidos (SC, SB e líquor) sem a utilização de máscara sobre a lacuna cirúrgica.

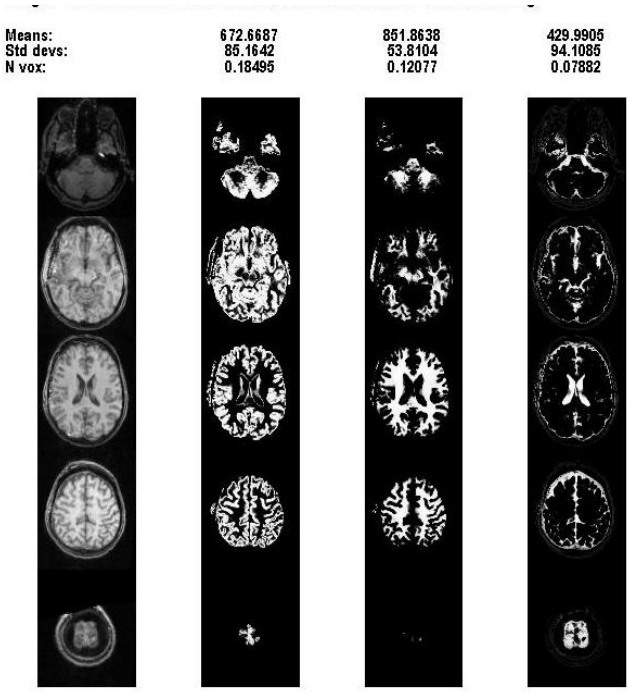


Figura 2. Resultado da segmentação do cérebro em diferentes tecidos (SC, SB e líquor) com a utilização de máscara sobre a lacuna cirúrgica.

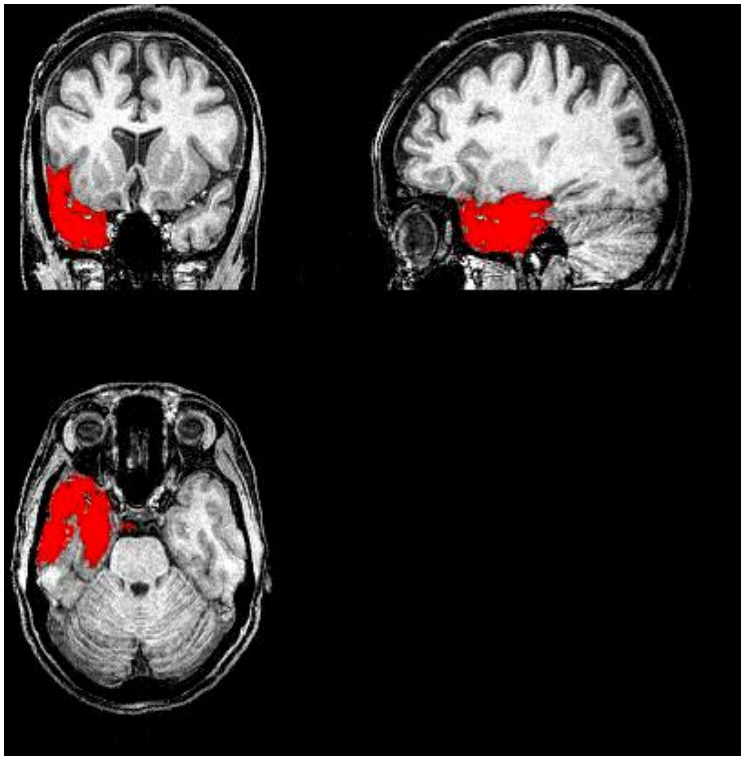


Figura 3. Exemplo da delimitação da lacuna cirúrgica para criação da máscara a ser utilizada durante o processo de morfometria baseada em voxel.

Análise estatística das imagens:

Realizamos análise de cérebro total com um limiar estatístico de falso positivo de 1% (FDR1%) a fim de controlarmos as comparações múltiplas(172). Nós aplicamos uma rotina para o SPM denominada MARSBAR (http://marsbar.sourceforge.net) (173) que nos permite extrair uma média do volume de SB em regiões de interesse (ROI) pré-definidas, de acordo a com uma coletânea de regiões, Automatic Anatomic Labeling (AAL) ROI Library (174). Este procedimento melhora o poder estatístico da análise quando comparada a análise voxel a voxel uma vez que reduz significantemente o número de comparações. Aplicamos teste T e teste T pareado no SPM2, definindo contrastes para analisar áreas de atrofia e regeneração respectivamente.

Detalhes da utilização do VBM estão incluídos nos artigos apresentados na sessão de resultados.

ANÁLISE ESTATÍSTICA

Foram analisadas as características populacionais dos pacientes selecionados incluindo: idade atual, idade de início das crises, sexo e freqüência mensal de crises com comprometimento da consciência.

Para testar as hipóteses já citadas, foram utilizados testes apropriados para cada tipo de variável a fim de comparar as duas formas de tratamento. Entre eles, o teste-T e teste T pareado para analisar diferenças de variáveis contínuas e teste exato de Fisher para analisar distribuição de freqüências. Foi realizada a análise de sobrevivência ("Kaplan-Meier" com teste de "Log-rank Mantel" para comparação entre as duas curvas de sobrevivência). A vantagem deste método de análise é permitir a inclusão de indivíduos com tempos diferentes de seguimento sem que isso tenha uma grande interferência na análise.

ASPECTOS ÉTICOS DA PESQUISA

Os pacientes foram instruídos sobre os procedimentos a serem realizados, e informados de que sua participação seria voluntária; a recusa em participar de tal estudo não acarretaria prejuízos para seu tratamento. Os pacientes que concordaram em participar do estudo assinaram um formulário de consentimento específico para tal estudo.

O exame de Ressonância Magnética (RM) é seguro e não apresenta complicações ou efeitos colaterais. As únicas possíveis contra-indicações para o exame de RM são próteses metálicas, marca-passo cardíaco, clipes metálicos intra-cranianos (para aneurisma), devido à possibilidade de descolamento de partes ferro-magnéticas em um campo magnético potente como o de um sistema de RM.

A realização do procedimento cirúrgico foi explicada em detalhes para todos os pacientes, bem como os riscos envolvidos na sua execução, incluindo os déficits transitórios e ou permanentes. Os pacientes do grupo clínico, recebendo tratamento clínico-farmacológico, foram convidados a participar da pesquisa enquanto aguardavam a realização da investigação complementar e a convocação para a cirurgia.

Todos os pacientes foram informados que poderiam desistir de participar da pesquisa a qualquer momento, sem que ocorresse constrangimento ou qualquer espécie de prejuízo em seu tratamento.

Este projeto foi aprovado pelo Comitê de Ética da Instituição.

RESULTADOS

Os resultados estão apresentados na forma de artigos (publicados e submetidos) com exceção dos resultados da *"Comparação prospectiva entre as formas de tratamento clínico e cirúrgico"* no Capítulo 1.

A análise entre a área de ressecção cirúrgica e o prognóstico cirúrgico está apresentada no artigo 1 (Capítulo 2): *"Does Resection of the Medial Temporal Lobe Improve the Outcome of Temporal Lobe Epilepsy Surgery?"*

O estudo das alterações plásticas em substância branca após a cirurgia para ELTM unilateral refratária estão apresentados no artigo 2 (Capítulo 3): *"Regeneração de Atrofia de Substância Branca após a Cirurgia de Epilesia: Evidências estruturais através da morfometria baseada em Voxel".*

A investigação dos diferentes padrões de atrofia de substância branca e substância cinzenta nos pacientes com ELTM refratária e sua relação com o prognóstico cirúrgico, bem como as alterações plásticas (aumento relativo de substância branca e cinzenta) que ocorrem após o tratamento cirúrgico desses pacientes estão expostos no artigo 3 (Capítulo 4): *"Dynamic changes in white and gray matter volume are associated with outcome of surgical treatment in temporal lobe epilepsy".*

Os diferentes padrões de atrofia de substância branca e substância cinzenta e as diferenças dos resultados da avaliação neuropsicológica entre o *Grupo esporádico* (sem antecedente familiar para epilepsia) e o *Grupo familiar* (com antecedente familiar para epilepsia) estão apresentados no artigo 4 (Capítulo 5): *"Brain Morphometry and cognitive differences in familial and sporadic forms of refractory MTLE"*

Os resultados do estudo das alterações do músculo temporal após a craniotomia para a ressecção das estruturas mediais do lobo temporal estão apresentados no Anexo 1 *"Post-craniotomy temporal muscle atrophy: mri volumetry and emg investigation"*.

CAPÍTULO 1

Comparação prospectiva entre o tratamento clínico e tratamento cirúrgico.

Avaliamos prospectivamente um total de 112 pacientes com atrofia hipocampal unilateral refratária. Quarenta e seis pacientes foram submetidos à cirurgia entre agosto de 2002 e fevereiro de 2009, levando em conta que 18 pacientes inicialmente faziam parte do grupo clínico. Assim temos o Grupo clínico com 85 indivíduos (18 desses passaram ao grupo cirúrgico no decorrer do estudo) e Grupo cirúrgico com 45 indivíduos.

	GRUPO CLÍNICO (85)	**GRUPO CIRÚRGICO (46)**	**P**
Homens/mulheres	30/55	16/30	1 (Fisher)
Idade de início das crises (anos)	10±9	6±6	0,01(Teste T)
Idade na entrada do estudo (anos)	40±10	36±10	0,06 (Teste T)
Freqüência de crises na entrada do estudo (mensal)	9±9	7±10	0,3 (Teste T)
Convulsão febril	8	13	0,006 (Fisher)
Duração da epilepsia antes da entrada no estudo (anos)	30±10,8	29,8±10,6	0,9 (Teste T)
Politerapia/monoterapia	65/20	39/6	0,2 (Fisher)
Tempo de seguimento (anos)	5,3± 1,6	5,2±2	0,9 (Teste T)

O resultado cirúrgico segundo a classificação de Engel é mostrado nos gráficos 1e 2.

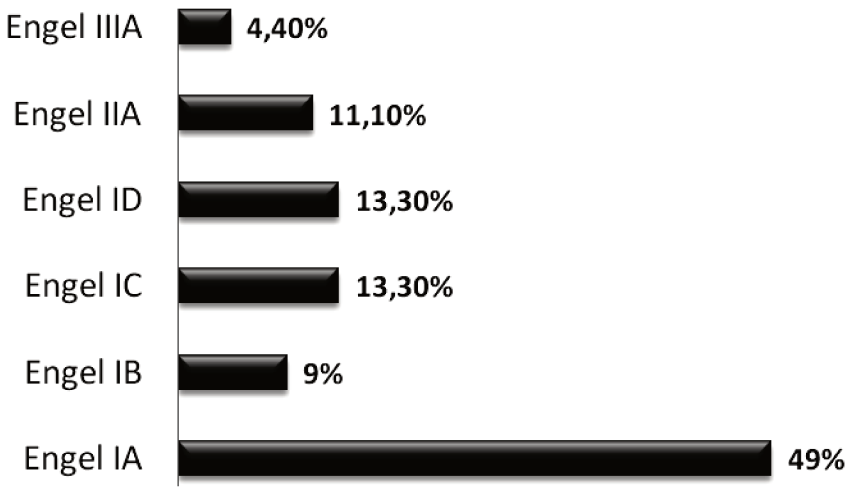


Figura4. Distribuição dos pacientes operados de acordo com a classificação pós-operatória de Engel.

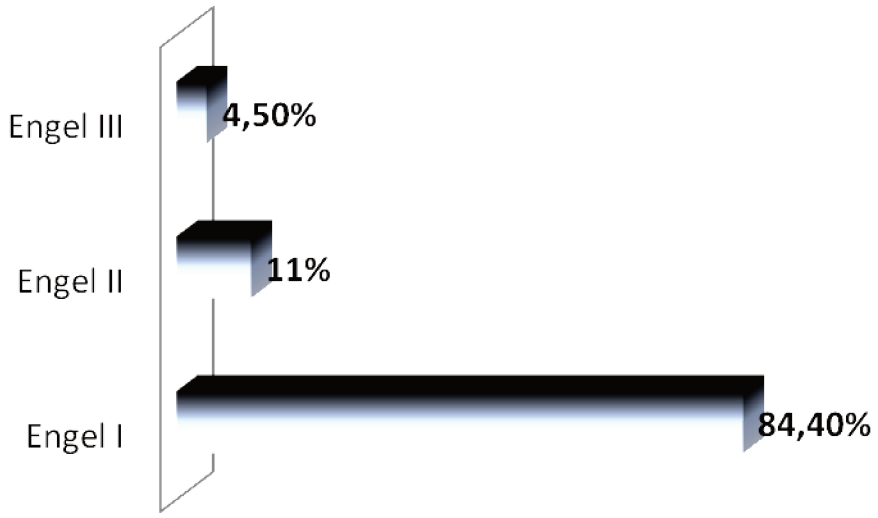
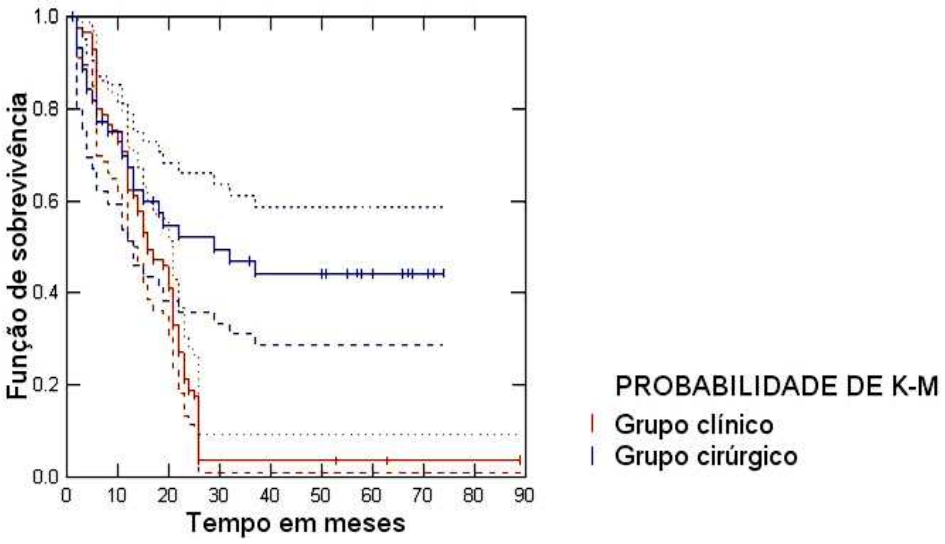


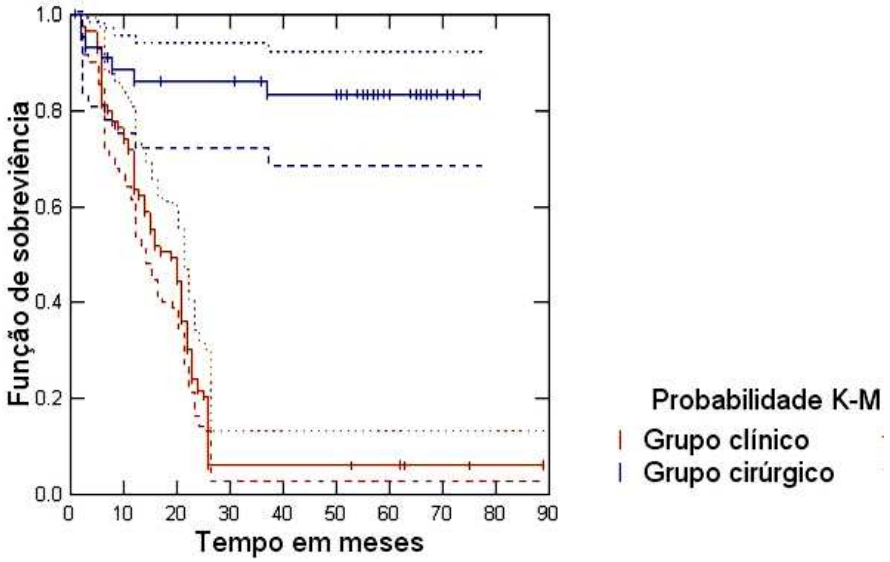
Figura5. Distribuição dos pacientes operados de acordo com a classificação pós-operatória de Engel, agrupando todos os indivíduos com bom controle de crises (Engel I).

Dividimos a análise do controle das crises (tratamento clínico x tratamento cirúrgico) em duas etapas:

- Análise 1: de acordo com o controle total de crises; pacientes operados com Engel IA (22 indivíduos, 49% dos operados) e pacientes sob tratamento clínico sem nenhum tipo de crises (3 indivíduos, 3,5% dos pacientes clínicos); p= <0,001 (Mantel)



- Análise 2: de acordo com um "bom controle de crises"; pacientes operados com Engel I (38 pacientes, 84%) e pacientes no grupo clínico com no máximo 3 crises por semestre (6 pacientes,7%); p<0,001 (Mantel).



No grupo de tratamento clínico encontramos um indivíduo que inicialmente apresentava um quadro refratário à politerapia, mas apresentou controle de crises com a introdução de uma terceira droga já que se recusava submeter ao tratamento cirúrgico. Está livre de crises desde fevereiro de 2007.

- Complicações cirúrgicas: um dos pacientes (2%) apresentou infecção necessitando retirada do flap ósseo e antibioticoterapia; um pacientes apresentou fístula liquórica tratada clinicamente (2%); um paciente apresentou amaurose monocular (2%) e outro paciente (2%) necessitou uma reoperação para drenagem de hematoma epidural no pós-operatório imediato.

- Mortalidade:

    - No grupo cirúrgico não houve nenhum óbito durante o período de estudo, já no grupo clínico tivemos o óbito de um indivíduo;

CAPÍTULO 2

Artigo "*"Does Resection of the Medial Temporal Lobe Improve the Outcome of Temporal Lobe Epilepsy Surgery?"*

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Does Resection of the Medial Temporal Lobe Improve the Outcome of Temporal Lobe Epilepsy Surgery?

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Summary: *Purpose:* Surgical removal of the hippocampus is the standard of care of patients with drug-resistant medial temporal lobe epilepsy (MTLE). The procedure carries a success rate of ~75%, but the reasons that some patients fail to achieve seizure control after surgery remain inexplicable. The question of whether the resection of medial temporal lobe structures in addition to the hippocampus would influence the surgical outcome in patients with MTLE was examined.

Methods: We conducted voxel-based statistical analyses of postoperative high-resolution MRI of MTLE patients who underwent anteromedial temporal resection. We applied a cost function transformation of the resection maps for each patient to a common set of spatial coordinates, and we analyzed the contribution of histologically distinct segments of the medial temporal lobe cortex to the surgical outcome. We also performed a voxel-wise mapping of surgical outcome to the temporal lobe.

Results: We observed that the extent of hippocampal removal was associated with better outcomes. However, when the resection of the hippocampus was combined with the resection of the medial temporal lobe, specifically the entorhinal cortex, a greater likelihood of higher seizure control after surgery was found.

Conclusions: Based on this finding, it is possible that the efficiency of the surgical treatment of MTLE can be improved by adjusting the procedure to include the resection of the entorhinal cortex, in addition to the resection of the hippocampus.
Key Words: Entorhinal cortex—Hippocampus—Medial temporal lobe.

Anterior temporal lobe removal combined with amygdalohippocampectomy is the conventional treatment for patients with drug-resistant medial temporal lobe epilepsy (MTLE) (Engel, 1997). Up to three fourths of drug-resistant MTLE patients who are submitted to surgery become seizure free after surgery (Spencer, 2002b). Nonetheless, the reason that ≥20% of these patients do not achieve complete seizure control after surgery remains unknown.

MTLE is by far the most common form of partial epilepsy (Wiebe, 2000). It is estimated that ~100,000 patients within the United States are candidates for epilepsy surgery (Salanova et al., 2005), and 66% of these patients have MTLE (Wiebe, 2000). In the past, patients with drug-refractory MTLE were given prolonged drug therapy before surgery was attempted (Salanova et al., 2005). Lately it has been shown that patients with MTLE who do not respond to two antiepileptic drugs (AEDs) are unlikely to respond to further drug treatment (Kwan and Brodie, 2000), and a randomized controlled trial of surgery for MTLE demonstrated that surgery is superior to prolonged medical therapy (Wiebe et al., 2001; Engel et al., 2003). Anteromedial temporal lobe resection for disabling complex partial seizures generated by MTLE is now the standard of care for patents with drug-refractory MTLE (Engel et al., 2003).

Medial temporal lobe sclerosis (MTS) is the most common postoperative pathology finding in patients with MTLE (Margerison and Corselis, 1966), and MTS now can be diagnosed in vivo with high-resolution magnetic resonance imaging (MRI) in the great majority of patients with MTLE (Cendes et al., 1993). Hippocampal atrophy, whether or not associated with increased T_2 signal, is the key MRI feature of MTS, because it can reliably be assessed by careful visual analysis and computer-assisted volumetric measurements (Cendes et al., 1993). The level of hippocampal atrophy correlates with the severity of the symptoms (Cendes et al., 1993) and outcome after surgery (Jack et al., 1992; Kuzniecky et al., 1993; Arruda et al., 1996). Despite recent advances concerning the diagnosis and surgical treatment of patients with MTLE, a large number of patients with MTLE due to unilateral hippocampal sclerosis who undergo surgery fail to achieve

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seizure control. Overall, the most important prognostic factor is believed to be the extent of hippocampal removal during surgery (Wyler et al., 1995; Arruda et al., 1996; Bonilha et al., 2004b).

When patients do not achieve a good outcome after surgery, reoperation with the intent to remove the remaining segments of the hippocampus yields freedom from seizures for up to almost two thirds of patients after repeated surgery (Hennessy et al., 2000; Salanova et al., 2005). Unfortunately, even when complete hippocampal resection is performed, surgery for MTLE does not abolish seizures for all patients. Approximately one fourth to one fifth of individuals with MTLE due to unilateral hippocampal pathology (i.e., patients who are expected to achieve the best surgical outcome) continue to experience seizures after surgery (Spencer, 2002b). Postoperative electroclinical investigation of patients who fail to achieve a good outcome despite having had complete hippocampal removal reveals that seizures after surgery arise in the hemisphere of resection, and commonly within the resected temporal lobe (Hennessy et al., 2000; Wennberg et al., 2002). This demonstrates that nonhippocampal structures within the temporal lobe are sufficient to initiate and maintain seizures. More speculatively, this finding may indicate that nonhippocampal regions play a crucial epileptogenic role in many operated-on patients with MTLE.

In a parallel line of research, it has been demonstrated that the neuronal damage in patients with drug-refractory MTLE extends beyond the hippocampus and affects mainly brain areas that are functionally or anatomically connected to the hippocampus and the limbic system. Conventional high-resolution MRI morphometric investigation of the medial portion of the temporal lobe demonstrated that the entorhinal cortex, which is the gate area for information reaching and leaving the hippocampus, is the most significantly atrophied area in these patients (Bonilha et al., 2003). These findings have been confirmed by automated voxel-based morphometry studies, which have also disclosed that the pattern of atrophy in the whole brain suggests that a network of damage exists that involves regions connected to the hippocampus or the limbic system (Bonilha et al., 2004c). Interestingly, electroclinical investigation, using intracranial depth electrodes in patients with MTLE before the resection of the hippocampus, has shown that seizures can be generated within the parahippocampal gyrus (i.e., within the entorhinal cortex) in ~20% of seizures (Wennberg et al., 2002).

The converging evidence that the medial portion of the temporal lobe, more specifically the entorhinal cortex, is damaged and responsible for seizure onset in patients with MTLE has led us to hypothesize that its resection is key to achieving seizure control after surgery for MTLE. Even though surgery for MTLE is refined for the resection of the hippocampus, the extent of resection of the entorhinal cortex can vary across individuals.

In this study, we tested the prediction that if the resection of the amygdala and the hippocampus also encompasses the excision of adjacent structures to the hippocampus, in particular the entorhinal cortex, seizure freedom is achieved. We tested this hypothesis by using an automated voxel-based statistical technique using structural MRI of patients with drug-refractory unilateral MTLE who underwent surgery for the treatment of epilepsy.

METHODS

Patient group

We investigated consecutive adult patients with drug-refractory unilateral MTLE. All patients were referred from the outpatient epilepsy clinic of the State University of Campinas with the diagnosis of epileptic syndrome, based on the ILAE criteria (Commission on Classification and Terminology of the International League Against Epilepsy, 1989), and the laterality of the seizures origin, was determined by using medical history, a comprehensive neurologic examination, interictal EEG, and prolonged video-EEG monitoring for seizure recording. Visual inspection of the MRI scans revealed that all patients had ipsilateral hippocampal atrophy, supporting the initial clinical and electrophysiologic laterality diagnosis. Only patients with MTLE due to hippocampal sclerosis, without dual pathology, with recorded seizure onset in the temporal lobe of hippocampal atrophy, were included in this study. Furthermore, all patients were refractory to medical treatment for epilepsy with two or more AEDs. The use of AEDs either before or after surgery was similar among all patients and comprised standard first-line medication against partial epilepsy.

The patients were submitted to a microscopically guided anteromedial temporal lobe resection performed through the dissection of the lateral sulcus or through the dissection of the superior temporal gyrus. Surgical outcome was assessed during follow-up visits and was defined after $\geq$1 year after surgery, according to the status of the last follow-up visit. Subjects were classified regarding their surgical outcome according to the Engel surgical scale; in summary: class I, seizure free; class II, rare seizures; class III, worthwhile improvement, with a reduction of >90% of seizures; class IV, no worthwhile improvement (<90% reduction in seizure frequency).

The study was approved by the ethics committee of our institution.

MRI scanning

All patients underwent routine MRI scanning $\geq$6 months after surgery, including T_1-weighted MRIs with either 1-mm isotropic voxels or with 1.5 $\times$ 0.97 $\times$ 0.97-mm voxels acquired on an Elscint Prestige 2 Tesla scanner (Haifa, Israel) using a spoiled gradient-echo sequence (TR, 22 ms; TE, 9 ms; flip angle, 35 degrees; matrix, 256 $\times$ 220).

Image analysis

Resection maps comprising the total resection area were manually delineated in MRIcro (Rorden and Brett, 2000) by one of the authors (L.B.) who is experienced with manual morphometry of the medial portion of the temporal lobe (Bonilha et al., 2004a) and who was unaware of the patients' surgical outcomes. The resection maps were defined in the patient's MRI space and were later transferred into the standard stereotaxic MNI space. Lateral, inferior, and medial surgical margins were defined according to the location of the dura mater, which usually remains close to floor of the medial cranial fossa, similar to its preoperative original configuration. The normalization of resection maps involved normalizing the postoperative MRI image with the resection map masking the abnormal area, followed by the application of the normalization matrix to the resection mask. This was accomplished as follows. The resection maps were transformed into binary and smoothed masks by using a full-width half-maximum of 8 mm, with a 0.001% threshold. Next, the resection maps were transformed from the shape and size of the patient's brain into the standard MNI stereotaxic space by using in-built routines from SPM2 (http://www.fil.ion.ucl.ac.uk/spm/software/spm2/). This normalization transform allows comparisons between individuals. We followed the cost–function masking technique devised by Brett and colleagues (Brett et al., 2001) to ensure that the abnormal appearance of the removed brain tissue would not disrupt this automated transformation (i.e., this realignment used resection masking to ensure accurate automated coregistration of brain shape independent of the size and location of the resection). The stereotaxic resection image was converted to Analyze format by using a 50% threshold (i.e., only voxels with >50% of probability of being resected were counted as a resection). This conservative threshold was chosen to assure that the resection maps would contain only resected areas, avoiding the marginal error from the manual delineation of the resection map. Images from patients who had right MTLE and right-sided surgery were left–right flipped and grouped with the images from patients with left MTLE for the voxel-based image analyses.

We performed two forms of voxel-based analysis. Both forms used the resection maps transformed into the stereotaxic standard MNI space.

In the first one, we aimed to define regions of interest (ROIs) that corresponded to the spatial location of medial temporal lobe structures in the standard MNI space. We then investigated the extent of each structure's resection by computing the intersection of the resection map in standard space and the location of each ROI. We defined these medial temporal lobe anatomic ROIs within a standard T_1 MRI normal brain template ("colin27" matched to an average of 305 brains, the MNI305, with symmetrical medial temporal lobe structures) by using a medial temporal lobe segmentation protocol (Bonilha et al., 2004a). We defined ROIs corresponding to the hippocampus, the amygdala, the entorhinal cortex, the perirhinal cortex, the temporopolar cortex, and the posterior parahippocampal cortex (Fig. 1). ROIs were visually confirmed to match the corresponding left or right medial temporal lobe structure. Each one of these six anatomic ROIs was overlaid to the stereotaxic resection map from each patient, and the volume of the intersection was quantified. We then examined the presence of a significant linear regression between the mean resection of each medial temporal lobe structure and the surgical outcome.

In the second analysis, we further investigated the relation between resection location and surgical outcome by using a technique independent of the manual definition of ROIs. This second analysis is termed resection-outcome mapping and depends only on the surgical maps transformed to the standard space. The statistical analyses of resection stereotaxic maps were performed with MRIcron (http://www.mricro.com/mricron) (Fig. 2). For each voxel, patients were divided into two groups according to whether they did or did not have a resection affecting that voxel. We first investigated surgery outcomes under

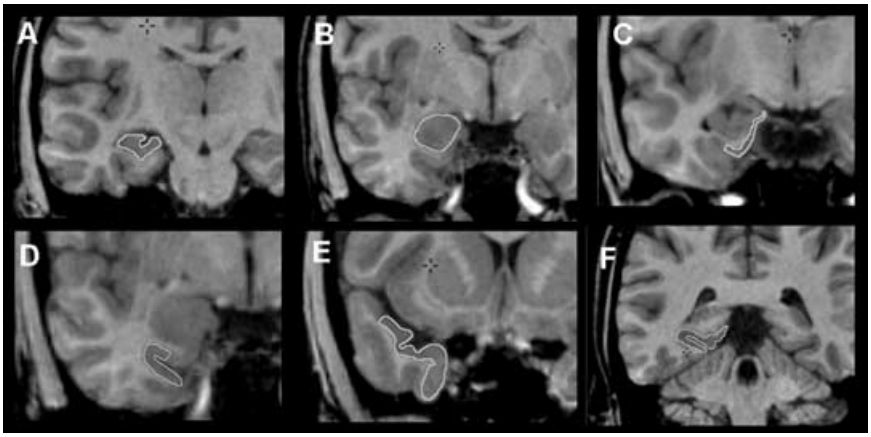

FIG. 1. Examples of the delineation of medial temporal structures are shown on coronal MR images: the hippocampus **(A)**, the amygdala **(B)**, the entorhinal cortex **(C)**, the perirhinal cortex **(D)**, the temporopolar cortex **(E)**, and the posterior parahippocampal cortex **(F)**.

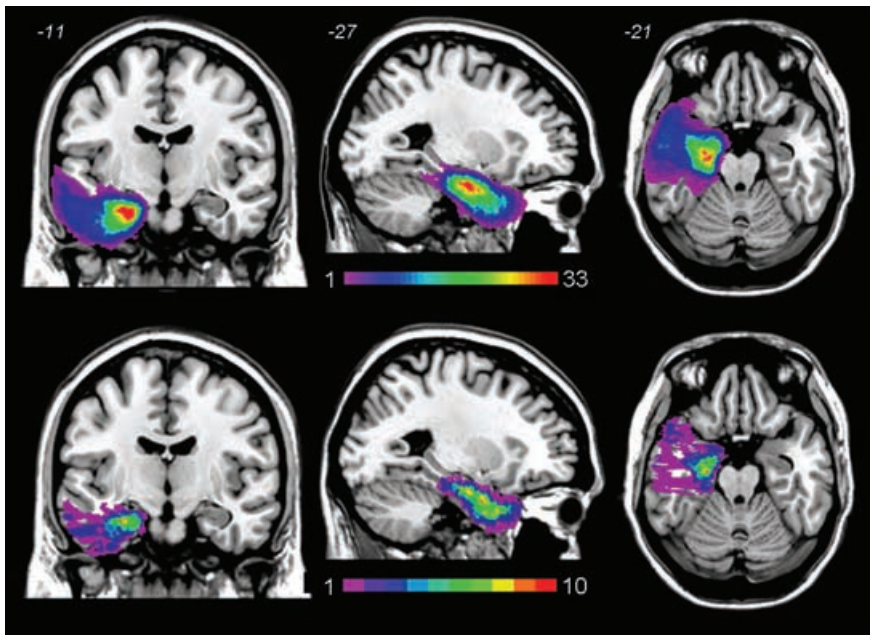

FIG. 2. Basic overlays of resection maps show, for each voxel, the number of patients (depicted by the scale bars) who had the space represented by that voxel resected during surgery. **Upper row:** Patients with a seizure-free surgical outcome [i.e., Engel I (n = 33)]. **Bottom row:** Patients with non-seizure-free outcome, Engel II–IV (n = 10).

the form of Engel scores (as a categoric variable, ranging from 1 to 4). We developed a voxel-wise permutation test to investigate differences in the distribution of Engel scores when each voxel was or was not resected during surgery (Fig. 3). The voxel-wise permutation test used the computation of 10,000 possible rearrangements of the data points. If the statistical value seen from the actual ordering of our real data was >95% of the permuted data, then the result was judged to be significant at the $p < 0.05$ level. The permutation test is a nonparametric test. It does not rely on normality assumptions about the data distribution and therefore is suitable to investigate the categoric nature of the Engel score.

We also tested the findings from the permutation analysis by grouping patients according to the Engel scores. Therefore we confirmed our findings by performing two other nonparametric voxel-wise analyses by using binary data comparing (a) seizure-free outcome with non–seizure-free outcome, and (b) good outcome with suboptimal outcome. Seizure-free outcome was defined as Engel class I, and non–seizure-free outcome as classes II–IV. Good outcome was defined as Engel classes I and II, and suboptimal outcome, as Engle classes III–IV. In the first binary data analysis, we computed the frequency of seizure-free outcome as well as non–seizure-free outcome for each voxel. The probability of observing differences in

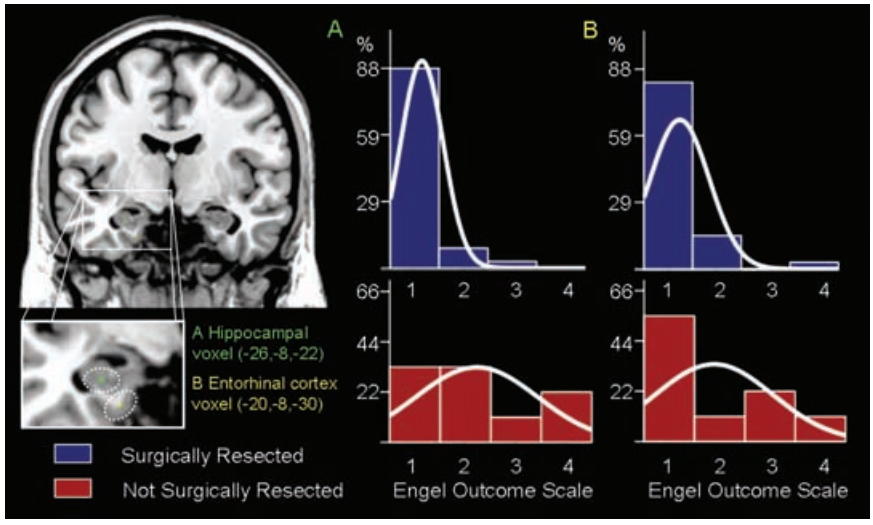

FIG. 3. The basics of voxel-wise statistical analyses of resection outcome mapping. For each voxel (for example, two voxels **A** and **B** belonging to the hippocampus and to the entorhinal cortex, respectively, shown in the coronal slice and magnification), it is calculated as to whether it is part of the surgical resection and what the clinical score is in both situations (defined by the Engel Outcome Scale). As an example, the data for these particular voxels are shown on the right. Note that the distribution of the surgical outcome is different when the voxel is part of the resection (blue) compared with when it is not (red). Data from both voxels is shown on the right. A greater percentage of patients (y-axis) have a better outcome when the resection involved each one of the highlighted voxels.

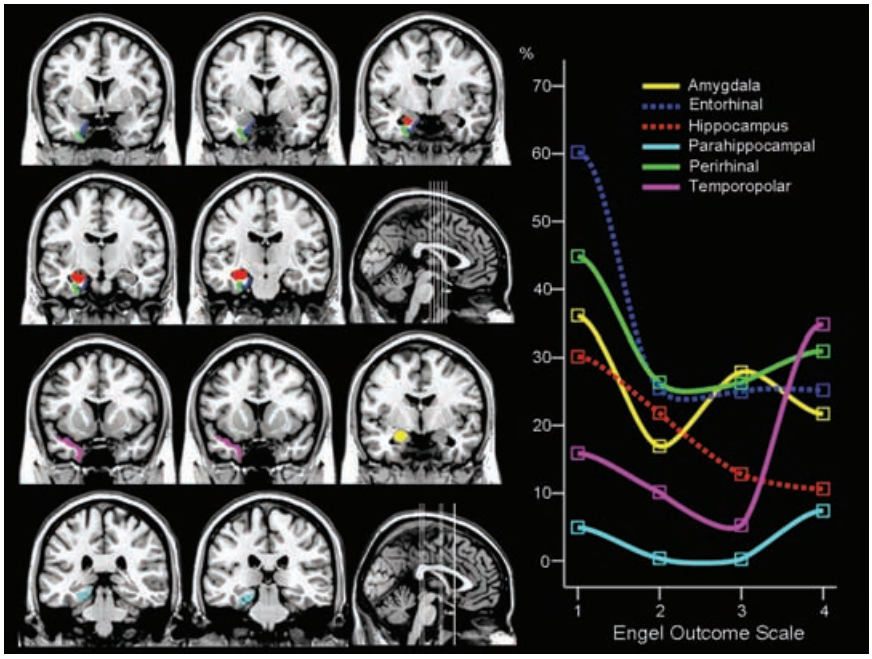

FIG. 4. The relation between resection extent and clinical outcome for six medial temporal lobe regions. Regions of interest in standard space corresponding to healthy medial temporal lobe structures (the entorhinal, the perirhinal, the temporopolar, and the parahippocampal cortices, the hippocampus, and the amygdala) are color coded and shown on multislice on the left. These regions of interest were intersected with the total resection areas from each patient as a resection map transformed from the shape and size of the patient's brain to a standard stereotaxic space. The vertical axis illustrates the percentage of removal, whereas the horizontal axis shows the success of the surgery. Subjects were classified regarding their surgical outcome according to the Engel surgical scale [class I, seizure free; class II, rare seizures; class III, worthwhile improvement, with a reduction of >90% of seizures; class IV, no worthwhile improvement (<90% reduction in seizure frequency)]. Each region is plotted individually. Note that the extents of hippocampal and entorhinal removals are the strong predictors of good clinical outcome.

frequency between seizure-free and non–seizure-free outcome was calculated for each voxel by using Fisher's test, with mid-p correction. In the second binary data analysis, differences in probability between good outcome and suboptimal outcome were calculated also by using Fisher's test, with mid-p correction.

We excluded voxels that were not part of the surgical resection in at least eight subjects in all analyses (this restriction attenuates correction for multiple comparisons), and we covaried out the overall resection size. The results were corrected for multiple comparisons by using False Discovery Rate (Genovese et al., 2002), and the level of statistical significance was set at $p < 0.05$.

RESULTS

In total, 43 patients with unilateral drug refractory MTLE were evaluated. The patient group had a mean age of 37 years (ranging from 17 to 56 years; standard deviation (SD), 10.3 years). Mean age at seizure onset was 7 years (ranging from 1 to 43 years; SD, 7.6 years). Mean duration of epilepsy was 29.8 years (ranging from 4 to 51 years; SD, 12.6 years). Mean follow-up after surgery was 40 months (ranging from 12 to 99 months; SD, 26 months). Eleven (26%) patients were submitted to surgery to the right temporal lobe, and 32 (74%) to the left.

Thirty-three (76%) patients were seizure free after surgery [i.e., were classified as Engel I (comprising patients who were classified as Engel Ia, b, or c]. Six (14%) patients had rare seizures (Engel II), two (5%) had reduction of >90% of seizures (Engel III), and two (5%) had no worthwhile improvement (Engel IV). No significant difference was found between the outcome of patients with right-sided surgery as opposed to left-sided surgery (Yates corrected $\chi^2 = 2.749$; $p = 0.097$).

No significant association was noted between surgical outcome and age at onset of seizures (Pearson correlation, 0.17; $p = 0.27$), duration of epilepsy (Pearson, -0.14; $p = 0.37$), age at the time of surgery (Pearson, -0.05; $p = 0.72$), or length of follow-up time (Pearson, 0.19; $p = 0.2$).

We evaluated the volume of the intersection between the stereotaxic resection maps and the anatomic regions defined on the stereotaxic T_1 template image. We computed linear regressions for the extent of resection of each region and the surgical outcome (Engel's score, all tests having 35 degrees of freedom). We observed a significant linear regression between outcome and the extent of resection of the hippocampus ($t = 2.371$; $p = 0.023$) and the entorhinal cortex ($t = 3.286$; $p = 0.002$) (Fig. 4). No significant linear regression occurred between outcome and the volume of the other structures (amygdala $t = 0.47$;

$p = 0.64$; perirhinal cortex $t = 0.076$; $p = 0.94$; temporopolar cortex $t = 1.63$; $p = 0.11$; posterior parahippocampal cortex $t = 0.54$; $p = 0.59$).

We also observed that no significant linear regression occurred between the overall surgical resection size and outcome ($t = -0.259$; $p = 0.79$).

We observed a significant linear regression for resection size and the resected volumes of the perirhinal cortex ($t = 4.75$; $p < 0.001$) and the temporopolar cortex ($t = 2.5$; $p = 0.019$). The volumes of resection of the other structures did not show significant linear regression with resection size (hippocampus $t = 1.49$; $p = 0.145$; amygdala $t = -1.36$; $p = 0.18$; entorhinal cortex $t = -1.249$; $p = 0.22$, posterior parahippocampal cortex $t = 0.48$; $p = 0.66$).

The results from the resection-outcome mapping analyses are shown in Fig. 5, which shows a map that is a colorized display of permutation, and Fisher's test results. Surgical outcome is demonstrated in a stereotaxic map with the probability of good outcome shown on a voxel-by-voxel basis. Similar to the results from the linear regression between the extent of resection of medial temporal structures and surgical outcome, the resection-outcome mapping analyses showed that a good surgery outcome was most affected by the combined resection of the hippocampus and the medial portion of the temporal lobe, specifically the entorhinal cortex.

The results from resection-outcome mapping, when the Engel Outcome Scale was investigated as a categoric variable, shows that resection of the hippocampus and the parahippocampal gyrus, specifically the upper limits of the perirhinal cortex and the entorhinal cortex, is associated with a better outcome When the group of seizure-free patients was compared with the group that remained non–seizure free (binary variable), the resection of the hippocampus and the entorhinal cortex was associated with seizure freedom. When good outcome was compared with suboptimal outcome, no voxels survived the threshold for correction for multiple comparisons, possibly because of the reduced number of patients with Engel classes III and IV. Nonetheless, a trend suggested that hippocampal and entorhinal cortex resection were associated with a good outcome (Fig. 5).

DISCUSSION

We demonstrated that a combined resection of the hippocampus and the upper medial temporal lobe is critical

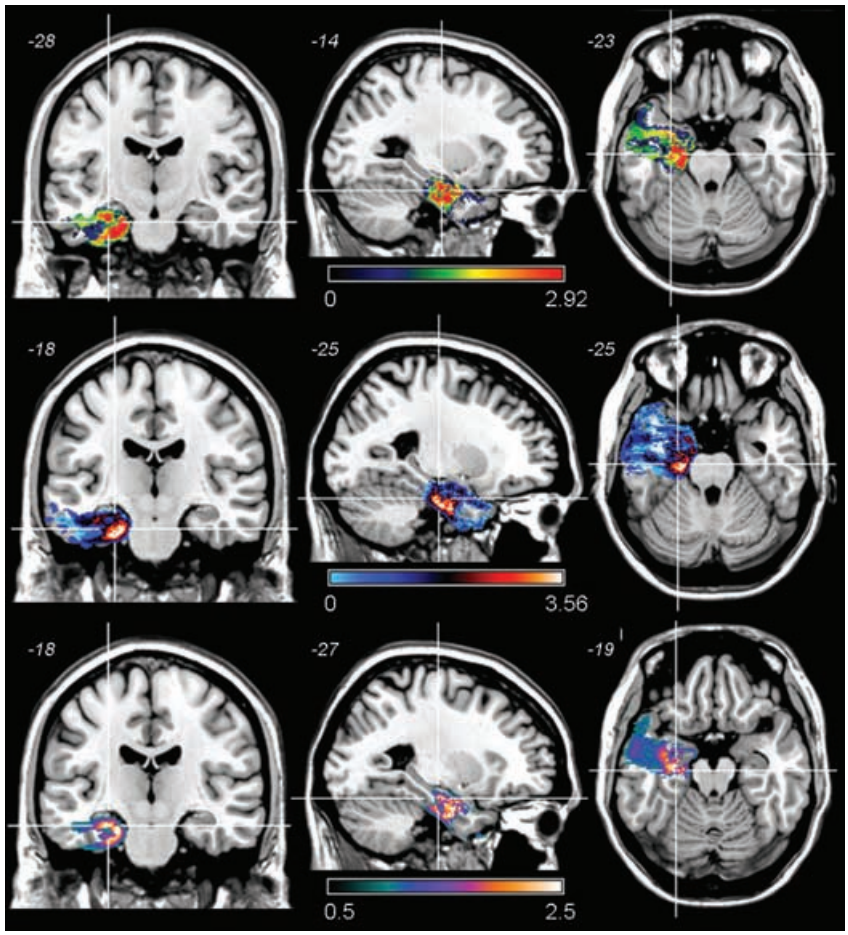

FIG. 5. Resection-outcome statistical maps highlight brain regions that, when resected during surgery, are associated with a better postoperative outcome. The first row shows the results of the permutation test with the Engel score as a categoric variable. It shows areas that, when resected, are associated with a higher likelihood of a small value in the Engel Outcome Scale. The middle and bottom rows show the results of the binary analyses by using the Fisher's test when patients were grouped according to their Engel scores. The middle row shows areas that are associated with seizure freedom (Engel I), as opposed to non–seizure freedom. The bottom row shows areas that, if resected, are likely to be associated with good outcome (Engel I and II), as opposed to suboptimal outcome (Engel III and IV). For top and middle rows, the scale bar shows $z =$ scores, the right extreme being the threshold for correction for multiple comparisons. Note the association between the likelihood of better outcome or seizure freedom with resection of the entorhinal cortex and hippocampus. The comparison shown in the bottom row does not yield voxels that survive the threshold for multiple comparisons ($z = 4.8$) because of the low number of subjects with suboptimal outcomes. However, note a trend toward good outcome when resection involves resection of the entorhinal cortex and the hippocampus.

to confer seizure freedom for patients with MTLE undergoing surgical treatment. Our findings confirm a series of previous studies that demonstrated a positive correlation between the extent of hippocampal removal and the success of surgery for MTLE (Kuzniecky et al., 1993; Arruda et al., 1996; Hennessy et al., 2000; Bonilha et al., 2004b; Salanova et al., 2005). Additionally, our study demonstrates that surgical procedures that remove the entorhinal cortex lead to a better prognosis than when this region is preserved intact. We observed that a better surgical outcome is not dependent on whether the overall resection is larger, but rather on when the specific removal of the hippocampus and the entorhinal cortex is accomplished.

These findings may help explain why some patients who exhibit clear-cut severe unilateral hippocampal atrophy and have been given a complete hippocampal resection (i.e., are expected to achieve the best surgical results) fail to achieve a seizure-free status after surgery.

Well-known predictors of good surgical outcome for MTLE are the greater extent of hippocampal removal (Kuzniecky et al., 1993; Arruda et al., 1996; Hennessy et al., 2000; Bonilha et al., 2004b; Salanova et al., 2005) and a more intense preoperative degree of hippocampal atrophy (Garcia et al., 1994; Arruda et al., 1996; Wennberg et al., 2002). It is still controversial whether age at surgery, duration of preoperative epilepsy, and age at onset of seizures are determinants of poor outcome (Hennessy et al., 2000; McIntosh et al., 2004). Certainly, the existence of bilateral hippocampal atrophy or extrahippocampal pathology is associated with a greater likelihood of seizure recurrence after surgery (Jack et al., 1995; Hennessy et al., 2000). It has also been hypothesized that patients who do not achieve a seizure-free status after surgery can harbor subtle isocortical dysplastic epileptogenic lesions that are not detected in the preoperative workup (Hennessy et al., 2000). However, recent advances in diagnostic neuroimaging techniques have greatly enhanced the capability of detecting the so-called "dual pathology," in which hippocampal atrophy coexists with focal cortical dysplasia (Montenegro et al., 2002). Even with better selection of patients for surgery, the results of the procedure for patients with unilateral hippocampal atrophy are still challenged by the somewhat consistent failure rate. In addition, the theory that poor outcome can be explained by small undetected isocortical dysplastic lesions outside the hippocampus does not support the fact that almost two thirds of patients who did not exhibit a good surgical outcome after a first procedure may achieve seizure control after a reoperation aimed to expand the resection of the hippocampus and the medial portion of the temporal lobes (Wyler et al., 1995; Salanova et al., 2005). It is more probable that the suboptimal surgery results are associated with (a) an incomplete resection of the hippocampus (Engel J, 1997; Bonilha et al., 2004b; Salanova et al., 2005); and (b) a partial resection of the medial portion of the temporal lobe, which is heavily connected to the hippocampus (the entorhinal cortex).

Our data suggest that the resection of the entorhinal cortex, associated with a complete resection of the hippocampus, is a condition of good initial surgical prognosis in patients with unilateral MTLE. This finding matches the notion that patients with MTLE do exhibit neuronal damage beyond the hippocampus, especially within the entorhinal cortex (Bernasconi et al., 2003; Bonilha et al., 2003; 2004c), and that the medial portion of the temporal lobe can generate seizures in ~20% of patients with MTLE (Spencer, 2002a; Wennberg et al., 2002). Interestingly, the same proportion of patients (i.e., 20%) does not achieve good seizure control after surgery for MTLE.

Probably other factors could account for the success of surgery for MTLE. For instance, genetic determinants of hippocampal sclerosis, environmental factors, and patterns of hippocampal connectivity are features that are not yet well understood and that could account for the variability in surgical results. However, based on our findings, we suggest that the anatomy of the surgical resection can be one important predictor of postoperative outcome. Likewise, our findings are related to early (after 1 year of follow-up) postoperative seizure control. It is not yet clear whether the resection of the medial temporal lobe would also contribute to the long-term prognosis of MTLE surgery.

Finally, our findings also generate new questions. For example, do any presurgical signs predict the necessity of entorhinal cortex removal (for example, relatively little hippocampal atrophy as observed on MRI)? In addition, voxel-based resection mapping could be used to investigate whether quantitative removal of different medial temporal lobe brain areas implies different cognitive postsurgical-outcome profiles.

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CAPÍTULO 3

Artigo *"Regeneração de Atrofia de Substância Branca após a Cirurgia de Epilesia: Evidências estruturais através da morfometria baseada em Voxel"*

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Regeneração de Atrofia de Substância Branca após a Cirurgia de Epilesia: Evidências Estruturais Através da Morfometria Baseada em Voxel

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ABSTRACT

Recovery of white matter atrophy after epilepsy surgery: structural evidences through Voxel-Based Morphometry

Objectives: To study pre and postoperative WMA in MTLE patients. **Methods**: We performed Voxel-Based Morphometry (VBM) with volume of interest (VOI) in 69 controls (mean age, 34.3±11.1 years) and 67 operated patients (mean age, 34.1±10.4 years) with unilateral MTLE. 34 became seizure-free (*SzFree-Group*), 23 improved (Engel IB-IIA [*Partial recovery-group*]) and 10 did not improve (Engel III-IV [*Failure-Group*]). All had pre and postoperative MRIs (one year minimum). We flipped MRIs of right MTLE patients in order to avoid right-to-left analysis cancelation. VBM was performed on SPM2/MATLAB7.0 with individual masks for surgical lacunae and 1% false-discovery-rate to control for multiple comparisons. We used MARSbar <www.marsbar.sourceforge.net> routine to select ROIs and *t-test* for statistical analyses. **Results**: Mean postoperative follow-up was 60.2 (±SD 30.7) months. On baseline MRI, *SzFree-Group* showed White Matter Atrophy (WMA) involving temporal lobes [TL], ipsilateral occipital, parietal and frontal regions, with areas of significant recovery of WMA on postoperative MRI. *Partial recovery-Group* presented a more restricted pattern of WMA, involving ipsilateral temporal lobe, contralateral superior temporal gyrus and few areas in bilateral cingulated and orbitofrontal areas. In this group we also identified areas with relative increase of WM after surgery. By contrast, *Failure-Group* showed more widespread bi-hemispheric areas of WMA on baseline MRI without postoperative improvement. **Conclusions**: Although we have identified some differences in baseline WMA, we were unable to correlate a more widespread pattern with a worse prognosis, as *SzFree-Group,* also presented a bilateral distribution of WMA. The recovery of WMA in *SzFree-Group* and *Partial recovery-group* is in agreement with previous MRS and PET studies and suggests that a network of neuronal dysfunction in MTLE can be, at least in part, reversible after successful postoperative seizure control.

Key words: Temporal lobe epilepsy, white matter, surgery, VBM, plasticity.

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INTRODUÇÃO

O impacto da cirurgia de epilepsia não se restringe ao controle das crises, uma vez que a melhora da qualidade de vida dos pacientes também é um resultado esperado e deve estar parcialmente associada à melhora de déficits cognitivos detectados nas avaliações neuropsicológicas pré-operatórias. Alterações de substância branca (SB) de cinzenta (SC) tanto em regiões do lobo temporal quanto em áreas extratemporais já foram anteriormente descritas através da técnica de morfometria baseada em voxel (VBM)[1] provavelmente estão associadas aos déficits cognitivos detectados nas avaliações neuropsicológicas[2] incluindo memória e déficits de aprendizado,[3] assim como depressão. Todas essas alterações resultam em uma baixa qualidade de vida.[4] Essas alterações estão provavelmente relacionadas a um aumento progressivo das descargas epilépticas bilaterais que por sua vez resultam em disfunção neuronal em regiões remotas ao foco epileptogênico.[5,6]

O tratamento cirúrgico para epilepsia tem sido indicado com um índice de sucesso de aproximadamente 70%.[7] Como a ressecção das estruturas mesiais do lobo temporal contribui para a restauração de uma função cerebral normal ainda é uma questão não totalmente elucidada, mas é provável que esteja relacionada com a diminuição das descargas elétricas anormais. Evidências metabólicas de recuperação neuronal após a cirurgia já foram descrita através de técnicas como espectroscopia por ressonância magnética e tomografia por emissão de prótons (^{18}F-FDGPET),[5,8-10] mas alterações estruturais correspondentes ainda não foram descritas.

Utilizamos a técnica de VBM[11-13] antes e depois da cirurgia, comparando alterações estruturais entre os pacientes que ficaram livres de crises e os que permaneceram com crises mesmo após uma ressecção adequada das estruturas mesiais do lobo temporal.

MÉTODOS

Pacientes

Incluímos 69 controles (39 mulheres), idade média ± DP (34,3±11,1 anos) e 67 pacientes com Epilepsia de Lobo temporal Mesial (ELTM) e atrofia hipocampal confirmada por análise histopatológica, (41 mulheres, idade média ± DP, 34±10,4 anos). Pacientes foram selecionados de acordo com critérios já descritos previamente.[14]

Pacientes foram separados em três grupos, de acordo com a classificação pós-operatória de Engel:[15] *Grupo livre de crises* com 34 pacientes (Engel: IA), *Grupo recuperação parcial* com 23 pacientes (Engel: 8 IB, 3 IC, 6 ID, 6 IIA) e *Grupo crises refratárias* com 10 pacientes (Engel: 1 IIB, 6 IIIA, 3 IVA). Este estudo foi aprovado pelo comitê de Ética de nossa instituição.

Imagens

Aquisição: Todos os indivíduos foram submetidos ao mesmo protocolo de aquisição 3D, num aparelho de 2T (Elscint Prestige, Haifa, Israel).

Análise

As imagens adquiridas no formato DICOM foram transformadas para o formato ANALYSE com o software MRIcro <www.mricro.com>.[16] Com o mesmo software nós invertemos para a esquerda as imagens com atrofia hipocampal direita a fim de estudarmos simultaneamente todos os pacientes, evitando cancelamentos do tipo direito-esquerdos. Com a ferramenta de desenho de ROIs (*Region of interest*) nós segmentamos manualmente a lacuna cirúrgica de cada paciente na imagem 3D.

Nós utilizamos o software SPM2 <www.fil.ion.ucl.ac.uk> junto ao MATLAB 7.0 para obter mapas probabilísticos da substância branca.

MORFOMETRIA BASEADA EM VOXEL

VBM otimizado e lacunas cirúrgicas

A presença de uma lacuna cirúrgica na imagem gera um grande problema durante as etapas de normalização e segmentação, uma vez que tais processos levam em conta informações globais do encéfalo. Nós desenvolvemos uma versão modificada da segmentação com o SPM que aceita uma máscara como parâmetro e ignora, para efeito global, todos os voxels dentro da região da máscara correspondente.

Análise estatística

Realizamos análise de cérebro total com um limiar estatístico de falso positivo de 1% (FDR1%) a fim de controlarmos as comparações múltiplas.[17] Nós aplicamos uma rotina para o SPM denominada MARSBAR <http://marsbar.sourceforge.net>[18] que nos permite extrair uma média do volume de SB em regiões de interesse (ROI) pré-definidas, de acordo a com uma coletânea de regiões, Automatic Anatomic Labeling (AAL) ROI Library.[19] Este procedimento melhora o poder estatístico da análise quando comparada a análise Voxel a Voxel uma vez que reduz significantemente o número de comparações. Aplicamos teste T e teste T pareado no SPM2, definindo contrastes para analisar áreas de atrofia e regeneração respectivamente. Para facilitar a visualização dos resultados, as imagens foram geradas a partir dos mapas de análise de cérebro total.

Utilizamos o pacote estatístico SYSTAT 12 (Systat Software Inc. – SSI) para analisar variáveis contínuas (teste T com correção de Bonferroni) e o teste exato de Fisher para variáveis categóricas. A fim de compararmos médias entre 3 grupos utilizamos o teste ANOVA com teste *post hoc* Tukey's HSD.

RESULTADOS

Pacientes e controles estavam balanceados quanto ao gênero (p=0.58) e idade (p=0.89).

Não identificamos diferenças significativas entre os grupos em relação à idade de início de crises ou idade no momento da cirurgia. Entretanto, a duração da epilepsia foi mais curta no *grupo Recuperação Parcial* comparada a do *grupo Livre de Crises* (p=0.046) e tempo de seguimento do *grupo Recuperação Parcial* foi inferior ao tempo do *grupo Livre de Crises* (p=0.004) e do *grupo crises refratárias* (p=0.001). Convulsões febris foram mais freqüentes nos *grupos Livre de Crises* e *Recuperação Parcial*.

Atrofia de SB nas imagens pré-operatórias

O *grupo crises refratárias* apresentou extensas áreas de atrofia envolvendo bilateralmente lobos temporais, regiões frontais e parietais (mais intensamente a região ipsilateral) (Fig. 1).

O *grupo livre de crises* mostrou um padrão extenso de atrofia de SB, envolvendo os lobos temporais, frontais, occipitais e parietais (Fig. 2).

O *grupo recuperação parcial* apresentou um padrão de atrofia de SB mais restrito que os grupos descritos anteriormente, envolvendo todo o lobo temporal ipsilateral e o giro temporal superior contralateral. Conseguimos identificar áreas de atrofia bilateral envolvendo o giro do cíngulo, regiões orbitofrontais, giros reto e olfatório. No lobo parietal, apenas o giro angular ipsilateral apresentou áreas de atrofia (Fig. 3).

Nós identificamos áreas de atrofia envolvendo o lobo occipital ipsilateral nos três grupos. Ao contrário, identificamos atrofia de SB cerebelar bilateral nos grupos *livre de crises* e *crises refratárias*, mas não encontramos no *grupo recuperação parcial*.

Recuperação de Substância Branca

Observamos áreas de recuperação de SB nos *grupos livre de crises* e *recuperação parcial* envolvendo o lobo temporal contralateral, cíngulo bilateral, regiões frontais e occipitais. O *grupo livre de crises* ainda apresentou áreas de recuperação no giro angular ipsilateral e nas regiões contralaterais do precuneus e região motora suplementar (Figs. 4-5).

Não identificamos áreas com recuperação de SB no *grupo crises refratárias*.

DISCUSSÃO

A análise de atrofia de SB mostrou uma distribuição temporal bilateral, além de regiões extratemporais, de acordo com estudos realizados previamente.[20,21] O *grupo crises refratárias* apresentou áreas de atrofia de SB nos dois hemisférios, poupando parte dos lobos parietais e o lobo occipital contralateral. No *grupo livre de crises* identificamos um padrão extenso de atrofia de SB envolvendo regiões temporais e extratemporais, num padrão mais extenso que o apresentado pelo *grupo recuperação parcial*. Apesar de pequenas diferenças entre os três grupos, não foi possível associar um padrão extenso de atrofia de SB com um pior prognóstico cirúrgico, em acordo com um estudo prévio que utilizou a técnica de tensor de difusão para analisar anormalidades de substância branca.[22]

Os mecanismos fisiopatológicos da atrofia de SB em regiões temporais e extratemporais não foram totalmente esclarecidos, mas estudos anteriores sugerem o envolvimento de processos tais como heterotopia neuronal,[23,24] microdisgenesia,[25] disfunção da mielina[26] e desmielinização.[27] Nossos resultados sugerem que a epilepsia crônica de lobo temporal está associada a alterações de SB, podemos então especular a hipótese de que tais anormalidades crônicas possam estar envolvidas com as disfunções cognitivas que esses pacientes comumente apresentam.[28,29]

REVERSIBILIDADE DAS LESÕES DE SUBSTÂNCIA BRANCA

O desenvolvimento de uma nova ferramenta para o MATLAB/SPM foi essencial para a análise dos processos dinâmicos que se sucedem após a remoção cirúrgica das estruturas temporais mesiais. Estudos anteriores tinham mostrado evidências de recuperação funcional da SB,[5,9,30] mas alterações estruturais correspondentes ainda não tinham sido demonstradas. Neste estudo conseguimos realizar análise de cérebro total, identificando áreas com recuperação de SB apenas nos pacientes que alcançaram um bom controle de crises. Nossos resultados confirmam os resultados de estudos prévios relatados por Cendes et al.[5] e Hugg et al.,[8] nos quais demonstraram que pacientes livres de crises após a cirurgia tiveram uma normalização dos valores de NAA/Cr na região temporal contralateral, enquanto aqueles que persistiram com crises não conseguiram normalizar tais valores.

Nos *grupos recuperação parcial* e *livre de crises* conseguimos identificar áreas de recuperação de SB envolvendo tanto as regiões temporais quanto extratemporais. Ao contrário, Concha et al não conseguiram identificar áreas de recuperação de SB através da técnica de tensor de difusão (DTI). A aplicação de técnicas diferentes e o grande número de indivíduos em nosso estudo podem explicar as diferenças entre os resultados. Outro estudo aplicou a mesma técnica (DTI) e conseguiu obter evidências de recuperação de SB no lobo occipital contralateral após a lobectomia unilateral, sugerindo plasticidade como forma de respostas adaptativas.[30]

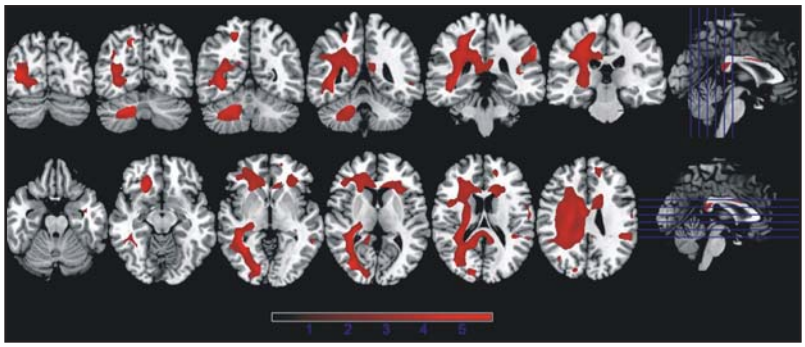

Figura 1. Mapa estatístico de áreas com atrofia de SB identificadas no *grupo crises refratárias* quando comparado ao grupo controle. O mapa foi sobreposto a um "template" do tipo T1.

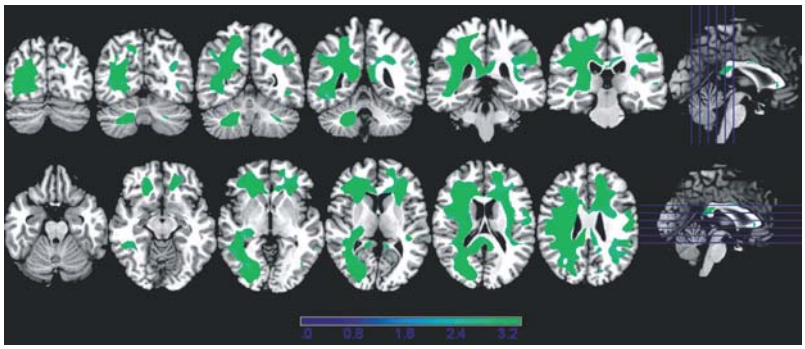

Figura 2. Mapa estatístico de áreas com atrofia de SB identificadas no *grupo livre de crises* quando comparado ao grupo controle. O mapa foi sobreposto a um "template" do tipo T1.

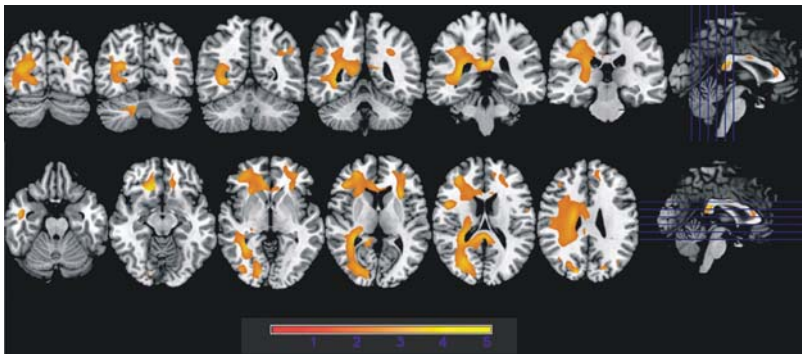

Figura 3. Mapa estatístico de áreas com atrofia de SB identificadas no *grupo recuperação parcial* quando comparado ao grupo controle. O mapa foi sobreposto a um "template" do tipo T1.

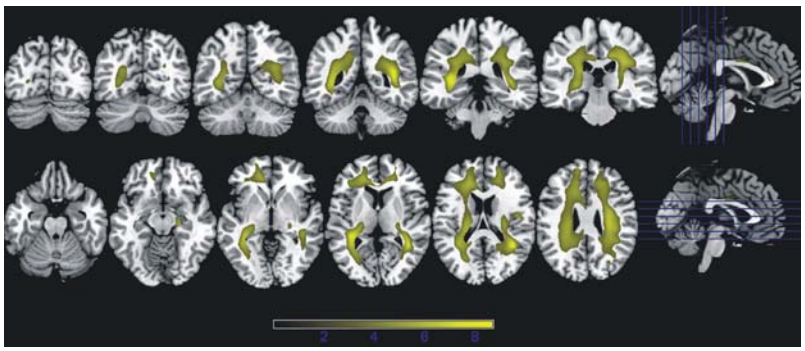

Figura 4. Mapa estatístico de áreas com recuperação de SB identificadas no *grupo recuperação parcial* quando comparado ao grupo controle. O mapa foi sobreposto a um "template" do tipo T1.

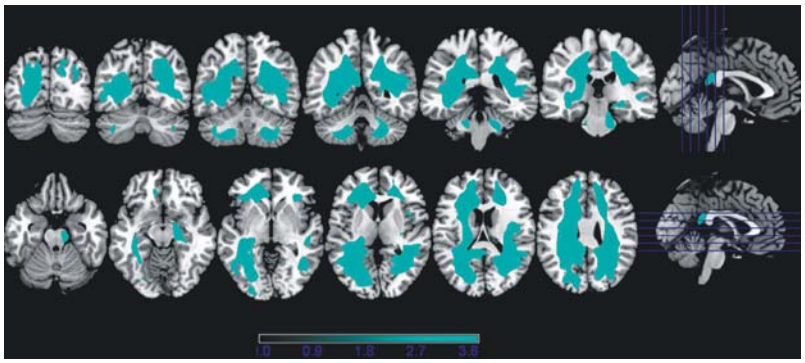

Figura 5. Mapa estatístico de áreas com recuperação de SB identificadas no *grupo livre de crises*. O mapa foi sobreposto a um "template" do tipo T1.

Acreditamos que a recuperação de concentração de SB não seja um processo isolado e único; ao contrário, deve ser resultante de uma combinação de fatores envolvendo a reversão de disfunção metabólica, plasticidade neuronal com sinaptogênese secundária e "sprouting" de dendritos e neurogênese. Embora os mecanismos de reparo ainda não tenham sido totalmente elucidados podemos especular idéias de que tais áreas recuperadas possam estar relacionadas com a reversão de disfunção neuronal, expressas através da melhora em testes cognitivos após a cirurgia em pacientes com controle de crises.[31]

A evidência de reversibilidade das lesões cerebrais causadas pela epilepsia crônica nos leva a enfatizar o conceito de que a cirurgia precoce para casos refratários deve prevenir danos além de permitir a restituição da atividade cerebral normal antes que a vida social desses indivíduos seja devastada pelo estigma e preconceito das crises recorrentes.

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CAPÍTULO 4

Artigo *"Dynamic changes in white and gray matter volume are associated with outcome of surgical treatment in temporal lobe epilepsy"*

Submetido à revista NEUROIMAGE

Dynamic changes in white and gray matter volume are associated with outcome of surgical treatment in temporal lobe epilepsy

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Abstract

Background: The reasons for surgical failure in 30% of patients with unilateral MTLE are still unclear. We investigated if different outcomes could be associated to different patterns of subtle gray matter (GMA) and white matter) atrophy(WMA, and searched for post-operatory structural changes.

Methods: We studied 69 controls and 67 operated patients with refractory unilateral MTLE. Patients were grouped as *Seizure Free (SF)* group (34 patients Engel's IA), worthwhile *Improvement group* (23 patients, Engel's IB-IIA) and *Failure group* (10 patients Engel's IIB-IV). We created a Voxel Based Morphometry/MATLAB code to mask the surgical lacuna, and performed T-test and paired T-test to evaluate pre and post operative MRI scans.

Results: *Failure-group* showed a widespread pattern of preoperative GMA. On *SF* and *improvement groups* we identified a more restricted pattern of GMA. The three groups presented a widespread, bilateral pattern of WMA. In contrast, post-operative analyses showed bilateral hemispheric recovery (a relative increase of WM concentration) on *SF* and *improvement groups*, but few changes on *failure group*. We also identified areas with relative postoperative increase of GM on both *SF* and *improvement groups*, more widespread on *SF* group.

Conclusion: Areas of subtle GMA may be related to poorer surgical outcome. In addition, we demonstrated a post-operative relative increase of WM and GM concentration associated with seizure control. These changes may represent neuroplasticity related to improvement of brain function after seizure control. Further studies with a multimodal approach may help to predict surgical outcome and improve selection of patients for surgical treatment of MTLE

Introduction

Surgical treatment for refractory unilateral mesial temporal lobe epilepsy (MTLE) has been indicated with a successful rate of complete seizure freedom of about 70%(ENGEL, JR. 1993). Regardless restricted and uniform selection of candidates with unilateral hippocampal atrophy associated to ipsilateral EEG seizure onset, one third of patients do not become seizure free after adequate resection of medial structures of temporal lobe(WIEBE *et al.* 2001;YASUDA *et al.* 2006). The surgical approach, selective amygdalohippocampectomy or anterior temporal lobectomy, appears to have no influence in outcome (ARRUDA *et al.* 1996;PAGLIOLI *et al.* 2004).

The perpetuation of seizures after surgery is multifactorial and results from the combination of facts that include insufficient resection of hippocampus, amygdala, parahippocampal gyrus and enthorinal cortex(SIEGEL *et al.* 1990;BONILHA *et al.* 2007b), bilateral hippocampal atrophy, multiplicity of potential ictal generators within the temporolimbic system (WENNBERG *et al.* 2002), along with the post-operative persistence of extralimbic abnormalities that may also be involved in the seizures' generation(BERTRAM 2003). Some preoperative factors are associated to a high probability of achieving seizure control after surgery and include: history of prolonged febrile seizures or multiple seizures in early infancy (6 months to 4 years) (ABOU-KHALIL *et al.* 1993), unilateral hippocampal atrophy (ARRUDA *et al.*1996), interictal temporal hypometabolism on PET scans and age at surgery (TELLEZ-ZENTENO *et al.* 2007). Despite these evidences, our understanding about the functional anatomy of limbic epilepsy is incomplete and the investigation of prognostic tools remains necessary in order to predict individual's surgical outcome and simplify the selection of candidates.

The metabolic recovery of neuronal function after surgery has been described by means of proton MR spectroscopy and ^{18}F-FDGPET (CENDES *et al.* 1997a;HUGG *et al.* 1996;SPANAKI *et al.* 2000), but evidences of associated structural changes are still lacking. In this study we used the Voxel Based Morphometry (VBM) method (GOOD *et al.* 2001) to characterize distinct patterns of preoperative regions with atrophy of both gray

(GM) and white matter (WM) that could be specifically associated to surgical outcome. With the same technique, we also investigated the postoperative MRI changes in WM and GM compared to preoperative MRI on patients rendered free of seizure and on those who were not free of seizures. As we had previously studied the amount of surgical resection relation to surgical outcome (BONILHA *et al.*2007b) we now concentrated in investigating the influence of extrahippocampal subtle morphometric changes in surgical outcome as well as to search for morphometric changes after surgery in patients with refractory mesial temporal lobe epilepsy (MTLE).

Methods

2.1 Patients selection

We selected a group of operated patients with as much as possible homogeneous clinical, EEG and routine MRI preoperative features. All patients underwent our routine outpatient investigation that includes detailed neurological examination, series of electroencephalography (EEG), magnetic resonance imaging (MRI), neuropsychological and psychological assessments. Seizures were lateralized according to the medical history, interictal EEGs and comprehensive neurological examination. Patients with unclear origin of ictal discharges were admitted to the hospital for video-EEG and ictal SPECT when necessary(YASUDA *et al.*2006).

All had clinical and EEG features of MTLE as described previously (ENGEL, JR. 2001), which included clear-cut interictal EEG epileptiform discharges in anterior-infero-mesial temporal regions, absence of EEG abnormalities outside temporal lobe regions; simple partial or complex partial seizures, or both, with characteristics of mesial temporal lobe origin such as rising epigastric sensation, unexpected fear, and other psychic phenomena such as déjà vu and jamais vu, and complex partial seizures with staring, oroalimentary automatisms, dystonic posturing of one hand and post-ictal confusion, and no suggestion of any other partial epilepsy syndrome. Patients had failure of seizure control with at least two anti-epileptic drugs (AED) regimens and seizure frequency of at least one seizure per month over the year before surgery.

The diagnosis of unilateral hippocampal atrophy was carried out by visual analysis of our MRI diagnostic protocol for epilepsy that consists of T1- and T2- weighted MRIs in three orthogonal planes, axial fluid-attenuated inversion recovery, as well as thin coronal (3 mm) T1 inversion recovery (IR) and T2 images as described below. Visual analyses were performed by one of the investigators with experience in neuroimaging in epilepsy (F.C.) who confirmed unilateral hippocampal atrophy, with or without hyperintense T2 signal, absence of mesial temporal atrophy or signal changes in the contralateral hippocampus by visual analyses of routine MRI as well as absence of any other suspected MRI abnormalities, therefore, excluding MTLE patients with bilateral hippocampal atrophy, normal MRI and dual pathology. We also performed hippocampal volumetry in all patients according to an anatomic protocol (BONILHA *et al.* 2004a).

We included 69 controls (39 women, mean age 34.3±11.0 years) and 67 patients, (41 women, mean age 34±10.4 years). We excluded 23 patients with unilateral hippocampal atrophy who had significant artifacts on volumetric (3-D) MRI sequence. Therefore, this group does not represent our surgical series of MTLE.

2.2 Surgical procedure

The surgical approach depended on the surgeon's experience and consisted of anterior cortical resection with amygdalohippocampectomy (16 patients) and selective trans-Sylvian amygdalohippocampectomy (51 patients), both with similar surgical outcome (ARRUDA *et al.*1996). Hippocampal sclerosis was confirmed for all patients after histological analysis which detected the typical pathological findings of mesial temporal sclerosis: presence of gliosis and neuronal loss (predominant in dentate gyrus, CA1 and CA3, with sparing of CA2)(BABB *et al.* 1987).

2.3 Group formation

Between August and November 2007 we updated the outcome of all included patients according to Engel's outcome scale (ENGEL, JR.2001) and separated them in three different groups: *Seizure-free* (SF) group with 34 patients (Engel's: IA), worthwhile

improvement-group with 23 patients (Engel's: 8 IB, 3 IC, 6 ID,6 IIA) and *Failure-group* with 10 patients (Engel's 1 IIB, 6 IIIA, 3 IVA). It is important to state that patients included in this present study do not represent the final outcome of our entire surgical series as we did not include all MTLE patients submitted to surgery as described above.

This study was approved by Ethics Committee of our institution and patients gave us a written informed consent.

2.4 Magnetic Resonance Imaging

2.4.1 ACQUISITION

The MRIs were acquired in a 2T scanner (Elscint Prestige,Haifa, Israel) with the following parameters: (1) *sagittal* T_1 spin echo; 6 mm thick; flip angle, 180°; repetition time (TR), 400; echo time (TE), 12; matrix, 320X320; and field of view (FOV), 25X25cm; (2) *coronal images*, perpendicular to long axis of hippocampus, defined on the sagittal images: (a) T_2-weighted and proton density fast spin echo; 3mm thick; flip angle, 160°; TR, 4600; TE, 108/18; matrix, 256X256; FOV, 22X22 cm; (b) T_1-weighted inversion recovery; 3mm thick; flip angle, 180°; TR 2700; TE, 14; inversion time, 860; matrix, 155X256; and FOV,18X18 cm; (3) *axial images* parallel to the long axis of the hippocampi: (a) T_1-weighted gradient echo; 3mm thick; flip angle,70°; TR, 200; TE, 5.27; matrix, 230X230; and FOV, 22X22 cm; (b) FLAIR (inversion recovery fast spin echo); 5 mm thick; flip angle, 110°;TR, 10099; TE, 90; matrix, 250x250; and FOV, 24X24 cm; and (4) *T_1-weighted 3-dimensional* gradient echo with 1-mm isotropic voxels, acquired in the sagittal plane (1mm thick; flip angle, 35°; TR, 22; TE, 9; matrix, 256x220; and FOV, 25x22cm) (BONILHA *et al.* 2007a).

We used the same 3D protocol for patient's pre and post-operative scans as well as for healthy controls.

2.4.2 MRI VOLUMETRIC ANALYSIS

In accordance with a previously described protocol (BONILHA *et al.*2004a), we performed manual volumetry of hippocampi from patients and controls using DISPLAY (David McDonald, www.bic.mni.mcgill.ca/software) . Besides hippocampal volume we obtained the asymmetry index (AI) for each patient and control (defined as the ratio of the smaller by the larger hippocampus). Volumes and/or AIs that were 2 standard deviations (SD) below the mean values of controls were considered as evidence of hippocampal atrophy. Both hippocampal volumes and AIs were transformed into Z-scores (standardized scores defined by the number of SDs away from the mean of control group) in order to facilitate presentation of data.

2.4.3 IMAGE PREPROCESSING FOR VBM ANALYSES

We used MRIcro (www.mricro.com) (RORDEN *et al.* 2000) to transform the original format (DICOM) to ANALYSE® ,mark the anterior commissure for the normalization process and flipp the brains right hippocampal atrophy in order to combine patients with right and left hippocampal atrophies, avoiding left to right cancelations on VBM analyses. We decided to flip right-sided patients to take advantage of statistical power and improve the probability of detecting areas with atrophy in relation to surgical outcome. Despite some particularities of right and left MTLE, both showed signs of similar pattern of atrophy distribution. As a result, the analysis of patients as a homogeneous group may increase the ability to identify areas with atrophy that are similar to both right and left MTLE and related to surgical results (BONILHA *et al.* 2006). One neurosurgeon (CLY) used the drawing tool to manually segment the surgical lacuna of each patient's post operative volumetric MR scan, creating individual region of interest (ROI), or the mask imaging. Each individual ROI was transformed into binary mask and then smoothed to be applied during the VBM process of post-operative scan.

We used software package SPM2 (Wellcome Trust Centre for Neuroimaging, London, England; www.fil.ion.ucl.ac.uk) on MATLAB 7.0 to apply the technique of VBM to all preprocessed images, both pre and post operative scans.

2.4.4 VOXEL BASED MORPHOMETRY

Voxel Based Morphometry (VBM) has been proposed in 1995 and different methods have appeared since then (ASHBURNER *et al.* 2000). VBM is a technique that uses global information from high resolution MRI for characterizing regional cerebral volume and tissue concentration differences.

The standard VBM method can be summarized by the following sequence of steps:

1. Spatial normalization: All brains in study are transformed to the same stereotactic space by the registration with a T1 template (SPM2 standard template), reducing individual brain size variability. We used the SPM2 default settings for normalization parameter estimation (it included 12 linear parameters and 7x8x7 non-linear functions), as well as a brain mask to ensure that the fit was based on the shape of the brain rather than surrounding scalp. Spatially normalized images are then resliced to an isotropic 1.5mm voxel size.
2. Segmentation: The normalized brains are segmented in gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). We used the automatic segmentation provided by SPM2.
3. Smoothing: The normalized and segmented image is then smoothed by a 10mm full-width at half-maximum (FWHM) isotropic Gaussian kernel filter. This process minimizes inter-individual gyral variability and has the effect of rendering the data more normally distributed (GOOD *et al.*2001).

After Step 3, each voxel of the image is a locally weighted average of GM or WM density from a region of surrounding voxels, and statistical analyses can be performed.

Previous investigators (GOOD *et al.*2001) have identified some limitations of the segmentation used by the standard VBM protocol given that during normalization process

some brain areas with atrophy can be enlarged to match the standard template. Consequently, variations in GM and WM volume from our patients could be "washed out" due to nonlinear spatial normalization process. To overcome this distortion Good et al.(GOOD *et al.*2001) proposed an *optimized method* (*optimized-VBM)* with an additional processing step after segmentation, in order to preserve the volume of a particular tissue (GM, WM or CSF) within a voxel. The process consists in modulating voxel values in the segmented images by determinants derived from the normalization step, compensating the tissue deformation that occurs during the normalization process. The modulated data can be tested for regional differences in volume, and may reveal more subtle abnormalities in GM than the standard version of VBM (KELLER *et al.* 2004).

Besides correcting for volume changes, the *optimized-VBM* takes care of extracting whole-brain from scalps in order to achieve more accurate spatial normalization and segmentation steps.

Optimized-VBM and surgical resections

The *optimized-VBM* can be easily implemented by a MATLAB routine using SPM, since SPM has already efficient implementations of each step of the protocol.

Nevertheless, VBM has been widely used for the analysis of differences between individuals with different ages or gender, or differences between normal and pathological, without any surgical intervention. We have not found any application of VBM to study differences between the same brain prior to and subsequent to a surgical resection.

The presence of surgical *lacunae* or other focal lesion lead to a problem during the normalization and segmentation steps, since these steps use global information of the brain and global information of the template brain; in view of the fact that the template does not have the same lacunae as the post-surgical brain, such comparisons are not possible. The spatial normalization of images with focal lesions (as surgical lacunae) with application of automated algorithms attempts to reduce the image mismatch between the image and the template at the site of the lesion, leading to significant image distortion. The proposed solution to overcome this distortion is to use cost-function masking (masking the areas used

in the calculation of the image difference) to exclude the area of the lesion during the process and avoid bias during the transformations (BRETT *et al.* 2001) Supplemental data-Figure.1.

The implementation of spatial normalization available in SPM2 allows the application of a mask over the *lacunae*, so the registration process simply ignores the information under such mask and prevent the lacunae to contribute to the normalization [Brett *et al.* 2001]. Normalization with masks has already been correctly validated and is widely used by researchers in neuroimaging (CRINION *et al.* 2007). Since there is a validated solution for normalization, the segmentation is no longer a problem.

To analyze the post-operative scans we have implemented a modified version of the SPM segmentation, which accepts a mask as parameter and ignores, for global features computations, every voxel inside the region of the mask. Consequently, we have an *optimized-VBM-lesion*, with preserved defaults settings present in the original protocol, which permits VBM to be applied to brains with lacunas or lesions.

For the controls and patient's pre-operative MR scan we applied the built in *optimized VBM* routine, and for the post operative MR scans, we applied the new routine, *optimized-VBM-lesion* that requested individual masks for completing the process. After this step we obtained pre and post-operative individuals maps of GM and WM, both registered to the same stereotactic space, allowing us to compare them with those of healthy controls as well as between themselves, in a paired T-test (before and after surgery).

The MATLAB/SPM script is available online as a supplemental material of this article.

2.4.5 STATISTICAL ANALYSIS OF VBM

The whole-brain voxel analyses were corrected for multiple comparisons trough false discovery rate statistical threshold of 1% (GENOVESE *et al.* 2002), with an extent threshold looking for clusters with at least 32 contiguous voxels. This implicates that

approximately 1 of 100 voxels identified as statistically significant is actually a false positive.

We confirmed the stereotaxic coordinates provided in the SPM output by visual analyses and further converted them to anatomical names with the use of the MNI Space Utility and Talairach Space utility, running these routines on SPM (for the algorithms, see http://www.ihb.spb.ru/~pet_lab/MSU/MSUMain.html)(KOROTKOV *et al.* 2005).

For voxel-wise analysis we used T-test to compare patients with controls and paired T-test to compare pre and post-operative images from patients. All tests were performed on SPM2. The contrasts on 2 tailed paired T-test were defined to reveal areas of WM /GM increase and decrease after surgery. The analyses included proportional threshold masking (set to 0.8) and implicit masking.

The output for each comparison is a statistical parametric map of the *t statistic* (SPM t), which is transformed to a normal distribution map (SPM z). The maps were overlaid on a multislice display of coronal images of a smoothed T1-MRI template (simultaneous GM and WM results) with correspondent Z-score bar for each map. We used a SPM routine "display_slices" (http://imaging.mrc-cbu.cam.ac.uk/imaging/DisplaySlices) to build the structural T1 MRI slices. The smoothed brain was chosen since the results were obtained from smoothed data (RIDGWAY *et al.* 2008).

To assure the reliability of the comparisons among scans we divided the control group in two subgroups with similar age and sex distribution (Group1: 34 individuals (19 women, 34.1 ± [11.3] years and Group2: 35 individuals (20 women,34.4±[10.7] years of age) and performed a 2-tailed T-test between them in search of areas with either excess or atrophy of GM and WM. Absence of abnormal areas of GM and WM in this analysis gives further support against false positive findings (Supplemental data-Figure2).

With the purpose of certifying that the surgical lacuna had been properly preserved during segmentation process we also performed a T-test between the pre and post operative GM extracted maps, expecting an extremely high T-statistic over left hippocampus. (Supplemental data-Figure3).

2.5 Statistical analyses of clinical data

We used SYSTAT 12 (San Jose, California, USA, Systat Software Inc**.** -SSI) to analyze clinical variables from patients and controls. We used T-test with Bonferroni's correction to compare continuous data between patients and controls. For categorical variables we used Pearson χ^2 and Fisher's exact test. ANOVA with post hoc Turkey's HSD was used to compare means between the 3 groups.

Results

No statistically significant differences were observed between groups of controls and patients on gender (p=0.58) and age (p=0.89).

Clinical data of three groups are summarized in Table1. No significant differences between groups were identified in view of the age of the first seizure or age at surgery. In contrast, the duration of epilepsy was shorter in *improvement-group* compared to *SF-group* (p=0.046) and the follow up of the *improvement-group* was shorter than both *SF-group* (p=0.004) and *failure-group* (p=0.001). Febrile seizures were also more frequent on both *SF* and *improvement group*. The *failure-group* presented longer interval between surgery and post-operative scan than *improvement-group* (p=0.02). We observed differences in AI between *SF-group* and *failure-group* (p=0.04) and between *improvement-group* and *failure-group* (p=0.025), but not between *SF-group* and *improvement-group* (p=0.89).

Gray Matter atrophy(GMA):

Compared to controls, the distribution of areas with GMA was distinct for each of the three groups. *SF- group* showed atrophy within ipsilateral temporal lobe, thalamus, caudate and insula. In frontal lobes we found atrophy within bilateral inferior and middle frontal gyri, but ipsilaterally on superior frontal gyrus. We also identified areas of atrophy within bilateral cuneus and cerebellum. Some areas with GM atrophy were identified in ipsilateral lingual and middle occipital gyri (Table 2, Fig.1A).

A restricted pattern of GMA was identified on worthwhile *improvement-group*. Few areas within ipsilateral temporal lobe (hippocampus and parahippocampal gyrus) showed significant GMA. We observed atrophy in basal ganglia, ipsilateral thalamus and caudate, bilateral middle frontal gyri and ipsilateral superior frontal gyrus. In occipital lobe, only

contralateral cuneus showed atrophy. There was also bilateral cerebellar atrophy in this group (Table3, Fig. 1B).

Failure group showed a more widespread pattern of GMA. We identified significant GMA within both temporal lobes (more extensive ipsilaterally), insula, frontal and parietal lobes. We also observed atrophy on ipsilateral caudate and thalamus, and contralateral occipital lobe and cerebellum (Table4, Fig. 1C).

White Matter atrophy (WMA):

SF-group showed WMA in a restricted pattern, on bilateral precentral and postcentral gyri, as well as on inferior parietal lobule and supramarginal gyrus. Some areas with WMA were also found on ipsilateral cerebellum, cingulate gyrus, parietal and occipital lobe. Contralateral atrophy was identified on insula and on superior and middle frontal gyri (e-Table 5)(Figure 1A).

The *improvement-group* showed WMA within bilateral middle and inferior temporal gyrus, fusiform gyrus, cuneus and precuneus, ipsilateral middle frontal gyrus and contralateral precentral gyrus. In parietal lobe we detected atrophy on ipsilateral superior parietal lobule and on contralateral postcentral gyrus, inferior parietal lobule, supramarginal and angular gyri. We also identified WMA on ipsilateral cerebellum (e-Table 6)(Figure 1B).

We identified significant WM atrophy on *Failure-group* involving bilateral frontal and parietal lobes, ipsilateral cerebellum, cingulate gyrus, middle occipital gyrus and cuneus. Ipsilateral temporal lobe showed more extensive WMA than the contralateral temporal lobe (e-Table 7, Fig. 1C).

Postoperative WM changes

On *SF* group we identified areas with relative increase of WM on ipsilateral frontal lobe and cerebellum when comparing pre and post-operative MRI scans. The relative increase on contralateral hemisphere was more widespread, encompassing cerebellum as well as frontal, temporal, and occipital lobes (e-Table 8, Fig. 2A).

The evaluation of *improvement group* revealed a less extensive pattern of relative WM increase. In this particular group we identified relative increase only in the ipsilateral insula, transverse temporal gyrus, cingulated and inferior frontal gyrus. On contralateral hemisphere we observed the relative increase on cingulate gyrus, medial frontal gyrus and transverse temporal gyrus (e-Table 9, Fig. 2B).

We did not detect areas of post-operative changes of WM in the *Failure group* with FDR1% restrictions, but with a less conservative analysis (without FDR) we observed few areas in the bilateral frontal lobes and contralateral temporal lobe (e-Table 10).

From the 2-tailed paired T-test we also investigated areas with more atrophy in the post-operative scan, but did not identify suprathreshold results from any of the 3 groups.

Postoperative GM changes

In the *SF-group* we identified areas with relative increase of GM within the ipsilateral parietal and frontal lobes, as well as on transverse temporal gyrus. On the contralateral hemisphere the relative increase of GM encompassed more extensive regions on temporal, occipital, parietal and frontal lobes as well as on lentiform nucleus (e-Table 11)(Figure 2A).

The *improvement group* showed areas with relative increase of GM within the ipsilateral superior temporal and middle frontal gyri. We also identified some areas on contralateral hemisphere, involving part of temporal and frontal lobes, as well as on basal ganglia (e-Table 12)(Figure 2B).

In contrast, we did not identify areas with relative increase of GM in the *Failure group* with the restrictions of FDR on statistical analysis. Due to reduced number of patients in this group, we also performed less conservative analysis (without FDR), and identified few areas with relative increase of GM concentration in contralateral temporal lobe and insula. (e-Table 13).

From the 2-tailed paired T-test we also analyzed areas with more atrophy in the post-operative scan, compared to the pre-operative set of scans. We identified areas with more GMA after surgery in the ipsilateral temporal lobe, on both *SF-group* and *improvement-group* (confirming the surgical resection of hippocampus, T statistics 6.91-11.25), and in the contralateral temporal and frontal lobes of *improvement group*. (e-Tables 14 and 15, e-Figure 4A, B).

Although we did not identify areas with more post-operative GMA in the *Failure group* with restrictions of FDR 1%, we performed a less conservative analysis (without FDR) and observed a widespread pattern of post op GMA, involving ipsilateral hemisphere (confirming the mesial resection, T statistic 6.33-8.23), and the contralateral frontal and parietal lobes (e-Table 16, e-Figure 4C) .

Discussion

WM and GM patterns of atrophy

As the reasons for surgical failure remain unclear, we investigated the hypothesis that distinctive pre operative patterns of GMA and WMA would be related to different surgical outcome. The results outlined in this study revealed that patients exhibiting a widespread and bilateral pattern of GMA presented the worst outcome.

Areas with GM and WM atrophy on patients were not restricted to the ipsilateral temporal lobe, but instead encompassed both extratemporal and bilateral regions. As previously described by other authors we recognized areas with GM atrophy on bilateral temporal, frontal, parietal and occipital lobes, as well on cerebellum (BABB 1991; CENDES *et al.* 1997b; BONILHA *et al.*2007a;ARRUDA *et al.*1996). We also identified atrophy on subcortical regions including bilateral basal ganglia and insula (PULSIPHER *et al.* 2007). Bilateral thalamus atrophy was presented in all three groups, suggesting its participation in the seizure spread (GUYE *et al.* 2006). The analysis of WM atrophy also showed a bilateral temporal and extratemporal pattern, which had already been described with diffusion tensor imaging (DTI) (CONCHA *et al.* 2007).

In this study we confirmed previous findings (KELLER *et al.* 2007) which described an association of refractory post-operative seizures and widespread ipsilateral and bilateral pre-operative temporal lobe GM abnormalities. In addition, possibly due to a larger number of studied individuals, we could identify extratemporal areas with both GM and WM atrophy. Compared to controls, the *Failure-group* in our study showed areas of significant GM atrophy on contralateral hemisphere that were undetected by visual analysis (ARAUJO *et al.* 2006;MARGERISON *et al.* 1966). We believe that this widespread GM atrophy, in particular within contralateral temporal lobe, may be at least partially involved in the persistence of seizures after adequate removal of mesial structures of temporal lobe, in accordance with previous studies that also showed a poor surgical outcome related to bilateral pathology (ARRUDA *et al.*1996) or contralateral cortical hypometabolism on ^{18}FDG PET (CHOI *et al.* 2003). WM atrophy in this group was evident in the two hemispheres, sparing only contralateral occipital and part of parietal lobes. The underlying abnormality of WM is still unclear and some studies have suggested some processes like increased neuronal heterotopia (HAMMERS *et al.* 2002;SANKAR *et al.* 2007), microdysgenesis (THOM *et al.* 2000), myelin dysfunction and demyelination (MITCHELL *et al.* 2003). Another study evaluated extratemporal WM abnormalities with DTI (GROSS *et al.* 2006) and showed evidences of myelin degradation on external capsula and corpus callosum, but was unable to associate it with a worse surgical outcome. Unlike GM atrophy, the pre-operative WM atrophy in our study did not allow us to establish a specific pattern for each group. Therefore, we could not associate the pattern of widespread, bilateral WM atrophy to a poor surgical outcome.

We identified a more restricted pattern of GM atrophy on *SF-group,* but different from a previous study (KELLER *et al.*2007), we found bilateral atrophy on frontal lobes. This may be, in part, due to the larger number of individuals in our study. The association between unilateral mesial atrophy and good prognosis has been described previously (CENDES *et al.* 1996; ARRUDA *et al.*1996) and our results are in agreement with these, although we selected only patients with unilateral hippocampal atrophy on visual MRI analysis and hippocampal volumetry. In fact, we detected other extrahippocampal areas

with GM abnormalities that may be associated with hippocampal sclerosis, but we are not able to confirm if these findings lead to seizures or are consequence of repeated seizures. A previous study showed reduction of GM concentration in these areas which were negatively correlated with duration of epilepsy (BONILHA *et al.*2006). In contrast, prospective studies were unable to associate duration of epilepsy and surgical outcome (SPENCER *et al.* 2005b). Facing these observations we believe that these differences in extrahippocampal areas with GM atrophy may result from secondary injury caused by repetitive seizures through decades and by the type and severity of the initial precipitating injury (MATHERN *et al.* 1995). Thalamic abnormalities have also been described (BONILHA *et al.* 2005; GUYE *et al.*2006) and may reflect its association with limbic system in the process of generation and spread of seizures. WM atrophy in this group showed a bilateral pattern, encompassing both temporal and extratemporal areas. Our results are in agreement with a previous DTI study, (GROSS *et al.*2006) that showed similar extensive extratemporal, bilateral WM abnormality without association with a poor surgical outcome. These findings suggest that chronic temporal lobe epilepsy is associated to WM abnormalities, although its underlying pathophysiology is yet to be determined. We can speculate that these chronic abnormalities in WM are possibly related to the cognitive dysfunction in MTLE which etiology has always been difficult to be established (HERMANN *et al.* 2007).

The *improvement group* showed a peculiar pattern of GMA. Despite some similarities with *SF group* (for example, more restricted ipsilateral temporal atrophy), these patients persisted with some seizures after surgery. Facing the pattern of GMA in this group, one could expect the most favorable surgical outcome. We believe that the less favorable outcome in these patients is probably related to other factors, such as different sensitivity to antiepileptic drugs, alternative functional pathways of seizure generation and spread, and suboptimal surgical resection (BONILHA *et al.* 2004b).

Reversible injury

The present data are supported by the findings from previous MRS studies (HUGG *et al.*1996; CENDES *et al.*1997a). By means of whole brain analysis we could detect the

same pattern of WM recovery not only in temporal lobes, but within both hemispheres. Previous studies with proton MR spectroscopy were unable to assess the whole brain at once, instead, they used selected regions, as part of temporal white matter or corpus callosum, to evaluate changes after temporal surgery (SPENCER *et al.* 2005a; SPANAKI *et al.*2000;HUGG *et al.*1996). So far, no previous study showed similar, whole brain analysis with evidences of WM and GM post-operative changes, but one study outlined evidences of neuroplasticity by application of *optimized VBM* on MR scans from normal individuals pre and post-transcranial magnetic stimulation (MAY *et al.* 2007).

We observed that the WM changes after surgery were related to better seizure control, as we were unable to detect areas of recovery on the failure group (CENDES *et al.*1997a) Unlike our results, one previous study showed the persistence of bilateral WM diffusion changes after surgery (CONCHA *et al.*2007) and suggest that the abnormalities on WM are probably secondary to structural damage (e.g. myelin degradation). The use of different techniques and the larger number of individuals in our study may explain these different results. Another study using DTI analysis found evidences of WM recovery on contralateral occipital lobe after unilateral occipital lobectomy, suggesting plasticity changes for adaptive response (GOVINDAN *et al.* 2008).

The reasons for reversible WM abnormalities are yet to be determined. Some possible explanations are based on evidences of reversible metabolic impairment after removal of metabolic stress, neuronal plasticity with secondary synaptogenesis and dendritic sprouting (MAY *et al.*2007; MAJEWSKA *et al.* 2006). We believe that the recovery might be resultant from the combination of these hypothesis, rather than the result from a single process. Even though the mechanisms of repair are still unclear, we can hypothesize that the recovery areas are probably related to the reversible neuronal dysfunction, expressed as postoperative seizure freedom and improvement on neuropsychological tests in some of these patients (JOKEIT *et al.* 1999).

In our study we identified some areas with relative increase of GM, more expressive on *SF group* than on *improvement group*. Axonal and dendritic arborization, in addition to

neuronal size and number, appear to be important contributors to the density of gray matter observed in MRI (MECHELLI *et al.* 2005). This finding reinforces the main idea that the seizure control may related to a combination of changes in density of dendritic spines and the remodeling of connectivity through these synapses. The connections between basal ganglia and orbitofrontal regions (BARBAS 2007) as well those between basal ganglia and mesial temporal lobe (SEGER 2006) may be relieved after reduction of seizures, resulting in a functional recovery previously described in children(GLEISSNER *et al.* 2005).

Despite the evidences of recovery from chronic brain injury, we are not able to assure this phenomenon is time independent. It is possible that the poorer performance on neuropsychological tests of elderly (GRIVAS *et al.* 2006) who undergo surgical treatment and the postoperative deteriorations are consequence of a reduced capacity of recovery.

We also observed some areas with postoperative GMA in the ipsilateral temporal lobe of the 3 groups extending beyond the mesial structures, which are probably related to the surgical manipulation and tissue shrinkage after resection (MUELLER *et al.*). Areas with GMA on contralateral hemisphere of *improvement* and *Failure groups* may result from progression of damage. Further studies with larger number of patients are necessary to evaluate the progression of damage after surgery, correlating the structural abnormalities and cognitive dysfunction.

Our results are in accordance with one previous study (SIRVEN *et al.* 2000) which supports the concept that an early surgical intervention for refractory cases should not be delayed. It is possible that early control of seizure may not only prevent further damage but also offer patients a chance to restitute normal brain function.

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	SF GROUP	WI GROUP	F GROUP	P value
Z-scores of Asymmetry index	-6.8±3	-7.2±3	-4.6±3.6	Anova p=0.024
First seizure (years)	5.2±4.0	4.6±3.9	8.4±7.0	Anova p=0.087
Duration of epilepsy (years)	26.5±10.9	33.4±9.5	24.4±11.8	Anova p=0.026
Seizure frequency (monthly)	10.6±7.7	9.3±9.3	13.3±11.9	Anova p=0.5
Age at surgery (years)	31.7±10.6	38±9.2	32.8±10.8	Anova p=0.072
Febrile seizure (number of patients)	8	14	2	Pearson χ^2 p= 0.011
Follow up (years)	5.5 ± 2.5	3.5±1.9	6.9±2.6	Anova p<0.0001
Interval of post op MRI(months)	32.2±24.7	21.2±16.6	47.1±35	Anova p=0.02

Table 1. Clinical data from the three groups.
(SF= Seizure Free; WI= Worthwhile improvement; F= failure)

Figure 1. Areas with pre operatory GM and WM atrophy on 3 groups. Statistical maps are overlaid on a multislice display of coronal images of a smoothed T1 template. Each group have 2 maps, GM (red bar) and WM (blue bar), with respective z-score bar. We used the neurological convention, i.e. the right side of the images correspond to the right side of the brain.

A(Seizure free group); B(Improvement Group); C(Failure Group)

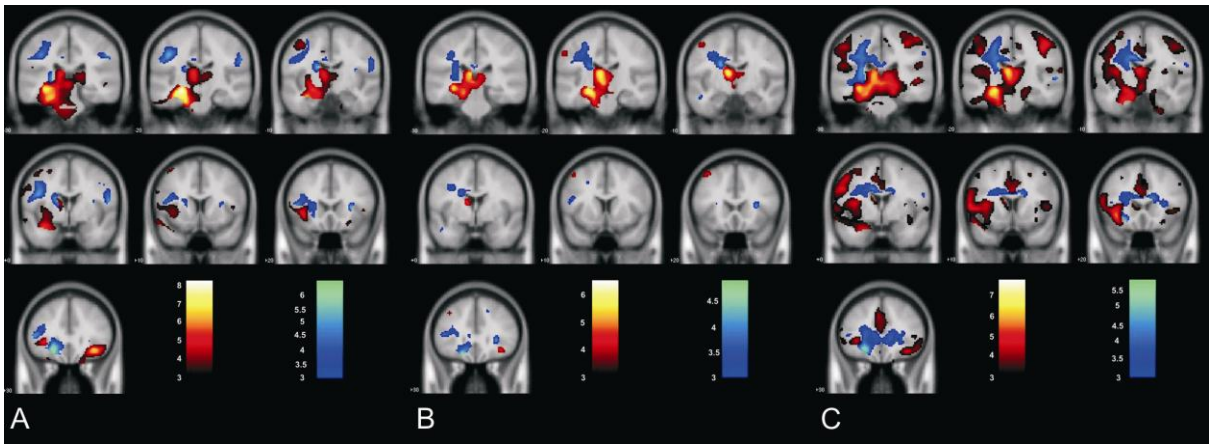
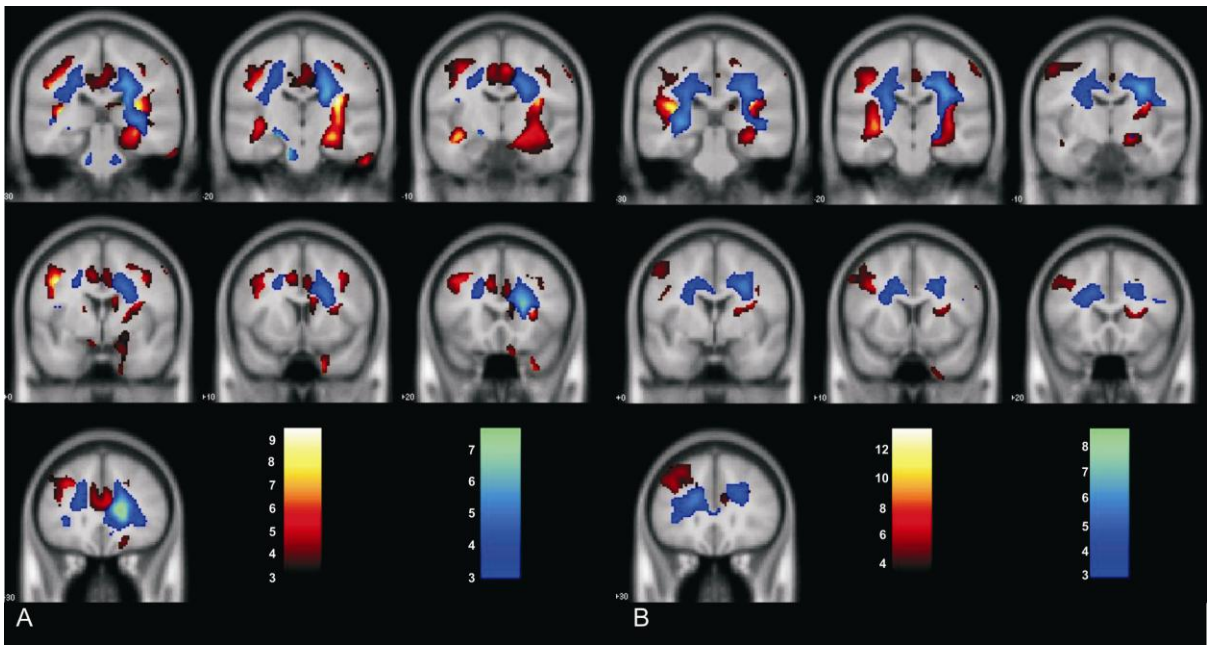
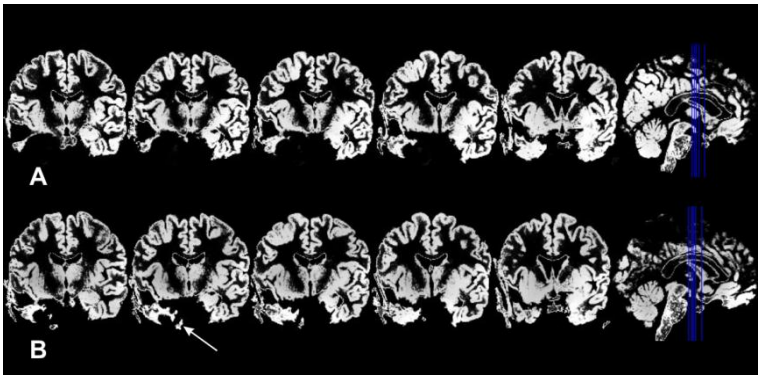


Figure 2. Areas of GM and WM post operatory relative increase on *Seizure free* and *Improvement groups*. Statistical maps are overlaid on a multislice display of coronal images of a smoothed T1 template . Each group have 2 maps, GM (red bar) and WM (blue bar), with respective z-score bar. We used the neurological convention, i.e. the right side of the images correspond to the right side of the brain.

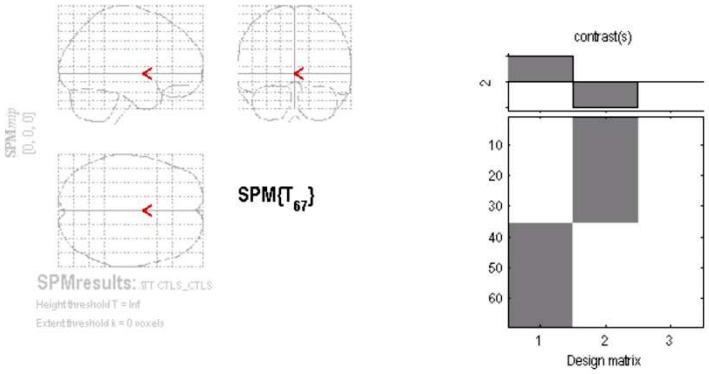
A(Seizure free group); B(Improvement Group)



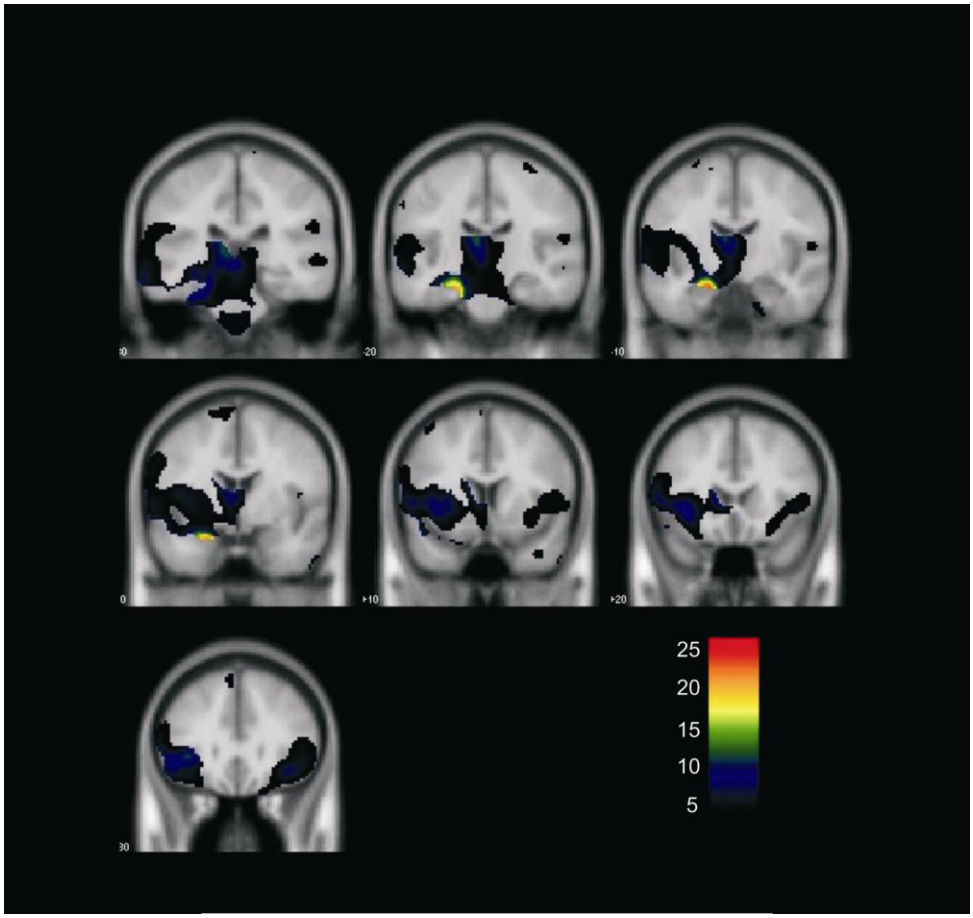
e-Figure 1. GM maps from one operated patient, obtained with cost-function mask (A) and without cost-function mask (B) applied during the normalization process. The white arrow points the left temporal lobe “filled” during the process without mask over the surgical lacunae.



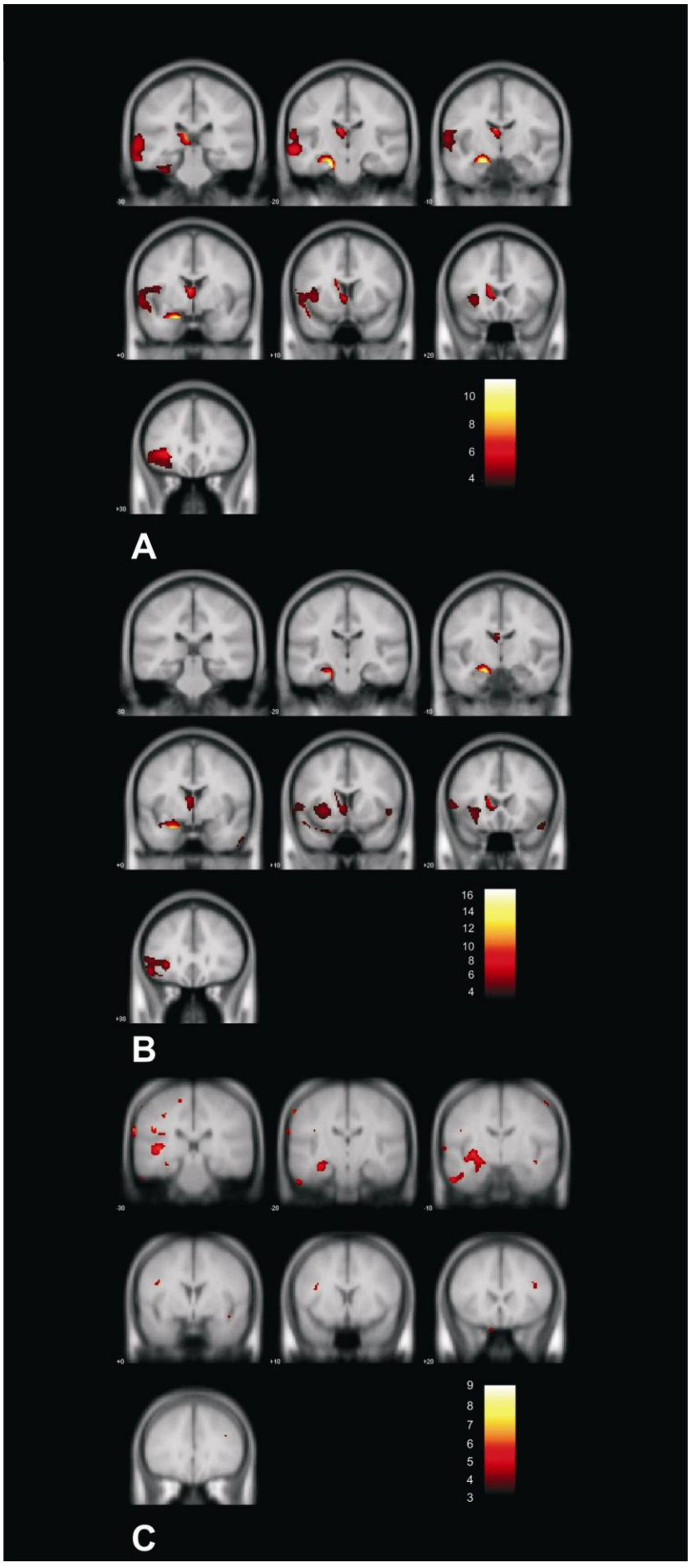
e-Figure 2. Statistical map obtained from the T-test between 2 groups of controls. No suprathreshold results were obtained.



e-Figure 3. Comparison between post- operatory and pre-operatory GM maps, showing the surgical lacunae over left hippocampus. We used the neurological convention, i.e. the right side of the image corresponds to the right side of the brain.



e-Figure 4. Areas of GM atrophy on post-operatory MR, from paired analyses. Statistical maps are overlaid on a multislice display of coronal images of a smoothed T1 template. Each group has 1 map, GM (red bar) with respective z-score bar. We used the neurological convention, i.e. the right side of the images corresponds to the right side of the brain.
A (Seizure free group); B(Improvement Group); C(Failure Group)


10
8
6
4
A
16
14
12
10
8
6
4
B
9
8
7
6
5
4
3
C

Optimized VBM with mask

```
% Optimized VBM with lesions.
% André Vital Saude
% saude@dcc.ufla.br
%
% This script is based on optimized_vbm.m, by Chris Rorden.
%
% Code lines removed from the original script were not deleted,
% but commented with %%% avs
%
% Single code lines added or modified by Saude are marked with the
% comment: %avs%
%
% Code blocks added by Saude begin with the comment %avs% and end
% with %--%


spm_defaults
global defaults
dseg                = defaults.segment;
dseg.write.wrt_cor  = 0;
dnrm                = defaults.normalise;
dnrm.write.vox      = [1 1 1];
dnrm.write.bb(1,3)  = -70;
dnrm.estimate.graphics = 0;
dnrm.estimate.weight = fullfile(spm('Dir'),'apriori','brainmask.mnc'); %avs% based on
Chris Rorden's lesionmask.m
```

```
V   = spm_vol(spm_get(Inf,'*.IMAGE','Select images'));     % V:   input image
VG0 = spm_vol(fullfile(spm('Dir'),'templates','T1.mnc'));  % VG0: T1 template
VG1 = spm_vol(deblank(dseg.estimate.priors(1,:)));         % VG1: all segmentation
templates


totalstart = cputime;
for i=1:length(V),
  subjectstart = cputime;
  [pth,nam,ext] = fileparts(V(i).fname);
  fprintf('VBM ON: %s\n',V(i).fname);

  %avs%
  % VWF: a lesion mask for V(i)
  % if there is one common lesion mask see optimized_vbm_lesion.m .
  wtsrcName = fullfile(pth,['m' nam ext]); %the mask image has the prefix 'm'
  VWF = spm_vol(wtsrcName);  % the lesion with prefix 'm'
  %--%

  %VT  = spm_segment(V(i),VG0,dseg); %%% avs
  VT  = spm_segment_lesion_individualmask(V(i),VWF,VG0,dseg); %avs%

  VT  = VT(1);
  %prm = spm_normalise(VG1,VT,",",",",dnrm.estimate); %%% avs
  prm = spm_normalise(VG1,VT,",dnrm.estimate.weight,VWF,dnrm.estimate); %avs%
  clear VT
```

```
  VN  = spm_write_sn(V(i),prm,dnrm.write);
  %VT  = spm_segment(VN,eye(4),dseg); %%% avs
  VT  = spm_segment_lesion_individualmask(VN,VWF,eye(4),dseg); %avs%
  clear VN

  VT(1).fname = fullfile(pth,['G' nam ext]);
  VT(2).fname = fullfile(pth,['W' nam ext]);
  spm_write_sn(VT(1),prm,'modulate');
  spm_write_sn(VT(2),prm,'modulate');
  clear VT

  disp(sprintf('time to process one subject %12.2f\n',cputime-subjectstart));
end;
 disp(sprintf('time to process all subjects %12.2f\n',cputime-totalstart));
```

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E-Table 2. Results from whole brain parametric analyses, areas with pre-operative GM atrophy on *Seizure-free group*.

Hemisphere, anatomical location		Voxel wise			MNI spatial coordinates
	cluster size	p(FDR-cor)	T	equivZ	x,y,z (mm)
1. Left. Hippocampus, parahippocampal gyrus, amygdala	114568	0.000	8.29	7.23	-24 -20 -12
Fusiform gyrus, thalamus, caudate.		0.000	7.34	6.55	-32 -34 -7
		0.000	6.94	6.26	-25 -35 -19
2. Left. Precentral gyrus, middle frontal gyrus.	4011	0.001	4.34	4.15	-40 -10 51
		0.001	4.00	3.84	-39 9 60
		0.002	3.95	3.80	-28 -3 54
3. Left. Superior temporal gyrus, supramarginal gyrus.	2326	0.000	5.53	5.16	-48 -51 16
4. Left. Inferior frontal gyrus, precentral gyrus.	1432	0.000	4.55	4.33	-57 4 32
5. Left. Lingual gyrus.	721	0.000	4.55	4.33	-2 -88 -17
6. Left. Middle occipital gyrus.	520	0.001	4.29	4.11	-37 -96 6
7. Left. Insula, Inferior parietal lobule.	370	0.002	3.84	3.70	-51 -34 23
8. Left. Cingulate gyrus.	263	0.003	3.65	3.53	-10 -6 42
9. Left. Inferior frontal gyrus.	185	0.004	3.63	3.51	-29 33 -22
10. Left. Postcentral gyrus	185	0.004	3.59	3.48	-60 -24 41
11. Right. Inferior frontal gyrus, middle frontal gyrus,	10467	0.000	6.64	6.03	35 30 -11
Orbital gyrus.		0.000	6.49	5.92	41 39 -10

		0.001	4.19	4.01	18 30 -26
12.Right. Cuneus.	1547	0.001	4.00	3.84	5 -85 35
13.Right. Posterior cingulated gyrus.	725	0.003	3.68	3.56	4 -53 7
		0.006	3.40	3.30	6 -58 16
14. Right. Precentral gyrus, inferior frontal gyrus, insula.	548	0.002	3.78	3.64	47 14 6
15. Right. Middle temporal gyrus	235	0.005	3.48	3.37	51 -35 2
16. Right. Middle frontal gyrus	151	0.004	3.54	3.43	25 53 -10

Results reported on a Height threshold: T= 3, FDR (0.01), clusters > 100 voxels.

E-Table 3. Results from whole brain parametric voxelwise analyses, areas with pre-operative GM atrophy on *improvement group*.

Hemisphere, anatomical location		Voxel wise			MNI spatial coordinates
	cluster size	p(FDR-cor)	T	equivZ	x,y,z (mm)
1. Left. Parahippocampal gyrus; Thalamus;Hippocampus;	30073	0.000	6.56	5.92	-29 -36 -4
Caudate.		0.000	5.86	5.38	-10 -9 14
		0.000	6.30	5.72	-22 -20 -12
2. Left. Middle Frontal Gyrus; Superior Frontal Gyrus.	990	0.001	4.60	4.35	-40 16 53
3. Left. Postcentral gyrus; Precentral Gyrus.	700	0.002	4.31	4.10	-57 -26 44
		0.005	3.95	3.78	-58 -19 38
4. Left. Cerebellum.	346	0.002	4.31	4.09	-23 -40 -41
5. Right. Middle Frontal Gyrus; Inferior Frontal Gyrus.	1966	0.001	4.76	4.48	40 40 -10
		0.001	4.51	4.27	35 32 -11
6. Right. Cerebellum.	1496	0.002	4.36	4.14	23 -63 -58
		0.005	3.95	3.78	14 -55 -46
7. Right. Cuneus.	189	0.003	4.16	3.97	4 -89 34

Results were reported on a Height threshold: T = 3, FDR (0.01), clusters >100.

E-**Table4.** Results from whole brain parametric voxelwise analyses, areas with pre-operative GM atrophy on *Failure group*.

Hemisphere, anatomical location	Cluster size	Voxelwise			MNI spatial coordinates
		p(FDR-cor)	T	EquivZ	x,y,z (mm)
1. Left. Hippocampus; Amygdala; Parahippocampal Gyrus; Insula;	216914	0.000	7.70	6.61	-29 -38 -4
Fusiform Gyrus; Transverse temporal Gyrus; Inferior frontal Gyrus;		0.000	6.62	5.87	-24 -20 -13
Postcentral Gyrus; Precentral Gyrus; Thalamus, Caudate;		0.000	6.32	5.66	-7 -22 12
2. Left. Cingulate Gyrus; Medial frontal Gyrus.	31763	0.000	4.48	4.21	-3 44 8
		0.001	4.39	4.13	1 10 29
		0.001	4.28	4.04	-6 5 41
3. Left. Inferior, Middle and Superior temporal gyri; Angular Gyrus;	6261	0.001	4.15	3.93	-60 -69 13
Supramarginal Gyrus		0.001	4.09	3.88	-47 -59 29
		0.001	4.02	3.82	-61 -69 4
4. Left. Inferior Frontal Gyrus	902	0.002	3.81	3.63	-49 42 -14
5. Left. Middle Frontal Gyrus.	238	0.004	3.47	3.33	-31 17 47
6. Left. Precentral Gyrus	126	0.008	3.12	3.02	-26 -27 63
7. Right. Precentral Gyrus; Postcentral Gyrus;	18737	0.000	5.12	4.74	41 -22 46
Inferior Parietal Lobule		0.001	4.31	4.06	40 -33 57
		0.001	4.30	4.06	49 -31 57
8. Right. Inferior Frontal Gyrus; Middle Frontal Gyrus.	13274	0.000	4.63	4.34	36 30 -14

		0.001	4.38	4.13	46 41 -10
		0.002	3.92	3.73	41 23 -1
9. Right. Inferior Frontal Gyrus.	1469	0.002	3.73	3.56	37 4 -16
10. Right. Superior Frontal Gyrus	328	0.004	3.52	3.37	25 9 51
11. Right. Insula; Precentral Gyrus; Inferior Parietal Lobule;	2069	0.001	4.01	3.81	51 -27 19
Postcentral Gyrus.		0.007	3.20	3.09	52 -11 12
12. Right. Inferior Parietal Lobule	392	0.004	3.49	3.36	56 -56 49
		0.004	3.42	3.29	61 -54 43
13. Right. Precuneus; Postcentral Gyrus.	717	0.001	4.08	3.87	9 -60 68
14. Right. Postcentral Gyrus.	467	0.002	3.93	3.74	66 -21 14
15. Right. Middle Occipital Gyrus.	226	0.004	3.47	3.33	21 -90 12
16. Right. Superior Temporal Gyrus	458	0.003	3.59	3.44	62 -4 6
17. Right. Middle Temporal Gyrus	122	0.006	3.27	3.16	52 5 -41
18. Right. Cerebellum	245	0.005	3.39	3.26	54 -62 -42

Results were reported on a Height threshold: T = 3, FDR (0.01), clusters >100.

E-**Table5.** Results from whole brain parametric voxelwise analyses, areas with pre-operative WM atrophy on *Seizure free group*.

Hemisphere. Anatomical location	**Cluster size**	**Voxelwise**			**MNI spatial coordinates**
		p(FDR-cor)	T	equivZ	x,y,z (mm)
1. Left. Sub gyral; Precentral Gyrus; Inferior frontal Gyrus;	36977	0.000	6.48	5.91	-21 27 -9
Postcentral Gyrus; Supramarginal Gyrus.		0.000	5.54	5.16	-46 3 21
		0.000	5.50	5.13	-17 -9 21
2.Left. Lingual Gyrus; Middle Occipital Gyrus; Cuneus.	10694	0.000	6.43	5.87	-16 -86 -7
		0.000	5.69	5.29	-30 -82 11
5. Left. Cingulate Gyrus.	1238	0.000	5.10	4.80	-11 -49 11
6. Left. Cerebellum	1395	0.000	4.95	4.67	-14 -71 -38
		0.001	4.01	3.85	-23 -68 -34
		0.007	3.25	3.16	-25 -57 -33
		0.000	5.45	5.09	-17 -86 13
8. Left. Precuneu; Superior Parietal lobule.	540	0.001	4.16	3.98	-17 -58 57
12. Left. Middle Temporal Gyrus.	270	0.003	3.73	3.60	-43 -59 9
14. Left. Superior Parietal Lobule; Inferior Parietal Lobule.	165	0.004	3.50	3.39	-28 -56 43

3. Right. Inferior Parietal Gyrus; Precentral gyrus; Postcentral Gyrus.	7456	0.000	5.74	5.33	55 -34 40
		0.000	5.68	5.28	56 -40 25
		0.000	5.42	5.07	54 2 16
4. Right. Subgyral; Insula.	1283	0.000	5.54	5.16	29 19 7
		0.002	3.98	3.83	35 -8 16
		0.004	3.52	3.41	34 -18 18
7. Right. Angular Gyrus; Supramarginal Gyrus.	806	0.001	4.49	4.28	51 -55 35
9. Right. Superior Frontal and Middle Frontal Gyrus.	967	0.001	4.05	3.89	19 41 35
		0.002	3.77	3.64	21 48 25
15. Right. Precentral Gyrus; Middle Frontal Gyrus.	107	0.007	3.30	3.21	50 -1 39
		0.008	3.18	3.10	42 -1 40

Results reported on a Height threshold: T = 3, FDR (0.01), clusters >100.

E-Table6. Results from whole brain parametric voxelwise analyses, areas with pre-operative WM atrophy on *Improvement group*.

Hemisphere. Anatomical location	**Cluster size**	**Voxelwise**			**MNI spatial coordinates**
	equivk	p(FDR-cor)	T	equivZ	x,y,z (mm)
1. Left. Middle Frontal Gyrus; Cuneus; Sub-gyral;	141286	0.014	4.92	4.62	-19 29 -17
		0.014	4.47	4.23	-16 -83 29
		0.014	4.25	4.05	-20 -11 25
2. Left. Inferior Temporal Gyrus; Middle Temporal Gyrus; Fusiform Gyrus.	1484	0.014	3.93	3.76	-49 -6 -19
		0.018	3.04	2.95	-41 -7 -31
3. Left. Cerebellum	1117	0.014	3.60	3.47	-11 -71 -31
		0.018	3.05	2.97	-12 -71 -39
		0.019	2.98	2.90	-21 -71 -32
6. Right. Sug-gyral; Angular Gyrus.	2890	0.015	3.41	3.29	48 -56 37
		0.016	3.21	3.11	31 -51 35
9. Right. Cuneus; Precuneus.	812	0.014	3.61	3.48	20 -77 27

Results reported on Height threshold: T = 3, FDR (o.o1), clusters >100 voxels.

E-Table 7. Results from whole brain parametric voxelwise analysis, areas with pre-operative WM atrophy on *Failure group*.

Hemisphere. Anatomical location.	**Cluster size**	**Voxelwise**			**MNI spatial coordinates**
		p(FDR-cor)	T	equivZ	x,y,z (mm)
1. Left. Inferior Frontal Gyrus; Middle Frontal Gyrus;	106000	0.001	5.81	5.28	-26 23 -12
Middle Occipital Gyrus; Cuneus; Supramarginal Gyrus;		0.001	5.16	4.77	-35 -77 10
Cingulate Gyrus; Temporal lobe, Sub-gyral white matter.		0.001	4.79	4.47	-35 -51 -3
2. Left. Cerebellum; Posterior Lobe; Cerebellar tonsil.	9463	0.001	5.39	4.95	-25 -66 -34
		0.002	4.25	4.01	-34 -50 -40
		0.002	4.00	3.80	-36 -58 -44
3. Right. Superior Temporal Gyrus.	234	0.001	5.30	4.88	61 -23 6
		0.002	4.21	3.98	58 -15 2
4. Right. Inferior Parietal Lobule; Superior Temporal Gyrus;	1109	0.002	3.96	3.77	60 -38 36
Supramarginal Gyrus.		0.005	3.27	3.16	45 -39 26
		0.006	3.19	3.09	42 -37 15
5. Right. Precentral Gyrus; Postcentral Gyrus; Inferior Frontal Gyrus.	488	0.004	3.49	3.35	61 -14 20
		0.005	3.30	3.18	58 1 23
6. Right. Superior Frontal Gyrus; Medial Frontal Gyrus.	821	0.004	3.41	3.28	15 47 22

Results reported on Height threshold: T = 3, FDR (0.01), clusters >100.

E-Table 8. Results from whole brain parametric voxelwise analyses, areas with post-operative relative WM increase on *Seizure free group* (Paired analyses).

Hemisphere. Anatomical location.	**Cluster size**	**Voxelwise**			**MNI spatial coordinates**
		p(FDR-cor)	T	equivZ	x,y,z (mm)
1. Right. Frontal lobe, Sub-Gyral; Temporal Lobe Sub-gyral.	143453	0.000	7.69	5.78	18 29 11
		0.000	7.35	5.62	33 -51 2
		0.000	6.68	5.28	32 -38 4
2. Right. Cerebellum, Posterior lobe; Anterior lobe.	4461	0.000	4.65	4.05	20 -48 -45
		0.001	4.23	3.75	16 -32 -32
		0.003	3.49	3.20	37 -60 -40
3. Right. Lingual gyrus; Middle Occipital Gyrus; Cuneus.	201	0.001	3.99	3.58	25 -93 -4
4. Left. Cerebellum, Posterior lobe; Anterior Lobe.	5697	0.000	7.43	5.66	-14 -22 -29
		0.000	5.25	4.45	-18 -34 -33
		0.000	4.90	4.22	-13 -28 -35
5. Left. Inferior Frontal Gyrus; Middle Frontal Gyrus.	503	0.000	4.48	3.93	-34 30 -1

Results reported on Height threshold: T= 3, FDR (0.01), clusters>100

E-Table 9. Results from whole brain parametric voxelwise analyses, areas with post-operative WM relative increase on *Improvement group* (paired analyses).

Hemisphere. Anatomical location	**Cluster size**	**Voxelwise**			**MNI spatial coordenates**
	Equivk	p(FDR-cor)	T	equivZ	x,y,z (mm)
1. Left. Sub-Gyral; Insula; Transverse Temporal Gyrus; Cingulate gryus;	128679	0.000	8.74	5.68	-39 -48 162
1.1. Right. Sub-Gyral; Cingulate; Medial Frontal Gyrus;		0.000	7.78	5.34	33 -36 6
Transverse Temporal Gyrus.		0.000	6.67	4.88	35 -46 9
2. Left. Sub-gyral; Inferior Frontal Gyrus.	175	0.002	4.13	3.51	-46 19 21

Results reported on Height threshold: T = 3, FDR (0.01), clusters>100 voxels

E-Table 10. Results from whole brain parametric voxelwise analyses, areas with post-operative WM relative increase on *Failure group* (paired analyses).

Hemisphere. Anatomical location	**Cluster size**	**Voxelwise**			**MNI spatial coordenates**
	Equivk	p(FDR-cor)	T	equivZ	x,y,z (mm)
1. Left. Sub-gyral, cingulate gyrus;	16338	0.000	5.27	3.47	-24 -43 18
		0.000	5.23	3.46	-6 -3 41
		0.000	5.21	3.45	-21 -36 12
2. Left. Syb-gyral, anterior cingulate, medial frontal gyrus;	3230	0.000	5.50	3.55	-10 41 -3
		0.000	5.38	3.51	-10 43 7
		0.001	4.69	3.25	-20 24 20
3. Right. Sub-gyral, cingulate gyrus, middle frontal gyrus;	9833	0.000	5.69	3.62	19 -5 45
		0.000	5.48	3.55	24 -19 49
		0.000	5.40	3.52	32 12 36
4. Right.Sub-gyral, inferior parietal lobule;	223	0.000	4.97	3.37	45 -28 26
5. Right. Anterior cingulate, medial frontal gyrus;	204	0.000	4.95	3.36	11 37 19
		0.001	4.45	3.16	17 33 24
6. Right. Parahippocampal gyrus;	180	0.001	4.58	3.21	17 -13 -18
		0.001	4.37	3.12	22 -11 -11

Results reported on Height threshold: T = 3, no FDR, clusters>100 voxels

E-Table 11. Results from whole brain parametric voxelwise analyses, areas with post-operative GM relative increase on *Seizure free group* (paired analyses).

Hemisphere. Anatomical location		**Voxelwise**			**MNI spatial coordinates**
	Cluster size	p(FDR-cor)	T	equivZ	x,y,z (mm)
1. Right. Insula, parahippocampal gyrus.	148345	0.000	9.55	6.57	32 -23 15
1.1 Left. Precentral Gyrus; Transverse Temporal gyrus; Cingulate		0.000	9.27	6.46	-41 0 36
Postcentral Gyrus; Inferior Parietal Lobule; Supramarginal Gyrus;		0.000	8.44	6.12	-36 -28 8
Angular Gyrus; Middle Frontal and Superior Frontal gyrus.					
2. Right. Precentral Gyrus; Middle Frontal Gyrus.	6495	0.000	7.21	5.55	32 -17 46
		0.000	6.41	5.13	35 4 40
3. Right. Orbital Gyrus; Rectal Gyrus.	776	0.000	6.38	5.11	9 51 -29
		0.000	5.63	4.68	9 43 -31
4. Right. Middle Occipital Gyrus; Supramarginal gyrus;	7207	0.000	6.15	4.99	64 -43 -25
Inferior Parietal Lobule; Superior Temporal Gyrus;		0.000	6.00	4.90	60 -25 -35
		0.000	5.19	4.40	60 -38 49
5.Right. Rectal Gyrus.	714	0.000	5.48	4.59	8 18 -28
6. Right. Middle Frontal Gyrus.	788	0.001	4.69	4.08	22 34 -15
7. Right. Middle frontal gyrus; Superior Frontal Gyrus;	434	0.002	4.29	3.80	23 29 34
Medial Frontal Gyrus.		0.002	4.19	3.72	20 36 29
		0.005	3.65	3.32	24 19 42
8. Left. Orbital Gyrus.	151	0.001	4.43	3.89	-11 40 -31
9.Left. Lentiform Nucleus.	133	0.002	4.17	3.71	-16 0 12

Results reported on Height threshold: T = 3, FDR (0.01), clusters > 100 voxels.

E-Table 12. Results from whole brain parametric voxelwise analyses, areas with post-operative GM relative increase on *improvement group* (paired analyses).

Hemisphere, anatomical location	**Voxel wise**			**MNI spatial coordinates**
	cluster size	p(FDR-cor)	T equivZ	x,y,z (mm)
1. Right. Hippocampus, amygdala, parahippocampal gyrus.	26446	0.000	13.73 6.98	33 -25 21
		0.000	9.76 6.01	40 -41 18
		0.000	9.17 5.83	43 -47 9
2. Right. Precentral gyrus, postcentral gyrus,precuneus.	2953	0.000	6.76 4.92	33 -18 41
		0.000	5.72 4.43	31 -43 39
		0.001	5.40 4.26	26 -42 52
3. Right. Cerebellum.	4625	0.000	5.87 4.51	0 -52 -45
		0.002	4.71 3.88	8 -57 -40
4. Right. Inferior Parietal lobule, postcentral gyrus.	2897	0.000	6.06 4.60	67 -42 36
		0.000	5.95 4.55	62 -45 45
		0.000	5.92 4.53	58 -57 45
5. Right. Medial frontal gyrus, cingulate gyrus.	1506	0.002	4.82 3.94	12 30 19
		0.002	4.78 3.91	8 38 14
		0.006	4.05 3.46	11 27 27
6. Right. Cingulate gyrus, paracentral lobule, medial frontal gyrus.	1502	0.001	5.13 4.12	3 -18 46
		0.007	3.96 3.40	3 -28 45
		0.008	3.91 3.37	-3 -17 38
7. Right. Superior temporal gyrus.	480	0.000	6.25 4.69	25 13 -47
8. Right .Superior frontal gyrus.	344	0.001	5.55 4.34	15 60 -24

			0.004	4.40	3.69	15 67 -18
9.	Right. Inferior temporal gyrus.	286	0.002	4.80	3.93	65 -45 -24
10.	Right. Inferior frontal gyrus, precentral gyrus, middle frontal gyrus.	254	0.001	5.62	4.38	36 2 29
			0.009	3.82	3.31	43 -3 34
11.	Right. Fusiform gyrus, sub gyral.	210	0.002	4.82	3.94	47 -44 -7
			0.006	4.08	3.48	47 -40 -14
12.	Right. Superior frontal gyrus.	181	0.002	4.93	4.00	27 41 15
			0.007	3.99	3.42	28 35 22
13.	Right. Middle occipital gyrus, middle temporal gyrus.	158	0.000	5.79	4.47	36 -71 10
14.	Right. Lingual gyrus.	128	0.005	4.24	3.59	20 -71 -4
			0.008	3.87	3.34	66 -49 -17
15.	Left. Transverse temporal gyrus, insula, precentral gyrus, postcentral gyrus, inferior parietal lobule, middle frontal gyrus	41702	0.000	11.89	6.58	-35 -29 10
			0.000	11.60	6.51	-40 -31 17
			0.000	10.27	6.16	-46 -33 22
16.	Left. Middle temporal gyrus, superior temporal gyrus.	968	0.000	7.19	5.10	-41 -61 12
17.	Left. Anterior cingulate, medial frontal gyrus.	556	0.002	4.86	3.96	-16 44 10
			0.003	4.65	3.84	-13 37 13
			0.004	4.43	3.71	-16 45 0
18.	Left. Cingulate gyrus.	251	0.004	4.33	3.65	-6 -33 31
19.	Left. Cerebellum	173	0.002	4.88	3.97	-42 -41 -45
20.	Left.Angular gyrus.	100	0.003	4.61	3.82	-40 -57 29

Results reported on Height threshold: T = 3, FDR (0.01), clusters > 100 voxels.

E-Table 13. Results from whole brain parametric voxelwise analyses, areas with post-operative GM relative increase on *Failure group* (paired analyses).

Hemisphere,anatomical location	**Voxel wise**				**MNI spatial coordinates**
	cluster size	p(FDR-cor)	T	equivZ	x,y,z(mm)
1. Right. Uncus, parahippocampal gyrus;	1230	0.000	7.72	4.18	20 -14 -24
2. Right. Medial frontal gyrus;	428	0.000	7.05	4.01	3 64 9
		0.000	6.96	3.99	2 62 17
3. Right. Cerebellum;	297	0.000	9.92	4.62	38 -84 -43
		0.000	5.21	3.45	31 -88 -42
		0.001	4.48	3.17	27 1 -26
4. Right. Middle and superior temporal gyri;	290	0.000	7.61	4.15	49 11 -18
		0.000	5.32	3.49	42 14 -23
5. Right. Insula	112	0.001	4.61	3.22	37 7 6

Results reported on Height threshold: T = 3, no FDR, clusters>100 voxels

E-Table 14. Results from whole brain parametric voxelwise analysis, areas with GM atrophy on post op *SF group's* MR (paired analyses).

Hemisphere, anatomical location		Voxel wise		MNI spatial coordinates	
	cluster size	p(FDR-cor)	T	equivZ	x,y,z (mm)
1. Left. Hippocampus, amygdala, parahippocampal gyrus.	5419	0.000	11.25	7.16	-19 -15 -22
		0.000	10.47	6.90	-21 -1 -22
		0.000	9.10	6.39	-22 -24 -27
2. Left. Thalamus, caudate nucleus.	8018	0.000	7.77	5.82	-8 -29 10
		0.000	7.71	5.79	-5 -4 14
		0.000	7.25	5.57	-7 -13 19
3. Left. Transverse temporal gyrus, insula, superior temporal gyrus, inferior frontal gyrus.	28162	0.000	6.81	5.34	-61 -21 -6
		0.000	6.74	5.31	-31 31 -2
		0.000	6.30	5.07	-48 15 -18
4. Left. Cerebellum.	509	0.001	5.28	4.46	-52 -65-35

Results reported on Height threshold: T = 3, FDR (0.01), clusters > 100 voxels.

E-Table 15. Results from whole brain parametric voxelwise analysis, areas with GM atrophy on post- op *Improvement group's* MRs (paired analyses).

Hemisphere, anatomical location		Voxel wise			MNI spatial coordinates
	cluster size	p(FDR-cor)	T	equivZ	x,y,z (mm)
1. Left. Hippocampus, amygdala, parahippocampal gyrus.	16198	0.000	17.18	7.59	-19 -16 -23
		0.000	13.36	6.91	-24 1 -24
		0.000	8.88	5.73	-32 27 -5
2. Left. Caudate nucleus.	3861	0.000	8.60	5.63	-12 20 6
		0.000	6.98	5.02	-5 1 8
		0.000	6.51	4.81	-5 -9 20
3. Left. Medial frontal lobe.	5077	0.000	6.98	5.02	-4 58 5
		0.000	6.88	4.98	1 63 -2
		0.001	6.00	4.57	1 60 -13
4. Left. Precentral gyrus, insula.	266	0.002	5.13	4.12	-44 5 10
5. Left. Inferior temporal gyrus, fusiform gyrus.	221	0.005	4.62	3.82	-56 -43 -24
6. Right. Superior temporal gyrus	765	0.002	5.30	4.21	53 17 -15
		0.002	5.12	4.11	49 11 -5
		0.003	4.93	4.00	48 22 -23
7. Right. MIddle frontal gyrus, superior frontal gyrus.	265	0.003	4.86	3.96	28 61 11
8. Right. Inferior temporal gyrus.	174	0.003	4.94	4.01	57 1 -36
		0.005	4.68	3.86	53 -2 -43

Results reported on Height threshold: T = 3, FDR (0.01), clusters > 100 voxels.

E-Table 16. Results from whole brain parametric voxelwise analysis, areas with GM atrophy on post- op *Failure group's* MRs (paired analyses).

Hemisphere, anatomical location		**Voxelwise**			**MNI coordinates**
	Cluster size	P(FDR-cor)	T	Equiv-Z	X,y,z(mm)
1. Left. Hippocampus, amygdala, parahippocampal gyrus,	6943	0.000	8.23	4.29	-46 -45 23
Middle temporal gyrus, superior temporal gyrus, transverse temporal gyrus		0.000	7.98	4.24	-47 -35 3
		0.000	6.33	3.81	-40 -30 3
2. Left. Lingual gyrus, parahippocampal gyrus;	1031	0.000	5.46	3.54	-22 -65 -8
		0.001	4.52	3.19	-15 -71 -3
3. Left. Inferior temporal gyrus, fusiform gyrus;	1021	0.000	7.49	4.12	-55 -15 -35
		0.000	5.10	3.41	-58 -6 -32
		0.001	4.78	3.29	-45 -9 -27
4. Left. Cerebellum;	941	0.000	9.04	4.46	-16 -65 -39
		0.001	4.53	3.19	-10 -69 -32
5. Left. Superior temporal gyrus, inferior parietal lobule, postcentral gyrus;	698	0.000	7.20	4.05	-69 -33 27
6. Left. Posterior cingulate, parahippocampal gyrus;	566	0.000	5.68	3.61	-10 -49 9
		0.001	4.77	3.28	-11 -48 19
		0.001	4.60	3.22	-13 -46 2
7. Left. Insula, inferior parietal lobule,	529	0.000	7.24	4.06	-46 -31 26
		0.000	6.13	3.75	-34 -27 22
8. Left. Insula, precentral gyrus, inferior frontal gyrus;	420	0.000	5.47	3.54	-46 -8 23
		0.000	5.24	3.46	-36 9 18
		0.000	5.13	3.42	-42 -1 26
9. Left. Postcentral gyrus;	126	0.000	5.66	3.61	53 -12 58
	163	**0.000**	**6.26**	**3.79**	**-61 -34 -32**
10. Left. Inferior frontal gyrus, middle frontal gyrus;	158	0.000	9.22	4.49	-54 38 17

		0.000	5.26	3.47	-50 45 18
11. Left. Middle occipital gyrus;	121	0.000	6.15	3.76	-56 -77 5
		0.001	4.69	3.25	-60 -70 0
12. Left. Paracentral lobule;	114	0.000	6.48	3.86	-13 -34 60
13. Left. Rectal gyrus, orbital gyrus;	111	0.000	5.83	3.66	-9 17 -30
	117	0.000	5.79	3.65	-62 -21 47
		0.001	4.68	3.25	-59 -28 53
14. Right. Inferior parietal lobule, supramarginal gyrus;	860	0.000	7.79	4.19	49 -39 25
		0.000	5.06	3.40	46 -33 31
		0.001	4.71	3.26	47 -21 30
15. Right. Supramarginal gyrus, inferior parietal lobule;	767	0.000	5.88	3.68	30 -41 40
		0.000	5.63	3.60	33 -48 36
		0.000	5.42	3.53	48 -41 40
16. Right. Cingulate gyrus, precunes;	472	0.000	6.54	3.87	17 -47 31
		0.000	5.09	3.41	12 -41 29
		0.000	4.95	3.36	11 -33 29
17. Right. Middle frontal gyrus;	331	0.000	4.94	3.35	40 20 21
		0.000	4.81	3.30	37 27 26
18. Right. Superior temporal gyrus;	128	0.000	4.80	3.30	43 -5 -14
		0.001	4.71	3.26	42 4 -13

Results reported on Height threshold: T > 3, no FDR, clusters>100 voxels

E-Table 17. Results from whole brain parametric voxelwise analysis, areas with GM atrophy on post- MRs, compared to pre-operatory MR (T-test).

Hemisphere, anatomical location	**Voxelwise**				**MNI coordinates**
	Cluster size	P(FDR-cor)	T	Equiv-Z	x,y,z(mm)
1. Left. Hippocampus, amygdala, parahippocampal gyrus,uncus;	5040	0.000	17.91	Inf	-19 -12 -21
		0.000	15.17	Inf	-18 -3 -21
		0.000	12.54	Inf	-20 -22 -26
2. Left. Sub-lobar,thalamus, caudate;	5233	0.000	6.54	6.08	-10 20 3
		0.000	6.06	5.68	-5 1 10
		0.000	5.91	5.55	-10 -35 5
3. Left. Insula, inferior frontal gyrus;	5948	0.000	5.83	5.49	-52 36 -11
		0.000	5.53	5.23	-30 25 -7
		0.001	4.50	4.34	-54 39 -2
4. Left. Medial frontal gyrus;	1477	0.000	5.06	4.83	-2 64 -3
5. Left. Middle temporal gyrus, superior temporal gyrus;	591	0.003	4.24	4.10	-67 -27 -16
		0.005	4.03	3.91	-65 -26 -5
		0.007	3.89	3.78	-62 -17 -7
6. Left. Fusiform gyrus, inferior temporal gyrus;	143	0.004	4.08	3.95	-53 -47 -22

Results reported on Height threshold: T = 3, FDR (0.01), clusters > 100 voxels.

CAPÍTULO 5

Artigo *"Brain Morphometry and cognitive differences in familial and sporadic forms of refractory MTLE"*

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"Brain Morphometry and cognitive differences in familial and sporadic forms of refractory MTLE"

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Abstract

Objective: To investigate clinical, neuropsychological and MRI structural abnormalities (grey matter atrophy, [GMA] and white matter atrophy, [WMA]) in patients with sporadic and familial refractory mesial temporal lobe epilepsy (MTLE) who underwent surgical treatment.

Methods: We evaluated 69 operated patients with unilateral MTLE, separating them in *Sporadic-group*: 29 patients (mean age 35.8±10.4 years) and *Familial-group:* 40 patients (32.8±10 years). We performed voxel based morphometry (VBM) on preoperative MRIs and investigated possible clinical and neuropsychological findings between the two groups. We used SPM2 on MATLAB to run VBM and T-test for comparing patients' groups with normal controls.

Results: The *Sporadic group* had lower IQ scores (p=0.01), performed poorer on Boston naming test (p=0.02) and on delayed recall (p=0.03), presented more prominent asymmetry index of hippocampal volume (p=0.04) and more frequent initial precipitating injuries (IPIs) (p=0.04). VBM showed a more restricted pattern of GMA on *Familial-group,* and more bilateral and widespread pattern of GMA on *Sporadic-group*, involving temporal, frontal, parietal and occipital lobes. WMA was widespread and bilateral in both groups.

Conclusions: The more widespread structural VBM abnormalities and worse IQ performance identified in the MTLE *Sporadic-group* may result from stronger environmental influence, including IPIs. This is further support for the hypothesis that in MTLE *Familial-group* hippocampal atrophy is determined by stronger genetic predisposition with less influence of environmental factors as compared to the *Sporadic-group*.

Introduction:

Mesial temporal lobe epilepsy (MTLE) is one of the most common forms of refractory epilepsy referred to surgical treatment. Some of these patients present as sporadic form of the condition, and others have familial recurrence. The development of hippocampal sclerosis in patients with familial mesial temporal epilepsy (FMTLE) appears not to be the result of recurrent seizures, but determined by a strong genetic predisposition (KOBAYASHI *et al.* 2001) . Some of these patients develop refractory MTLE, and the surgical treatment offers a good outcome when unilateral or clearly asymmetric hippocampal atrophy can be identified (KOBAYASHI *et al.* 2003; WIEBE *et al.* 2001) . Patients with familial or sporadic MTLE present similar clinical features and the pre surgical investigation can be performed without distinction between the groups (KOBAYASHI *et al.*2003).

In refractory MTLE, areas with grey matter (GM) and white matter (WM) atrophy have been identified in temporal and extratemporal regions (BONILHA *et al.* 2007b) and may be related to the cognitive impairment present in most of these patients (ALESSIO *et al.* 2006) Surgical treatment has offered chances of functional recovery in addition to seizure control (HELMSTAEDTER *et al.* 2006) as well as post-operatory metabolic recovery as previously described (HUGG *et al.* 1996; CENDES *et al.* 1997).

In this study we aimed to investigate differences in extratemporal GM and WM atrophy between groups of patients with sporadic MTLE and MTLE with family history for epilepsy, as well the differences in the IQ performance.

Methods

Patients:

We included 69 normal controls (39 women), mean age ± SD (34.3±11.1 years) and 69 consecutive MTLE patients, (42 women), mean age ± SD (34.1±10.2 years) who underwent surgical treatment at our institution (ENGEL, JR. *et al.* 1993). Patients underwent a comprehensive preoperative investigation that confirmed clinical and EEG features of unilateral MTLE and MRI evidence of hippocampal sclerosis (YASUDA *et al.* 2006;

ENGEL, JR. 2001). We included patients with unilateral hippocampal atrophy, with or without hyperintense T2 signal, detected by visual analyses on routine MRI with thin coronal cuts and confirmed by hippocampal volumetry performed manually according to an anatomic protocol (BONILHA *et al.* 2004), absence of contralateral mesial temporal atrophy or signal changes, as well as absence of any other suspected MRI abnormalities, therefore, excluding MTLE patients with dual pathology, normal MRI, and bilateral hippocampal atrophy. Clinically, they presented features of typical MTLE (ENGEL, JR.2001), including clear-cut interictal EEG epileptiform discharges in anterior-infero-mesial temporal region; simple partial or complex partial seizures, or both, with typical mesial temporal lobe origin such as rising epigastric sensation, psychic phenomena, complex partial seizures with staring, oroalimentary automatisms, dystonic posturing of one hand and post-ictal confusion, and no suggestion of extratemporal epilepsy syndrome. We confirmed failure of seizure control with at least two anti-epileptic drugs (AED) regimens and seizure frequency of at least one seizure per month over the year before surgery. We considered as possible initial precipitating injury (IPI) the following events: febrile seizures, head trauma with unconsciousness, meningitis, meningoencephalitis and neurocysticercosis (CT scan with calcifications).

Our routine outpatient presurgical investigation included MRI (full protocol described below), electroencephalography (EEG), neuropsychological and psychological assessments. We also performed video-EEG and ictal SPECT for patients with unclear origin of ictal discharges. We excluded 23 patients with significant artifacts on either pre-operative scan; therefore, the patients studied here do not represent our surgical series of MTLE.

One investigator with expertise on MRI and epilepsy (F.C.) performed the diagnosis of unilateral hippocampal atrophy (HA) by visual analyses which were histologically confirmed after surgery, according to typical pathological findings of hipocampal sclerosis: presence of gliosis and neuronal loss (predominant in dentate gyrus, CA1 and CA3, with sparing of CA2)(BABB *et al.* 1987). Sixteen patients had anterior temporal lobe resection with amygdalohippocampectomy and 53 had selective transsylvian amygdalohippocampectomy.

This study was approved by Ethics Committee of our institution and patients gave us a written informed consent.

Clinical classification:

Patients were separated in *Sporadic-group* with 29 patients (11 men, 35.8±10.4years) and *Familial-group* with 40 patients (16 men, 32.8±10 years).

We questioned all patients regarding the occurrence of epilepsy in their families (KOBAYASHI *et al.*2001). For some patients we were unable to confirm MTLE in the affected relatives, because they reside far away from out center and could not come for evaluation. Therefore, it is possible that some of the affected family members of these patients had different phenotypes (CENDES *et al.* 1998). "*Familial epilepsy*" was defined here when there was at least another individual (first or second-degree relative) with epilepsy in the family of the operated patient, and "*Sporadic epilepsy*" was considered if the operated patient was the single individual presenting seizures in whole family up to three generations.

Neuropsychological evaluation:

Neuropsychological preoperative investigation included Wechsler Adult Intelligence Scale – Revised (WAIS-R) to estimate IQ, Boston Naming Test (BNT) Wechsler Memory Scale-Revised (WMS-R) to investigate verbal memory (Logical Memory and Verbal Paired Associates) and visual memory (Figural Memory, Visual Reproduction and Visual Paired Associates). We did not use the same MRI control group for neuropsychological data, as the tests were adapted for our population (ALESSIO *et al.*2006).

Images:

Acquisition: The MRIs were acquired in a 2T scanner (Elscint Prestige,Haifa, Israel) with the following parameters: (1) *sagittal* T_1 spin echo; 6 mm thick; flip angle, 180°; repetition time (TR), 400; echo time (TE), 12; matrix, 320X320; and field of view (FOV), 25X25cm; (2) *coronal images*, perpendicular to long axis of hippocampus, defined on the sagittal images: (a) T_2-weighted and proton density fast spin echo; 3mm thick; flip angle, 160°; TR, 4600; TE, 108/18; matrix, 256X256; FOV, 22X22 cm; (b) T_1-weighted inversion recovery; 3mm thick; flip angle, 180°; TR 2700; TE, 14; inversion time, 860; matrix, 155X256; and FOV,18X18 cm; (3) *axial images* parallel to the long axis of the hippocampi: (a) T_1-weighted gradient echo; 3mm thick; flip angle,70°; TR, 200; TE, 5.27; matrix, 230X230; and FOV, 22X22 cm; (b) FLAIR ((fluid attenuated inversion recovery); 5 mm thick; flip angle,

110°;TR, 10099; TE, 90; matrix, 250x250; and FOV, 24X24 cm; and (4) *T_1-weighted 3-dimensional* gradient echo with 1-mm isotropic voxels, acquired in the sagittal plane (1mm thick; flip angle, 35°; TR, 22; TE, 9; matrix, 256x220; and FOV, 25x22cm) (BONILHA *et al.* 2007a).

We used the same 3D protocol for patients and for healthy controls.

MRI VOLUMETRIC ANALYSIS:

We performed manual volumetry of hippocampi (BONILHA *et al.*2004) from patients and controls using DISPLAY (David McDonald, www.bic.mni.mcgill.ca/software) and obtained the asymmetry index (AI) for each patient and control (defined as the ratio of the smaller by the larger hippocampus). Volumes and/or AIs that were 2 standard deviations (SD) below the mean values of controls were considered as evidence of hippocampal atrophy. Both hippocampal volumes and AIs were transformed into Z-scores (standardized scores defined by the number of SDs away from the mean of control group) in order to facilitate presentation of data.

Pre-processing: We used the MRIcro software to convert the original DICOM format to ANALYZE format (www.mricro.com) (RORDEN *et al.* 2000), mark the anterior commissure (for the normalization process) and flip to left the brains with right hippocampal atrophy in order to simultaneously study right and left hippocampal atrophies, avoiding left-to-right cancelations.

Voxel Based Morphometry: To perform the optimized version VBM (ASHBURNER *et al.* 2000; GOOD *et al.* 2001) we used SPM2 software (www.fil.ion.ucl.ac.uk) on MATLAB 7.0. The standard VBM follows the sequence of processes: normalization, segmentation and smoothing of images. The optimized VBM included a "modulation" step after segmentation, which corrects volume changes that occurs during non-linear spatial normalization. This optimization of VBM is used when GM/WM volume is important instead of GM/WM concentration, and it may reveal more subtle abnormalities in GM volume than with the standard version of VBM.

Statistical analysis: We used SYSTAT 12 (Systat Software Inc**.** -SSI) to analyze clinical variables from groups of patients and controls, by applying T- Test with Bonferroni correction to compare continuous data and Fisher's exact test for categorical variables.

The statistical analyses of images were performed with the SPM2 software, including T-test to compare groups of patients with control group and regression analysis to study the relation between GM and IQ scores. We defined contrasts on T-test to assess areas of specific GM and WM reduction, based on the probability of a voxel being grey or white matter. This analysis included proportional threshold masking and implicit masking.

The regression analysis was performed between the total volume of GM and WM using individual IQ score as regressor. The contrast was created with two one-tailed *t contrasts* representing negative or positive correlation of IQ score and GM amount in each voxel. To control for multiple comparisons we applied family wise error correction with a *P* threshold of 0.05 (FOCKE *et al.* 2008). To focus the analyses where the effects were more intense, we applied an extent threshold looking for clusters with at least 50 contiguous voxels.

The output for each comparison is a statistical parametric map of the t statistic (SPM t), which is transformed to a normal distribution map (SPM z). The statistical significance threshold for the resulting SPM *t* was set at $p<0.05$ (FDR-corrected).

The MNI coordinates resultant from SPM outputs were confirmed visually and then transformed into anatomical names using the routines MNI Space Utility and Talairach Space utility, on SPM2 (for the algorithms, see http://www.ihb.spb.ru/~pet_lab/MSU/MSUMain.html) (KOROTKOV *et al.* 2005).

We used in-built SPM2 routine "display_slices" (http://imaging.mrc-cbu.cam.ac.uk/imaging/DisplaySlices) to show the statistical maps from the SPM overlaid on coronal images of a SPM2's smoothed T1MRI template (RIDGWAY *et al.* 2008) with correspondent Z-score bar for each map (simultaneous GM and WM results).

Results:

No statistically significant differences were observed between groups of controls and patients in regards of gender ($p=0.73$) and age ($p=0.92$).

Patients' groups presented similar pre-operative clinical characteristics, although *Sporadic-group* presented lower educational level ($p=0.03$), accentuated hippocampal asymmetry index ($p=0.04$) and elevated incidence of IPI ($p=0.04$) (Table1).

On neuropsychological tests, *Sporadic-group* performed less well on WAIS-R test (p=0.004), BNT (p=0.02) and WMS-R delayed recall (p=0.03) (Table 2).

GM atrophy (GMA)

From the comparison with control group the *Family-group* presented areas with GMA in the ipsilateral occipital, parietal, insula and temporal lobe (encompassing the hippocampus, amygdala, parahippocampal and superior temporal gyri) and in the contralateral frontal lobe (Figure 1A, e-table 1). The GMA in the *Sporadic-group*, on the contrary, presented a bilateral and widespread pattern, encompassing the entire ipsilateral temporal lobe, as well as areas in the cerebellum, occipital, parietal and frontal lobes. In the contralateral hemisphere GMA was identified in frontal, temporal, and parietal lobes (Figure 1B, e-table 2).

The T-test between groups confirmed more widespread GMA in the *Sporadic-group*, mainly in the contralateral hemisphere, involving both temporal and extratemporal regions (Figure 2, e-table 3 in supplemental material).

WM atrophy (WMA)

The pattern of WMA was bilateral and widespread in both groups, although less pronounced in the *Family-group* ((Figure 1A, e-table 4) than in the *Sporadic-group* (Figure 1B; e-table 5) when each group was compared to controls. However, the T-test on SPM did not show differences on WMA between the *Family-group* and the *Sporadic-group*.

Correlation between IQ score and GM

Correlations between GM and IQ scores presented no suprathreshold results, for both groups, including positive and negative analyses.

Discussion:

In agreement with previous studies (CENDES *et al.*1998), patients presented early onset of seizures (~5 years) (KOBAYASHI *et al.*2003;HERMANN *et al.* 1997), long duration of epilepsy (~30 years) (KOBAYASHI *et al.*2003), most of them were under AED polytherapy (NOLAN *et al.* 2003) and presented high frequency of seizures (ALESSIO *et al.* 2004). Different from a previous study (NDRADE-VALENCA *et al.* 2008), the incidence of IPI on *Sporadic-group* (51%) was significantly higher than in *Familial-group* (25%), and this may result from the sample size and or the inclusion of heterogeneous patients in our *Familial-*

group. Despite these differences, our results are in accordance with one previous study which showed similar surgical outcome for both sporadic and familial cases and the occurrence of IPI in *FMLTE* varying from 10-35% (KOBAYASHI *et al.*2003). We also observed more severe asymmetry index of hippocampi in *Sporadic-group,* suggesting that different mechanisms may be involved in the development of hippocampal sclerosis in the *Familial-group (CENDES et al.1998; KOBAYASHI et al.2003; NDRADE-VALENCA et al.2008).* So far we are unable to explain the underlying mechanisms, but facing the complexity of hippocampal circuitry we hypothesize that besides the influence of genetic background, the neuroplastic response to different insults (cellular loss, epileptic discharges, neuronal deafferentation) are different between the two groups (NDRADE-VALENCA *et al.*2008).

Neuropsychological profile was in agreement with previous reports (HERMANN *et al.*1997; ALESSIO *et al.*2006), confirming the memory impairment in both groups. We also observed that *Familial-group* was in the average IQ range, but IQ values in the *sporadic-group* were in the low average range, with significant differences between them (p=0.004). Some studies have confirmed the intellectual impairment in both children (BOURGEOIS *et al.* 1983) and adults (HERMANN *et al.*1997) with MTLE, associating it with early onset of seizures, duration of active epilepsy, polytherapy and seizure frequency (BOURGEOIS *et al.*1983;NOLAN *et al.*2003;VASCONCELLOS *et al.* 2001). Since the two groups were equivalent in regards of all these characteristics, we believe that the genetic factor, (i.e. the familial or sporadic type of epilepsy) as well as the lower educational level may play some role in the complex results of intelligence performance. It is less probable that the generalized neuropsychological effects of MTLE are exclusively attributable to the hippocampal atrophy; instead, it may reflect the widespread harmful neurobiological effects caused by recurrent seizures or by the IPIs (HERMANN *et al.*1997). In support of this conception our results from whole brain VBM analysis demonstrated a bilateral, widespread pattern of pre-operative GM and WM atrophy in the group with low average IQ (*Sporadic-group*), contrasting with a more restricted pattern in the *Familial-group*. It is conceivable that, at to some extent, the worse performance of *Sporadic-group* might be related to the widespread brain injury revealed by morphometry, which may be related to more frequent initial precipitating injury in these patients.

Unfortunately we do not have the IQ performance during the childhood or adolescence from these refractory patients to exclude a progressive cognitive decline throughout their

lives (THOMPSON *et al.* 2005). Further prospective studies comparing the cognitive performance between familial and sporadic patients remain necessary to elucidate whether these two groups have different progression of cognitive impairment.

In addition, the *Sporadic-group* presented a poorer performance on BNT and delayed recall tests. So far we did not identify studies comparing neuropsychological performance between familial and sporadic patients with MTLE, but we can hypothesize that the differences we found may be related to the severity of hippocampal atrophy in the *Sporadic-group*. Since the H.M. case described in the early 1950s, it has been known that circumscribed brain lesions within the limbic system may deteriorate the ability to form new memories (MARKOVITSCH 2000). The hippocampus is a central component of the medial temporal lobe memory system, and its structural integrity is necessary for declarative memory, mainly episodic memory, as measured by WMS-R delayed recall test (ECONOMOU *et al.* 2006). Recently, hippocampus also has been associated with semantic processes (like naming pictures in BNT) as demonstrated by strong correlations between hippocampus grey matter density and a confrontation-naming test in patients with Alzheimer's disease (VENNERI *et al.* 2008). As proposed by these authors, the primary role of this region would be the combination of the different representations of a given object, as part of a process of multimodal synthesis spread over different cortical areas. Moreover, we showed in a previous study that volume of the left hippocampus was significant and independent predictor of verbal memory and BNT performance in patients with MTLE ALESSIO *et al.*2006). Thus, hippocampal atrophy most likely contribute for reduction of retrieval efficiency in refractory MTLE patients (STEWART *et al.* 2009).

Pre-operative GMA/WMA

We identified a restricted pattern in the *Family-group* and a widespread distribution in the *Sporadic-group*. The bilateral, extratemporal extent of GM atrophy and WM atrophy in patients with refractory MTLE had been described previously (BONILHA *et al.*2007b; CONCHA *et al.* 2009), but with no distinction between patients with sporadic or familial epilepsy . The reasons why the two groups presented different patterns of GMA remain unclear, but we can hypothesize that in *Familial-group* the development of hippocampal atrophy is determined by much stronger genetic predisposition, considering that for some patients, genetic effects may be strong enough to induce HA and MTLE with

minimal influence of environmental factors (KOBAYASHI *et al.* 2002). It is probable that in the *Sporadic-group,* the hippocampal sclerosis results from a complex interaction of stronger environmental factors (brain infection, trauma, etc.) (MATHERN *et al.* 1996). In agreement with this hypothesis, one previous study revealed a more pronounced mossy fiber sprouting in the fascia dentate of sporadic MTLE group, suggesting that familial MTLE patients respond differently to plastic changes induced by cellular loss, neuronal deafferentation or recurrent seizures(NDRADE-VALENCA *et al.*2008). From this perspective, it is possible that recurrent "brain insults" are required to the development of HA, with simultaneous involvement of different brain regions; therefore, it would originate a widespread bilateral pattern of damage. Therefore, we cannot exclude the hypothesis that recurrent seizures have different effects in *familial* and *sporadic forms* of MTLE (TASCH *et al.* 1999; SUTULA *et al.* 1999). Abnormalities within white matter in both temporal and extratemporal areas in these refractory MTLE patients have been described by previous authors applying different techniques as Diffusion Tensor Imaging (CONCHA *et al.*2009) and VBM (BONILHA *et al.*2007b). The underlying mechanisms for these abnormalities are still unclear, and may involve different factors as myelin dysfunction and demyelination (MITCHELL *et al.* 2003) as well as microdysgenesis (THOM *et al.* 2000). These results suggest that chronic refractory temporal lobe epilepsy is associated to WM abnormalities, regardless its genetic or sporadic aspect. Therefore we can hypothesize that these chronic abnormalities in WM are possibly related to the cognitive dysfunction observed in patients with MTLE (HERMANN *et al.* 2007).

We believe that the lower IQ performance in the *Sporadic-group* is somehow related to the more widespread pattern of GM and WM atrophy. We carried out whole brain VBM correlations with individual neuropsychological scores, without anatomically localized results. This is in accordance with one previous study (FOCKE *et al.*2008) which showed positive correlations between gray matter loss and cognitive dysfunction on a global level in patients with left MTLE, but without anatomically localized results, suggesting that IQ performance is subserved by widespread network, rather than an anatomical localized region. This finding supports our hypothesis that the IQ performance in *Sporadic-group* is probably related to the widespread pattern of structural abnormalities as compared to the *Familial-group*.

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Figure 1. Areas with GM and WM atrophy in *Familial group* (A), *Sporadic group* (B). Statistical maps are overlaid on a multislice display of coronal images of a smoothed T1 template. Each group have 2 maps, GM (red bar) and WM (blue bar), with respective z-score bar.

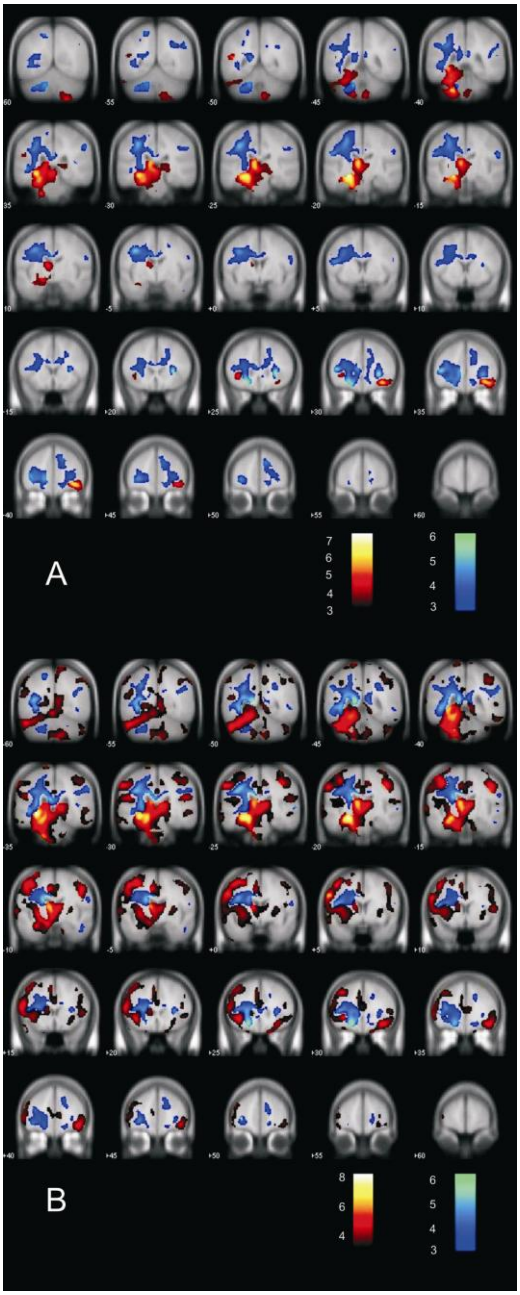

Figure 2. Areas with more GM atrophy in *Sporadic* compared with *Familial group*. Statistical maps are overlaid on a multislice display of coronal images of a smoothed T1 template. The respective the z-score bar is with red bar.

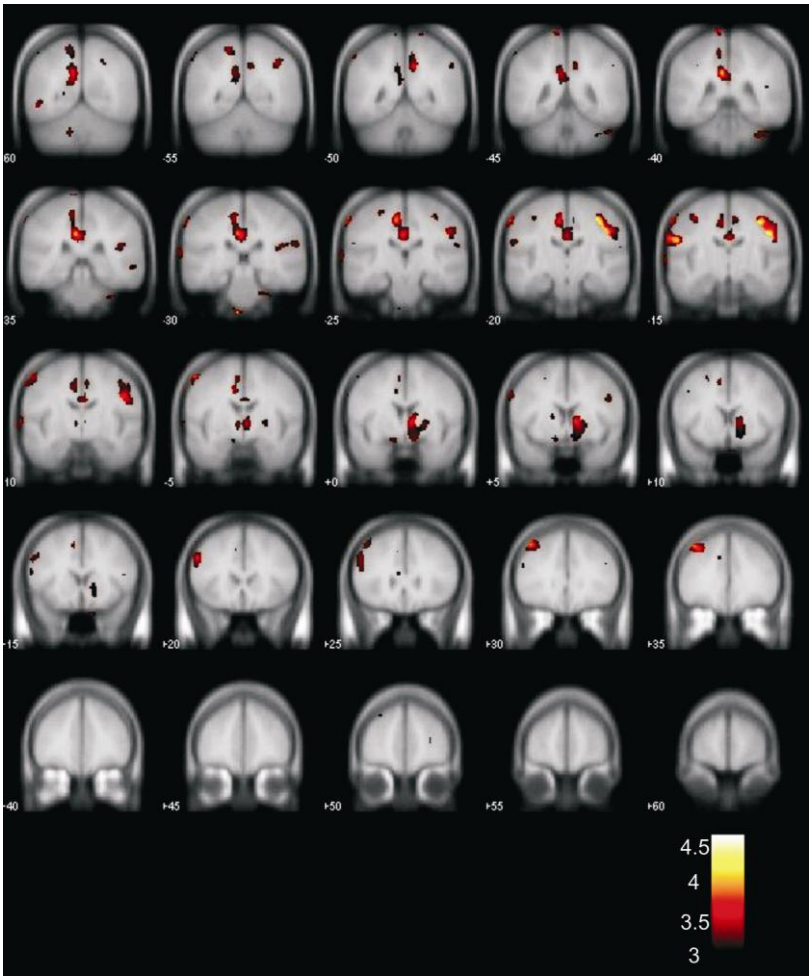

Table1. Clinical data from familiar and sporadic groups

	FAMILIAR	SPORADIC	P
NUMBER OF WOMEN	24(60%)	18(62%)	1
LEFT SIDE	19 (48%)	16 (55%)	0.63
AGE OF SEIZURE ONSET (years)	5.4±5	5.7±4.2	0.78
EDUCATION (years)	8.3±4.24	6±4.1	0.03
SZ frequency/month	10±9	10±8	0.7
Z-SCORES OF ASYMMETRY INDEX	-5.8±3.6	-7.5±2.6	0.04
DURATION OF EPILEPSY(years)	27.6±10.8	30.2±10.9	0.33
AED POLYTHERAPY	35(87.5%)	27 (93%)	0.39
IPI	10(25%)	15 (51%)	0.023
AGE SURGERY(years)	32.8±10.1	35.8±10.4	0.23
SURGICAL OUTCOME (Engel IA)*	21(53%)	15(52%)	0.23
Engel IB-II*	12 (30%)	12 (41%)	
Engel III-IV *	7 (17%)	2 (7%)	
FOLLOW UP (months)	57.7±32.1	66.4±29.3	0.25

Values are means ± SD; SZ=Seizure; IPI = initial precipitating injury; AED= antiepileptic drugs. * Qui-square test, non significant differences between groups.

Table2. Results from neuropsychological evaluation (Z scores, except on WAIS)

	Familiar group	Sporadic group	P
WAIS–R IQ	92.85±8.69	86.15±9.33	0.004
BNT	-1.93±2.78	-3.95±4.03	0.02
WMS-R general memory	-0.32±1.25	-0.8±1.14	0.13
WMS-R verbal memory	-0.26±1.3	-0.54±1.12	0.35
WMS-R visual memory	-0.36±0.97	-0.82±1.06	0.08
WMS-R delayed recall	-0.33±1.28	-1.02±1.10	0.03

Results from T-test with Bonferroni's correction

e-TABLE 1. Results from whole brain parametric analyses, areas with GM atrophy on *Family- group*.

Hemisphere. anatomical location		**Voxel wise**			**MNIcoordinates**
	Cluster size	P (FDR corr)	T	Equiv Z	
1. Left. Hippocampus, amygdala, parahippocampal gyrus, thalamus;	52923	<0.0001	7.49	6.7	-22 -20 -12
		<0.0001	6.57	6	-30 -36 -6
		<0.0001	6.33	5.82	-28 -28 -12
		<0.0001	6.11	5.64	35 32 -11
2. Left. Inferior frontal gyrus, insula;	1353	<0.0001	5.09	4.81	-37 27 0
3. Left. Superior temporal gyrus, supramarginal gyrus;	725	<0.0001	5.28	4.96	-47 -50 15
4. Left. Insula. inferior parietal lobule;	254	0.002	4.05	3.89	-52 -34 24
5. Left. Cuneus. middle occipital gyrus,	131	0.001	4.38	4.19	-8 -102 3
6. Right. Cerebellum;	6504	<0.0001	5.02	4.74	23 -63 -58
		0.001	4.37	4.18	6 -46 -52
		0.002	4.11	3.95	15 -55 -51
7. Right. Inferior frontal gyrus,middle	6043	<0.0001	6.33	5.82	36 40 -9

frontal gyrus;					
8. Right. Lingual gyrus;	404	0.002	3.99	3.85	19 -90 -7

Results reported on a Height threshold: T= 3, FDR (0.01), clusters > 100 voxels

e-TABLE 2 . Results from whole brain parametric analyses. Areas with GM atrophy on *Sporadic-group.*

Hemisphere. anatomical location		**Voxelwise**			**MNI coordinates**
	Cluster size	P (FDR corr)	T	Equiv Z	
1. Left . Hippocampus, amygdala, uncus, parahippocampal gyrus, thalamus, caudate, insula, inferior temporal gyrus, inferior occipital gyrus, fusiform gyrus, transverse temporal gyrus, middle temporal gyrus, superior temporal gyrus, inferior frontal gyrus, cingulate gyrus, angular gyrus, superior parietal lobule, inferior parietal lobule, precentral gyrus, postcentral gyrus;	512887	<0.0001	8.49	7.29	-25 -20 -12
		<0.0001	8.42	7.24	-31 -35 -5
		<0.0001	7.6	6.69	-32 -27 -10
2. Right. Thalamus, insula, angular gyrus, precentral and postcentral					

gyri, angular gyrus, supramarginal gyrus;					
3. Left, Cerebellum;	5044	0.001	4.11	3.92	-33 -79 -48
		0.001	4.05	3.88	-41 -74 -49
		0.001	3.8	3.65	-25 -80 -50
4. Left, Postcentral gyrus, superior parietal lobule;	4064	<0.0001	4.41	4.2	-16 -44 75
		<0.0001	4.35	4.14	-14 -31 77
		0.002	3.51	3.4	-31 -46 70
5. Left, Middle temporal gyrus;	335	0.003	3.38	3.28	-51 2 -45
6. Left, Cuneus;	123	0.006	3.02	2.94	-13 -93 30
7. Right. Inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, Fusiform gyrus;	6262	<0.0001	4.16	3.98	54 -31 -2
		0.001	4	3.83	54 -39 -21

Results reported on a Height threshold: T= 3, FDR (0,01), clusters > 100 voxels

e-TABLE 3, Results from whole brain parametric analyses, areas with more GM atrophy in *sporadic-group* compared to *family-group*.

Hemisphere, anatomical location		**Voxelwise**			**MNI coordinates**
	Cluster size	P (FDR corr)	T	Equiv Z	
1. Left, Cingulate gyrus, inferior occipital gyrus, lingual gyrus, middle occipital gyrus, precuneus, cuneus, superior parietal lobule, paracentral lobule;	61441	0.049	4.17	3.9	-7 -39 31
		0.049	4.03	3.78	-8 -24 49
		0.049	3.84	3.62	-2 -26 31
2. Left, Precentral gyrus, middle frontal gyrus, postcentral gyrus, inferior frontal gyrus, superior temporal gyrus;	24693	0.049	4.2	3.93	-58 -15 25
		0.049	4.09	3.83	-37 33 46
		0.049	4.01	3.77	-64 -23 47
3. Left, Cerebellum, fusiform gyrus,	4708	0.049	3.41	3.26	-27 -88 -39

middle occipital gyrus;					
		0.049	3.33	3.18	-51 -69 -29
		0.049	3.17	3.04	-51 -69 -17
4. Left, Middle temporal gyrus, superior occipital gyrus, middle occipital gyrus, angular gyrus;	1464	0.049	3.8	3.59	-37 -78 17
		0.049	3.23	3.1	-32 -77 27
5. Left, Inferior temporal gyrus, middle occipital gyrus, middle temporal gyrus;	879	0.049	3.7	3.5	-47 -63 -2
	767	0.049	3.86	3.64	-9 -37 78
6. Left, Cingulate gyrus;	520	0.049	3.16	3.03	-7 25 14
	484	0.049	3.33	3.18	-35 -42 41
	266	0.049	3.06	2.94	-71 -42 -8
		0.049	2.86	2.77	-69 -39 -20
	257	0.049	3.9	3.68	-6 -30 -54
7. Left, Cerebellum;	124	0.049	2.88	2.78	-16 -39 -32
8. Right, Cingulate gyrus, inferior frontal gyrus, thalamus, lentiform	19755	0.049	3.9	3.67	10 3 5

nucleus, caudate;					
		0.049	3.72	3.52	5 -4 2
		0.049	3.55	3.37	9 12 -29
9. Right, Transverse temporal gyrus, insula, superior temporal gyrus, precentral gyrus, inferior parietal lobule, postcentral gyrus;	18881	0.049	4.66	4.31	35 -17 46
		0.049	4.4	4.09	44 -18 34
		0.049	3.59	3.41	43 -33 19
10. Right, Inferior occipital gyrus, fusiform gyrus, lingual gyrus, middle occipital gyrus, cuneus;	7585	0.049	4.54	4.2	39 -93 -11
		0.049	4.19	3.92	12 -100 -13
		0.049	4.09	3.83	42 -76 -5
11. Right, Cerebellum;	4677	0.049	3.46	3.3	35 -36 -37
		0.049	3.34	3.2	20 -32 -35
		0.049	3.34	3.19	49 -44 -34
12. Right, Inferior frontal gyrus, middle frontal gyrus;	1280	0.049	3.08	2.96	44 33 25

		0.049	3.02	2.9	41 42 20
13. Right, Middle temporal gyrus, superior temporal gyrus;	1124	0.049	3.23	3.1	57 -35 -3
14. Right, Angular gyrus, inferior parietal lobule;	1103	0.049	3.61	3.43	49 -72 42
15. Right, Extra-nuclear, thalamus;	597	0.049	3.2	3.07	3 -32 7
	308	0.049	3.36	3.21	18 -48 76
16. Right, Middle frontal gyrus, superior frontal gyrus;	238	0.049	3.19	3.06	28 50 10

Results reported on a Height threshold: T= 3, no FDR, clusters > 100 voxels

e-TABLE 4. Results from whole brain parametric analyses, areas with WM atrophy on *Family-group.*

Hemisphere, anatomical location		**Voxelwise**			**MNI coordinates**
	Cluster size	P (FDR corr)	T	Equiv Z	
1. Left, Sub-gyral, cingulated gyrus, precentral gyrus, inferior and midle frontal gyri, inferior occipital gyrus, insula, lingual gyrus, middle occipital gyrus, middle temporal gyrus, supramarginal gyrus, angular gyrus, cuneus;	181240	<0,0001	6,27	5,77	-23 26 -11
		<0.0001	6.26	5.76	29 24 5
		<0.0001	5.78	5.38	-44 32 10
2. Left, Cerebellum;	9610	<0.0001	5.61	5.23	-12 -68 -38
		<0.0001	5.17	4.87	-26 -67 -34
		<0.0001	4.87	4.62	-15 -46 -31

3. Right, Supramarginal gyrus, angular gyrus;	2706	<0.0001	4.36	4.17	51 -56 37
		0.001	3.96	3.82	31 -54 36
4. Right, Transverse temporal gyrus, insula, superior temporal gyrus, precentral gyrus, postcentral gyrus, supramarginal gyrus, inferior parietal lobule;	6552	<0.0001	4.29	4.11	57 -15 26
		<0.0001	4.28	4.1	55 -33 40
		0.001	4.19	4.02	58 -39 32
5. Right, Middle frontal gyrus, cingulate gyrus;	566	0.003	3.21	3.13	22 -6 47
6. Right, Cingulate gyrus, precuneus;	258	0.003	3.33	3.24	11 -51 36
7. Right,Fusiform gyrus, inferior temporal gyrus;	113	0.003	3.23	3.14	50 -4 -30

Results reported on a Height threshold: T= 3, FDR (0,01), clusters > 100 voxels

e-TABLE 5, Results from whole brain parametric analyses, areas with WM atrophy on *Sporadic-group*

Hemisphere, anatomical location		**Voxelwise**			**MNI coordinates**
	Cluster size	P (FDR corr)	T	Equiv Z	
1. Left, Sub-gyral, insula, transverse temporal gyrus, inferior temporal gyrus, middle occipital gyrus, superior temporal gyrus, middle temporal gyrus, cuneus, supramarginal gyrus, cingulate gyrus, middle frontal gyrus, postcentral gyrus, inferior frontal gyrus, precentral gyrus;	182687	<0.0001	6.28	5.73	-14 -47 12
		<0.0001	6.15	5.63	-20 29 -12
		<0.0001	6.09	5.58	-26 -81 9
2. Left, Cerebellum;	5926	<0.0001	4.74	4.48	-13 -69 -32
3. Left, Sub gyral, fusiform gyrus, inferior temporal gyrus, middle	1271	0.001	3.58	3.46	55 -14 -20

temporal gyrus;					
4. Right, Precentral gyrus, postcentral gyrus;	2038	0.001	3.65	3.52	59 -12 26
		0.001	3.58	3.46	56 1 16
		0.006	2.97	2.9	56 -3 25
5. Right, Sub-gyral, inferior temporal gyrus, middle occipital gyrus;	1247	0.001	3.8	3.66	43 -63 -4
		0.001	3.56	3.44	37 -66 2
		0.007	2.88	2.82	49 -57 -6
6. Right, Middle temporal gyrus, superior temporal gyrus;	639	<0.0001	4.48	4.26	54 -49 1
7. Right, Cerebellum;	293	0.001	3.59	3.47	23 -65 -33
		0.001	3.57	3.45	47 -10 -33
8. Right, Superior temporal gyrus;	276	<0.0001	4.86	4.58	63 -24 6
9. Right, Precuneus;	139	0.005	3.04	2.96	16 -57 54
10. Right, Sub-gyral, precentral gyrus;	110	0.007	2.89	2.82	35 -5 36

Results reported on a Height threshold: T= 3, FDR (0,01), clusters > 100 voxels

DISCUSSÃO

Nossos resultados de seguimento prolongado confirmam a superioridade do tratamento cirúrgico para o controle de crises em relação ao tratamento medicamentoso, em acordo com estudos prévios (37;175) que mostraram um bom controle de crises (livre de crises incapacitantes) de aproximadamente 65% e controle total de crises entre 45,9 e 89%. O seguimento prolongado dos pacientes mostrou que o controle das crises incapacitantes em nossos pacientes operados (84% dos pacientes com Engel I) foi semelhante ao encontrado por (40) (83% com Engel I em 5 anos de seguimento) e por (176) (90% dos pacientes com Engel I ou II) e superior ao resultado de 65% apresentado na meta-análise de (177); esses resultados dão suporte ao conceito de que o benefício da cirurgia é duradouro para os candidatos selecionados adequadamente. Quanto ao controle total de crises (Engel IA), nosso resultado de 49% se assemelha ao apresentado por (176) que num seguimento de 5 anos observou que 40% dos pacientes submetidos a amigdalohipocampectomia via transcortical e 58% dos pacientes submetidos á amigdalohipocampectomia seletiva estavam livre de crises, sem no entanto encontrar diferenças entre os acessos cirúrgicos quanto ao controle das crises (p=0,38).

O tratamento cirúrgico mostrou-se eficaz no controle de crises além de seguro quanto às complicações já que alguns pacientes apresentaram complicações pós-operatórias transitórias sem seqüelas e apenas um indivíduo (2%) apresentou seqüela permanente, mostrando que nossos resultados estão em acordo com outros publicados anteriormente (178;179).

A análise de sobrevivência é um método robusto e apropriado para analisar as duas formas de tratamento uma vez que os pacientes apresentam tempos de seguimento variados e a duração do intervalo livre de crises também apresenta uma variação muito grande entre os indivíduos (39). Até o presente momento não encontramos outros estudos de longo prazo comparando o tratamento cirúrgico com o clínico, porém nossos resultados confirmam a tendência de melhor controle das crises com a cirurgia mesmo levando em conta que alguns dos indivíduos livre de crises logo após a cirurgia possam apresentar crises num período mais tardio. Em comparação com nossa análise realizada em 2005 (39), a proporção de indivíduos totalmente livre de crises (Engel IA) caiu de 73% para 49%, porém a proporção total de indivíduos com melhora significativa que

era de 92,3% (Engel I+ II) no primeiro estudo não diminui na análise atual (95,4%). É possível que o aumento para 95,4% dos pacientes com melhora significativa esteja associado à diminuição progressiva da freqüência de crises observada em alguns indivíduos, relacionada ao fenômeno de "running down" (180). Esses resultados sugerem que apesar de alguns indivíduos voltarem a apresentar crises após anos de cirurgia, essas crises não são incapacitantes (84% dos pacientes com Engel I) e eles continuam a desfrutar um controle de crises que jamais obteriam com o uso exclusivo de DAEs (apenas 7% dos indivíduos no grupo clínico obtiveram um controle razoável de crises).

Neste estudo conseguimos mostrar que o bom controle das crises com o tratamento cirúrgico é duradouro e que as chances de controle de crises com uso exclusivo de medicação antiepiléptica são baixas quando seguimos os pacientes por um tempo prolongado. Nossos resultados dão suporte ao conceito da indicação precoce de cirurgia para os casos confirmadamente refratários, devido à chance reduzida de controle de crises com uso exclusivo de DAEs; um melhor controle das crises, ainda que o indivíduo permaneça com eventos não incapacitantes, pode oferecer novas perspectivas quanto à reabilitação social, melhora na qualidade de vida e até mesmo oportunidades de emprego (38).

Apesar da seleção criteriosa, aproximadamente 30% dos pacientes permanecem com crises após a ressecção das estruturas mediais do lobo temporal afetado (175;177;181). As razões para a falha da cirurgia em controlar as crises têm sido associadas principalmente a ressecção incompleta do tecido epileptogênico (178) , visto que em algumas situações a reoperação com ampliação da ressecção inicial pode oferecer um melhor controle ou até mesmo o controle total das crises (161;162;182). Outros fatores relacionados à falha cirúrgica podem estar relacionados à atrofia hipocampal bilateral (183;184) e ao surgimento de novos focos epileptogênicos (como por exemplo, a região temporal medial contralateral) ou persistência de focos antes obscurecidos pelo predomínio da atividade epiléptica unilateral (162;162;178). Apesar dos esforços para se compreender as razões da falha cirúrgica, ainda persistem muitas dúvidas em relação a outros fatores tais como o papel de estruturas anatômicas relacionadas ao hipocampo que apresentam intenso potencial epileptogênico (185-187),

bem como a influência da duração da epilepsia antes da cirurgia , idade de início das crises (184;188), raça e sexo (189).

Para investigar algumas hipóteses sobre fatores relacionados à falha do tratamento cirúrgico realizamos uma análise da relação entre estruturas temporais mesiais contidas na lacuna cirúrgica e o prognóstico cirúrgico (artigo1) e outro estudo pesquisando a relação entre os padrões de atrofia de SB e SC pré-operatórias e o resultado cirúrgico (artigos 2 e 3).

No **artigo 1** mostramos que o melhor prognóstico cirúrgico está associado a ressecção do hipocampo atrófico em conjunto com o córtex entorrinal. As estruturas mesiais fazem parte de um circuito "olfatório-neocortical" que envolve o hipocampo, amígdala, os córtices entorrinal, perirrinal e piriforme. Essas estruturas estão intimamente conectadas e possuem células capazes de gerar potenciais excitatórios recorrentes que por sua vez podem resultar em atividade epileptiforme; as conexões entre essas estruturas permitem ainda uma amplificação da atividade epileptiforme bem como o recrutamento de outras células que por sua vez podem desencadear a propagação dessa atividade elétrica para outras partes do cérebro. Isso explica o fato de que a estimulação elétrica dessas estruturas num paciente com ELTM desencadeia os mesmos automatismos que ele apresenta durante suas crises espontâneas (190;191). Desta forma podemos compreender a importância da remoção associada (hipocampo e córtex entorrinal) como forma de oferecer maiores chances de controle adequado das crises.

A investigação da relação entre o prognóstico cirúrgico e diferentes padrões de atrofia de substâncias branca e cinzenta, foi realizada com a análise das RM pré-operatórias utilizando a técnica de Morfometria Baseada em Voxel. Os resultados dos **artigos 2 e 3** mostram que o controle de crises está associado a um padrão mais restrito de atrofia de substância cinzenta, sem no entanto se correlacionar com o padrão de atrofia de substância branca; a investigação das alterações plásticas (aumento relativo de substância branca e cinzenta) após a cirurgia foram explorados nos mesmos grupos de pacientes e confirmam os resultados de estudos prévios realizados com a técnica de espectroscopia (192;193)

A análise de atrofia de SB mostrou que esta acomete regiões temporais e extratemporais (194). No *Grupo falha cirúrgica* encontramos atrofia de SB nos dois hemisférios, poupando áreas na região occipital e parietal contralateral. A atrofia de SC também foi extensa, diferindo dos outros dois grupos, principalmente quanto à extensão na região temporal contralateral. No *Grupo livre de crises* identificamos atrofia de SB com padrão extenso e bilateral. Ao contrário, a atrofia de SC foi restrita e sem envolvimento do lobo temporal contralateral. Nossos resultados mostram que o *Grupo falha cirúrgica* apresentou um padrão de atrofia de SC extenso, antes da cirurgia, ao contrário dos outros dois grupos. Em relação à distribuição de atrofia de SB, não conseguimos associar o resultado cirúrgico a um padrão de atrofia mais extensor. De maneira similar, outro estudo prévio descreveu o mesmo achado, utilizando a técnica de análise por tensor de difusão (195).

Os mecanismos fisiopatológicos da atrofia de SB em áreas temporais e extratemporais ainda não foram totalmente esclarecidos, mas estudos anteriores sugerem mecanismos envolvendo heterotopia neuronal (196), microdisgenesia (197), disfunção da mielina e desmielinização (198). Esses achados sugerem que a ELTM crônica está associada a anormalidades de SB, e podemos ainda aventar hipóteses de que tais anormalidades crônicas podem estar relacionadas à disfunção cognitiva que esses pacientes apresentam após longo tempo de crises repetidas (199).

Reversibilidade da atrofia de SB e SC

O desenvolvimento de um novo programa para o software MATLAB/SPM foi essencial para a análise dos processos dinâmicos que ocorrem após a cirurgia. Os estudos anteriores mostraram evidências da recuperação funcional após a cirurgia (193;200;201), mas as alterações estruturais correspondentes ainda não tinham sido descritas. Neste estudo conseguimos aplicar a técnica de VBM nas imagens pós-operatórias e conseguimos identificar áreas com aumento relativo de SB e SC, principalmente nos pacientes que ficaram livres de crises ou com melhora significativa. Nossos resultados confirmam resultados previamente descritos (193) (192), em que os autores demonstraram que os pacientes que ficaram livres de crises obtiveram a

normalização dos valores de NAA/Cr no lobo temporal contralateral, enquanto que os pacientes que persistiram com crises não obtiveram essa normalização.

No *Grupo livre de crises* conseguimos identificar áreas de recuperação de SB em regiões temporal e extratemporal. Ao contrário, Concha et al (202)não identificou áreas de recuperação aplicando a técnica de análise por tensor de difusão nas imagens pós–operatórias. A incongruência com nossos achados deve estar relacionada à aplicação de uma técnica diferente, bem como ao pequeno número de pacientes estudados pelo grupo. Por outro lado, um estudo mais recente aplicando a mesma técnica de análise por tensor de difusão identificou áreas de recuperação de SB no lobo occipital remanescente após lobectomia occipital, sugerindo a ocorrência de plasticidade como resposta adaptativa (200).

É provável que o aumento relativo de SB e SC após a cirurgia não ocorra como um fenômeno isolado, mas seja a resultante de uma combinação de processos envolvendo a reversão de disfunção por estresse metabólico, neuroplasticidade com sinaptogênese, proliferação dendrítica e neurogênese. Embora os mecanismos de reparação não estejam totalmente elucidados, podemos especular que as áreas com recuperação estejam relacionadas com a reversão de disfunção neuronal, clinicamente expressa como um melhor desempenho dos testes neuropsicológicos nos pacientes com controle de crises (203). A evidência de reversibilidade das lesões causadas pelas crises recorrentes na ELTM dá suporte ao conceito de que a cirurgia precoce para os casos refratários pode prevenir danos futuros, bem como oferecer a chance de restituir uma função cerebral normal antes que a vida social desses indivíduos seja devastada pelo estigma e pelo preconceito das crises recorrentes.

A investigação da influência do antecedente familiar quanto ao prognóstico cirúrgico não revelou diferenças estatisticamente significativas quanto comparamos o *grupo Familiar* e *grupo Esporádico* quanto aos resultados cirúrgicos (**artigo 4**), em concordância com estudos prévios (77;204), porém encontramos diferenças significativas na distribuição de áreas com atrofia de substância branca e cinzenta, índice de assimetria hipocampal, freqüência de fatores precipitantes, bem como nos resultados da avaliação neuropsicológica (QI e memória). Apesar das limitações do

nosso trabalho (entre elas a dificuldade de detalhar as crises dos familiares dos pacientes do grupo Familiar), nossos resultados confirmam que a história familiar de epilepsia é comum entre os pacientes com ELTM (69;70) e que possivelmente o mecanismo de patogênese da esclerose hipocampal nos pacientes do *grupo familiar* decorra da interação entre fatores genéticos e ambientais, ao contrário do *grupo esporádico*, provavelmente mais exposto a fatores ambientais (69;77). As diferenças encontradas entre os dois grupos sugerem que de fato o *grupo esporádico* tenha sido mais exposto a fatores de injúria cerebral visto o padrão extenso de atrofia de substância cinzenta, associado a déficits cognitivos que recrutam funções de diversas regiões cerebrais e não simplesmente o sistema hipocampal.

Os resultados da volumetria e EMG dos pacientes operados (**ANEXO 1**) mostram que apesar do bom controle das crises, alguns pacientes apresentam uma atrofia do músculo temporal após a craniotomia para ressecção das estruturas mediais do lobo temporal. A ocorrência de atrofia do músculo temporal após craniotomias frontotemporais não é raro e já foi descrita previamente como seqüela de diversos acessos cirúrgicos para patologias diversas (205;206). Para a maioria desses indivíduos o defeito é cosmético e sem repercussão clínica, porém alguns podem desenvolver disfunção da articulação temporomandibular além da limitação da abertura bucal (207). Nossos resultados confirmam resultados de estudos prévios realizados sem o rigor da volumetria e eletromiografia e atentam para a necessidade de minimizar o dano cirúrgico ao músculo temporal, e de se oferecer a reabilitação (como fisioterapia) após a cirurgia a fim de evitar que esses pacientes evoluam com disfunção temporomandibular. Para os pacientes com epilepsia essa atenção é muito importante visto que para alguns a reoperação pode ser necessária e uma anquilose ou pseudo anquilose de mandíbula pode dificultar muito a intubação orotraqueal (208).

CONCLUSÕES

Nossos resultados confirmam que o tratamento cirúrgico oferece um controle de crises superior ao tratamento clínico para pacientes com ELTM que não responderam a pelo menos três esquemas terapêuticos adequados com DAEs.

A ressecção cirúrgica deve levar em conta não apenas o hipocampo, mas também as outras estruturas mesiais adjacentes. A remoção do córtex entorrinal em conjunto com o hipocampo parece ser de grande relevância para o controle adequado das crises.

A cirurgia é um método seguro, porém devemos ressaltar que complicações inerentes a craniotomia, tal como atrofia do músculo temporal, podem resultar em disfunção temporo-mandibular. Assim, devemos buscar técnicas que minimizem estas complicações.

O resultado cirúrgico está relacionado a outros fatores além da extensão da ressecção (hipocampo e estruturas adjacentes), tais como distribuição de áreas com atrofia de substância cinzenta não visíveis pela análise convencional de RM.

A plasticidade cerebral nos pacientes operados, caracterizada pelo aumento relativo de volume de substância branca e cinzenta, foi evidente para os pacientes que obtiveram um bom controle, mas não ocorreu nos pacientes que permaneceram com crises após a cirurgia.

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ANEXO 1

"POST-CRANIOTOMY TEMPORAL MUSCLE ATROPHY: MRI VOLUMETRY AND EMG INVESTIGATION"

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ABSTRACT

Background: Temporal muscle atrophy and fibrosis is an undesired effect of temporal and frontotemporal craniotomy that may affect some of the patients who undergo surgery due to refractory mesial temporal lobe epilepsy (MTLE). We investigated the atrophy of temporal muscle by means of magnetic resonance imaging, clinical and electromyography analysis.

Methods: We investigated 18 controls and 18 patients who underwent surgery for MTLE. We used the pre and post operatory magnetic resonance image scans to segment the temporal muscle with an image's analysis software (ITK-SNAP http://www.itksnap.org/download/snap/). Besides the clinical evaluation, patients also underwent electromyography of temporal muscle after surgery. We used u-test (Mann-Whitney), paired t-test, Pearson chi-square and linear regression test to analyze the data.

Results: Our preliminary results showed reduction of the volume of the temporal muscle on the operated side ($p=0.004$). The EMG results confirmed this atrophy with the reduction of electrical activity in the operated side. We also identified reduction of the maximal mouth opening in patients after surgery compared to controls ($p<0.0001$). Patients presented facial asymmetry, temporomandibular disorders (pain, disc displacement and joint sounds), and masticatory abnormalities.

Discussion: Despite the good control of seizures some patients may experience cosmetic and functional abnormalities of temporal muscle secondary to atrophy and fibrosis. Besides pain and difficulties on mastication, the reduction of mouth opening

may be severe enough to difficult future intubations when reoperation is necessary. It is necessary to develop prospective studies with pre and post operatory TMJ evaluation, as well as surgical techniques with minimal damage to temporal muscle.

INTRODUCTION

Surgical treatment for refractory mesial temporal lobe epilepsy (MTLE) has been indicated over decades with a better outcome compared to antiepileptic drugs and clinical treatment (WIEBE *et al.* 2001; YASUDA *et al.* 2006). Different surgical approaches (standard temporal lobectomy or selective transsyilvian amygdalohippocampectomy) may result in similar surgical outcome (ARRUDA *et al.* 1996). Craniotomy can be performed according to different techniques including pterional approach (YASARGIL *et al.* 1987), pre-temporal (TEDESCHI), or other frontotemporal approaches. Besides different options of craniotomy, the management of temporal muscle along with branch of facial nerve can also be carried out in different ways, i.e. interfascial (YASARGIL *et al.*1987), subfascial or submuscular (COSCARELLA, BOWLES,) and retrograde dissection (OIKAWA *et al.* 1996).

Considering the good results in seizure control, less attention has been directed to evaluate cosmetic effects and abnormalities of mastication that may occur after the craniotomy. These post-operatory abnormalities are not exclusive of epilepsy surgery, they can arise after pterional and fronto-temporal craniotomy, made to any other neurosurgical pathology as brain tumors or cerebral aneurysms (BADIE 1996; DE ANDRADE JUNIOR *et al.* 1998; DE ANDRADE JUNIOR *et al.*1998). Even with the good control of seizures, some patients may have some atrophy on temporal muscle as well as temporomandibular dysfunction (TMD) that can originate pain and masticatory impairment, delaying their return to their previous activity (OIKAWA *et al.*1996). Unfortunately, some patients may be affected by pseudoankylosis of the mandible after temporal or frontotemporal craniotomy, with severe reduction of mouth opening, increasing the risk of difficult intubation for posterior surgeries (KAWAGUCHI *et al.* 1996; KAWAGUCHI *et al.* 1995;COONAN *et al.* 1985).

In this preliminary study we proposed to evaluate both cosmetic and functional effects of temporal muscle atrophy, by means of clinical examination, magnetic resonance imaging and electroneuromyography. We performed manual volumetry of bilateral temporal muscle on pre and post operatively high resolution MR scans in order

to quantify the atrophy. Patients underwent electroneuromyography examination of temporal muscle to complement the investigation.

MATERIALS AND METHODS

We selected 18 patients (13female), age (mean ± standard deviation) 37.6 ± 11.5 years and 18controls (13 female) age of 37± 11.7 years. All patients were selected for surgery according to our investigative protocol (YASUDA *et al.*2006) and underwent surgical treatment for refractory MTLE in our institution between 2002 and 2004. The control group was matched in regards of age and gender and consisted of hospital's workers who did not present epilepsy, headache or TMD.

Surgical approach: all patients underwent pre-temporal craniotomy (TEDESCHI) with trans-sylvian selective amigdalohippocampectomy (YASARGIL *et al.* 1993), performed by two neurosurgeons (H.T. and E.O.). Temporalis muscle dissection was carried out according to Yasargil's interfascial dissection in order to maximize the visibility as well as preserve the facial nerve (YASARGIL *et al.*1987) without any additional incision of muscle. The reconstruction of temporalis muscle was based on re-attachment of muscle to a cuff of fascia-periostium complex left on free bone flap along the superior temporal line.

MR analysis:

Acquisition All patients underwent the same protocol for 3D acquisition on a 2T scanner (Elscint Prestige,Haifa, Israel). T1-weighted images (TR=22ms, TE=9ms, flip angle=35° matrix=256x220, field of view = 25x22cm, sagittal acquisition) with 1 mm isotropic voxel.

Analysis: The images were acquired in DICOM format transformed to ANALYSE by MRIcro software (www.mricro.com).

Segmentation: After format conversion, we used an image's analysis software (ITK-SNAP, *http://www.itksnap.org/download/snap/)* to segment the temporal muscle. ITK-SNAP is an interactive image segmentation software developed to implement an active contour segmentation of anatomical structures, allowing regional segmentation by

employing user-initialized deformable implicit surfaces that evolves to the most appropriate border between neighboring structures (YUSHKEVICH *et al.* 2006).Segmentation is the process by which appropriate image points (voxels) are assigned to be part of a specific anatomic structure.

We used the three views (coronal, sagittal and axial) to reassure the boundaries of temporal muscle. Manual segmentation was performed with a computer mouse by the neurosurgeon drawing a line around the muscle borders, enclosing the whole structure, on every single MRI slice. The operator selected the points to produce a visually appropriate tracing of the surface contour, following careful realignment of the region of interest. The 3D high resolution images allowed us to clearly identify the temporal muscles both pre and post operatory. Subsequent to the manual segmentation, a 3D graphical rendering of the volumetric object allows navigation between voxels in the volumetric image, enabling to scroll through the data (Figure 1). The software provides us the volume of those selected voxels in cubic mm.

Electroneuromyography (EMG)

Patients underwent EMG on a Neuropack 2™ Electromyographer (Nihon Kohden, Tokyo, Japan). We used surface recording electrodes, placed over the belly of the temporalis muscle (active) and malar proeminence (reference), to evaluate voluntary muscle contraction during clenching and swallowing. We set high and low filters of 5khz and 10hz, respectively. For each individual, analysis time was 200ms Amplitudes of maximal electrical activity, expressed in microvolt (μV), were simultaneously recorded in both sides. We defined the ratio of maximal electrical activity in the affected side/non affected side to characterize functional impairment of muscle fibers in the operated side. In normal individuals, this ratio is expected to be approximately one, since no significant differences exist between right and left side.

We used the ratio between the affected/non affected sides to show the atrophy of muscle fibers on the operated side. In normal individuals this ratio is expected to be approximated one, since no significant differences exist between right and left side.

Clinical examination:

A trained examiner performed the examination according to the Research Diagnostic Criteria for TMD (RDC/TMD). The RDC/TMD protocol includes metric measurement of the range of mandibular motion, muscle and joint palpation with defined pressure (DWORKIN S.F. *et al.* 1992). We also measured the mouth opening from all patients and controls.

Statistical analysis:

We used SYSTAT 12 (San Jose, California, USA, Systat Software Inc**.** -SSI) to analyze clinical data from patients and controls. We used non-parametric Mann-Whitney U Test to compare continuous data between patients and controls and paired T-test between pre and post operatory data. For categorical variables we used Pearson χ^2 . We also performed Pearson correlation to analyze the relation between time after surgery (months) and the mouth opening (in millimeters).

To evaluate the measurements of temporal muscle volume (normal and operated side) we used the ratio between affected side and normal side. We then obtained the pre operatory ratio and the post operatory ratio from each patient.

RESULTS

There were no significant differences between patients and controls considering age (p=0.89) and gender (p=1). The image, clinical and electroneuromyographic evaluation was accomplished with 25.5±10.8 months after surgery. The surgical outcome was 12 patients free of seizures (Engel IA), 2 patients Engel IB, 1patient Engel IC, 1 patient ID, 1 patient IIA and 1 patient IIIA. In this small group of patients we did not observe facial palsy secondary to facial nerve injury.

The volume of temporal muscle was reduced after surgery. The mean ratio ± standard deviation before surgery was 0.99±0.07, and the ratio after surgery was 0.86±0.15 (p=0.004). **Figure 2**. EMG findings supported volumetric MRI results. Temporal muscle atrophy was so severe in five individuals that we were not able to record electrical activity with surface electrodes. In the remaining 13 patients, mean

ratio ± SD was 0.55±0.20, indicating that electrical activity in muscle fibers of the operated side was nearly half that of the normal side.

The maximal mouth opening (interincisor gap) was 46.6±5.1mm for controls and 38.7± 6.9mm for patients, confirming the significant reduction in patients ($p<0.0001$) (**Figure 3**). We found a significant correlation between the measurement of mouth opening and the time after surgery $p=0.033$, $R=0.504$. (**Figure 4**)

We also detected facial asymmetry due to temporal atrophy in 10 (55.6%) patients. Muscle disorders were found in 11 (61.1%) patients, including pain in response to palpation (7 patients) and spontaneous pain (4 patients). The most affected muscles were ipsilateral temporal, masseter and in less frequency, medial and lateral pterygoids.

Twelve patients presented joint sounds during the TMJ evaluation and five of them also presented TMJ pain during palpation. Disc displacement with reduction was observed in 11 (61.1%) patients ipsilaterally to the surgery.

DISCUSSION

In this preliminary study we showed that some patients with epilepsy who undergo surgery to control seizures may have some cosmetic and even functional abnormalities related to temporalis muscle atrophy. These effects are not exclusive to the epilepsy surgery itself, they are associated to the craniotomy and can occur with surgeries for brain tumors and aneurysms (BADIE1996; SPETZLER *et al.* 1990; MATSUMOTO *et al.* 2001). Since epilepsy surgery aim to offer better quality of life besides seizure control (MELDOLESI *et al.* 2007), we understand that some attention should be directed to study the abnormalities resultant from temporalis muscle atrophy in order to avoid them. Although temporalis muscle atrophy has been widely described as an undesired common sequel in pterional and other cranio-orbital approaches, with several surgical modifications developed in order to minimize muscle damage and atrophy (BADIE1996, BOWLES, MIYAZAWA, WEBSTER) we performed this study not only to describe it in our patients, but mostly analyze the atrophy with both

structural (MRI volumetry) and functional (clinical examination and electroneuromyography) techniques.

The temporal muscle atrophy and fibrosis secondary to craniotomy have been recognized previously (KAWAGUCHI *et al.*1996; FERRARI *et al.* 1985; COONAN *et al.*1985;PORTER *et al.* 1991), but any volumetric or electroneuromyographic evaluation of these patients have been described. Even with our small sample of patients, our results from both volumetric and EMG studies confirmed the reduction of volume and function of the operated temporal muscle, formerly reported by different authors; besides we demonstrated that in some cases, the fibrosis is so intense, resulting in undetectable electrical activity from the remaining fibers. Clinically, we also observed facial asymmetry, disc displacement and spontaneous and elicited pain during palpation. We obtained significant results with both MR volumetry and EMG analyses of temporalis muscle, but due to the small number of patients included in our analysis, further studies with larger number of patients may be necessary to confirm our preliminary results.

Although we did not performed pre and post operatory evaluation of maximal mouth opening individually, we did confirm the reduction of interincisor gap when we compared the measurements between patients and the control group. It is in accordance with previous studies, and its etiology derives from a combination of scar formation inside the muscle after incision, devascularization (due to sustained traction during the surgery) and, in some cases, the organization of hematoma (COONAN *et al.*1985;KAWAGUCHI *et al.*1996). The reduction of mouth opening showed a tendency of improvement related to the months after the procedure, since Pearson correlation test was significant ($p=0.033$, $R=0.504$). This result implicates that the recovery of mouth opening is only 25% dependent of time, meaning that different factors may also be involved in this complex process. In our study, the mean time of post operatory was around 2 years, and despite time of follow up, the measurement of mouth opening was still reduced. As the correlation test showed a slightly tendency of ascent of mouth opening with time, a longer period of follow up with larger number of operated patients is required to certify whether or not patients may be able to recover entirely to their pre-operatory status.

The risk of pseudoankylosis with severe mouth opening reduce is of great importance considering that the reoperation is an alternative for some cases of refractory seizures, mainly those secondary to dysplasia (GONZALEZ-MARTINEZ *et al.* 2007;SALANOVA *et al.* 2005). The risk of a difficult intubation during the second or third reoperation would be minimized if the maximal opening mouth could be restored to the normal.

Since the temporal muscle is strictly involved in mastication (GEERS *et al.* 2005;GAUDY *et al.* 2001), it is expected that our patients experience some masticatory impairment, mostly during the first months after the surgery. This, along with the risk of permanent reduction of maximal mouth opening, raises the necessity of early recommendation of both passive and active jaw exercises after surgery, as well as the investigation of alternatives surgical approaches with minimal damage to the temporalis muscle as suggested by some authors. Many authors have developed different surgical approaches to preserve both the temporalis muscle and facial nerve. Different techniques for muscle management other than interfascial dissection (YASARGIL *et al.*1987) have been developed, as submuscular or subfascial dissection described by COSCARELLA ET AL, and retrograde dissection proposed by (OIKAWA *et al.*1996), in attempt to preserve deep temporal arteries and nerves and avoid muscle atrophy. Different techniques have also been created in order to provide a better reconstruction of temporalis muscle after intracranial procedure, i.e. the small cuff of fascia-periostium complex attached to the free bone flap for muscle closure (MIYAZAWA), the creation of several small holes (with air powered drill) along the superior temporal line to reattach the temporalis muscle with sutures (BOWLES), use of titanium microscrews (3mm) to reattach the muscle to the bone (WEBSTER) and the use of methylmethacrylate cement to fill the defect where extensive temporal bone resection took place, and preserve the contour before the muscle closure (BADIE1996).

Besides the cosmetic aspects, we believe it is also important to develop prospective studies including the pre operatory evaluation of a large number of surgical candidates, selecting those with previous pathologies and high risk of developing TMD after the surgical procedure.

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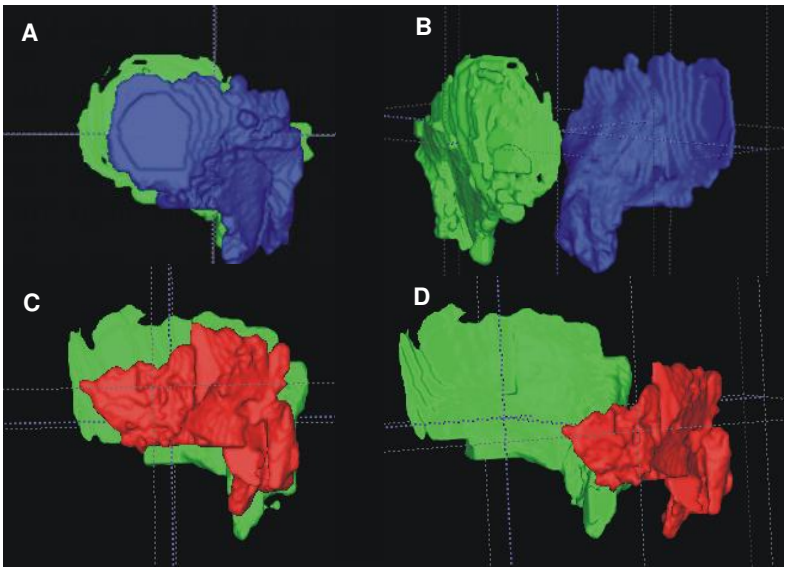

Figure1. Three D view of bilateral temporal muscle. (A and B: pre-operatory; C and D: post-operatory view, red is the operated muscle)

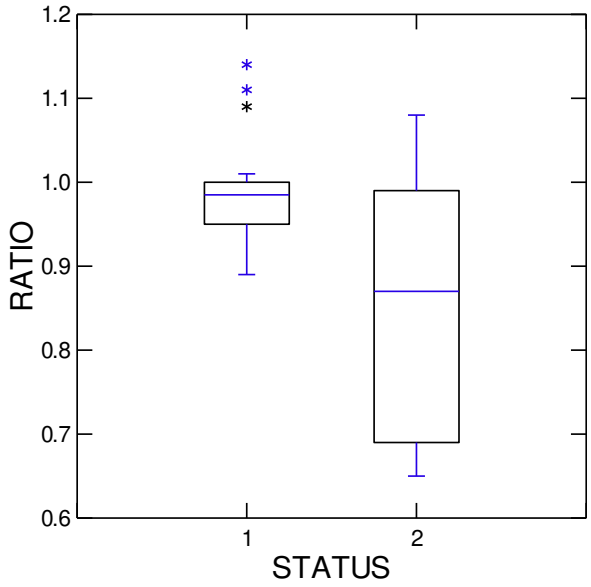

Figure2. Box plot showing the ratio between the volume of normal temporal muscle and the volume of the affected side. Status1=pre-operatory (0.99±0.07) and status2=post-operatory (0.86±0.15), p=0.004.

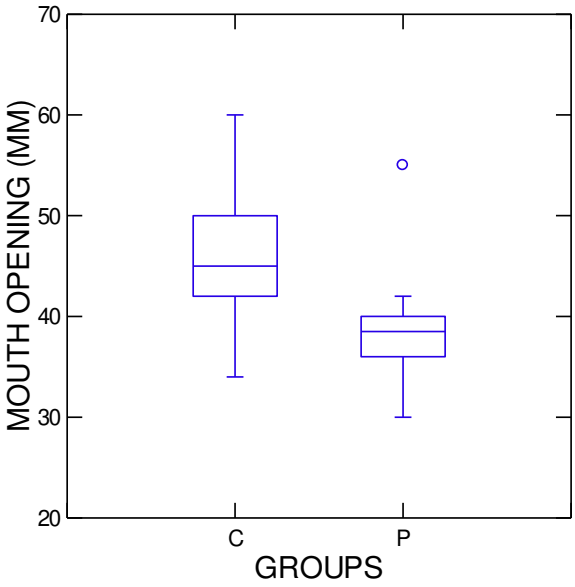

Figure 3. Box plot showing the maximal mouth opening for controls (C) and patients (P). Controls =46.6±5.1mm, patients =38.7± 6.9mm; p<0.0001.

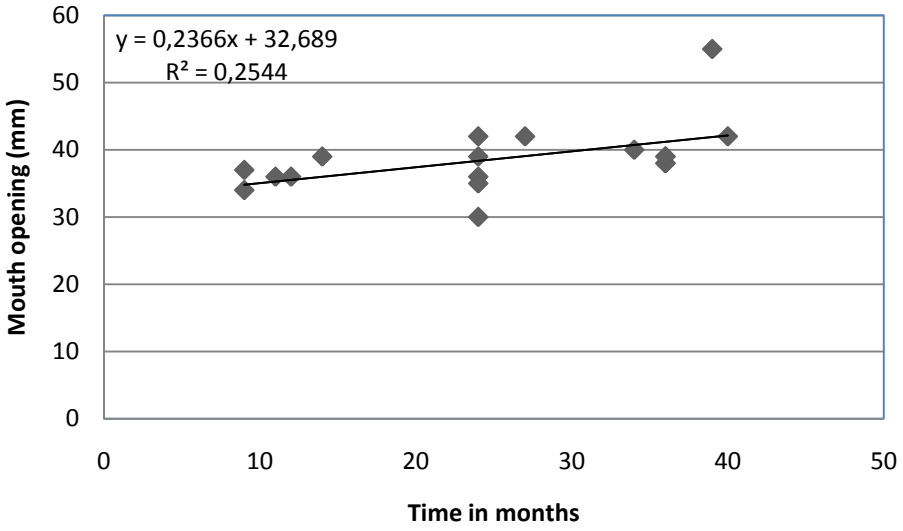

Figure 4. Pearson's correlation between mouth opening (mm) and time after surgery (months).