ANA FILIPA DUARTE LOPES

O IMPACTO DE DIFERENTES TIPOS DE EPILEPSIA NO FUNCIONAMENTO NEUROCOGNITIVO E NOS RESULTADOS ESCOLARES DE CRIANÇAS E ADOLESCENTES

Dissertação de Doutoramento em Psicologia, área de especialização em Neuropsicologia, apresentada à Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra e realizada sob a orientação do Professor Doutor Mário Manuel Rodrigues Simões.

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Universidade de Coimbra

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DISSERTAÇÃO DE DOUTORAMENTO

Título: O impacto de diferentes tipos de epilepsia no funcionamento neurocognitivo e nos resultados escolares de crianças e adolescentes
Ano: 2013
Autora: Ana Filipa Duarte Lopes
Orientação Científica: Professor Doutor Mário Manuel Rodrigues Simões
Domínio Científico: Psicologia
Especialidade: Neuropsicologia
Instituição: Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra

Este trabalho foi apoiado por uma Bolsa de Doutoramento concedida pela Fundação para a Ciência e Tecnologia do Ministério da Ciência e do Ensino Superior [SFRH/BD/40758/2007] e pelo Projecto de Investigação "Adaptação e Estandardização de Testes Neuropsicológicos: Estudos Normativos e de Validade" (Fundação para a Ciência e Tecnologia; 35410/PSI/2000, SAPIENS /POCTI).

Desenho de Capa: Afonso Teixeira Lopes
Design e Paginação: GODÉ - Arte e Design, Lda
Impressão: Digiset, Lda

Dedico esta dissertação à Lígia M. G. Santos (1979-2008)
em reconhecimento dos seus contributos para a
neuropsicologia pediátrica em Portugal.

AGRADECIMENTOS

Um Ofício que Fosse de Intensidade e Calma,

António Ramos Rosa

Um ofício que fosse de intensidade e calma
e de um fulgor feliz
E que durasse com a densidade ardente e contemporânea
de quem está no elemento aceso e é a estatura
da água num corpo de alegria
E que fosse fundo o fervor de ser a metamorfose da matéria
que já não se separa da incessante busca
que se identifica com a concavidade originária
que nos faz andar e estar de pé
expostos sempre à única face do mundo
Que a palavra fosse sempre a travessia
de um espaço em que ela própria fosse aérea
do outro lado de nós e do outro lado de cá
tão idêntica a si que unisse o dizer e o ser
e já sem distância e não-distância nada a separasse
desse rosto que na travessia é o rosto do ar e de nós próprios

Gostaria de agradecer ao meu orientador, Professor Doutor Mário Manuel Rodrigues Simões, com quem tive o privilégio de dar os primeiros passos enquanto psicóloga, e com quem nos últimos treze anos, desde o final da licenciatura, tenho colaborado em diversas investigações no domínio da avaliação psicológica. Agradeço as oportunidades proporcionadas ao longo do meu percurso académico e a orientação deste trabalho.

À Professora Faraneh Vargha-Khadem agradeço o carinho com que me acolheu e o inesquecível período de aprendizagem que me propiciou no Departamento de Neuropsicologia do *Great Ormond Street Hospital* e na Unidade de Neurociências do Desenvolvimento do *Institute of Child Health* (UCL).

À Fundação para a Ciência e Tecnologia, pelo financiamento concedido.

À Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra, pela formação científica e pelas lições de humanidade.

Às crianças, pais e professores que se mobilizaram de forma tão generosa para participar nesta investigação, por perceberem que esta demanda nos ajudaria a aperfeiçoar o conhecimento e o tratamento das crianças e adolescentes com epilepsia, mesmo quando não existia um benefício directo e imediato para elas.

À Maria José Fonseca, pela energia com que acolheu este trabalho no Centro de Desenvolvimento da Criança Torrado da Silva. Ainda, à Maria José Fonseca, ao José Paulo Monteiro, à Lurdes Ventosa, à Cristina Martins e à Laura Lourenço agradeço o entusiasmo e a colaboração na selecção dos sujeitos, o contacto inicial com as crianças e adolescentes que integram o nosso estudo e o trabalho de classificação das variáveis clínicas relativas à epilepsia. À Patrícia que prestou uma ajuda preciosa no secretariado. À Anabela pela cumplicidade. A todo o Centro de Desenvolvimento da Criança Torrado da Silva, agradeço a amizade e a cooperação prestadas durante a recolha dos dados.

À Conceição Robalo agradeço o interesse, o entusiasmo e o investimento nesta investigação. Agradecemos igualmente à Conceição Robalo, Isabel Fineza, Cristina Pereira e Olavo Gonçalves pela selecção dos sujeitos e classificação das variáveis clínicas relativas à epilepsia, no Centro de Desenvolvimento da Criança Luís Borges.

À Katrin Schulze pela amizade que fomos construindo, e pela valiosa ajuda em versões prévias dos artigos científicos incluídos nesta dissertação de doutoramento.

À Cláudia Lopes pela generosidade, disponibilidade e paciência no esclarecimento de dúvidas na área da metodologia.

Aos meus professores e, tantas vezes, companheiros de investigação, agradeço todos os ensinamentos e amizade: Professora Doutora Cristina Petrucci Albuquerque, Professora Doutora Filomena Gaspar, Professora Doutora Isabel Alberto, Mestre Manuela Vilar, Professor Doutor Marcelino

Pereira, Professora Doutora Maria João Seabra-Santos e Professora Doutora Salomé Pinho.

Às minhas queridas Bárbara, Carmen e Margarida pela cumplicidade que desenvolvemos, já crescidas, no banco da escola. À Andreia, à Catarina e à Marta, com quem a vida é muito mais fabulosa… À "fada azul", que está sempre lá, a voar, mas sempre perto… Aos meus amigos rubros, Raquel, Renato, Renatão, Ana e Paço, com quem as utopias ficam mais perto.

Aos meus pais, Suzel e Vasco, pelo amor imenso que me dá alento e confiança para fazer os caminhos mais difíceis.

Ao Afonso e ao Renato pelo amor, pela luta, e pelo caminho… agora chegou o tempo de ficar devagarinho…

ÍNDICE

RESUMO

A presente investigação centra-se no estudo das comorbilidades neurocognitivas da epilepsia em crianças e adolescentes. Em primeiro lugar, pretende caracterizar o funcionamento neurocognitivo – incluindo o funcionamento intelectual, memória, atenção, funções executivas, linguagem e rendimento escolar – em amostras bem definidas de crianças e adolescentes, com epilepsias comuns na idade pediátrica [Epilepsia do Lobo Temporal (ELT), Epilepsia do Lobo Frontal (ELF), Epilepsia de Ausências da Criança (EAC) e Epilepsia Benigna com Pontas Centro-Temporais (EBPCT)]. Os estudos apresentados analisam ainda a influência das variáveis relativas à epilepsia no funcionamento neurocognitivo deste grupo de crianças, incluindo o tipo de epilepsia, a idade de início da epilepsia, a duração activa e frequência da epilepsia, e o tratamento.

As crianças com epilepsia que participaram neste estudo cumpriam os seguintes critérios: (i) idade cronológica entre os 6 e os 15 anos de idade; (ii) diagnóstico de ELT, ELF, EAC ou EBPCT; (iii) resultados superiores ou iguais a 70 no QI de Escala Completa; (iv) medicadas com um ou dois fármacos, ou cuja medicação já havia sido retirada. O protocolo de avaliação contemplou a aplicação da Escala de Inteligência de Wechsler para Crianças – Terceira Edição e da Bateria de Avaliação Neuropsicológica de Coimbra. A primeira amostra clínica (estudo preliminar) incluiu 24 crianças com ELT e 24 controlos. A segunda amostra clínica inclui 90 crianças com epilepsia (30 com ELF, 30 com EAC, 30 com EBPCT), e 30 controlos.

No funcionamento intelectual, as crianças com ELF apresentaram resultados inferiores ao grupo de controlo no QI Verbal, QI de Escala Completa e no Índice de Velocidade de Processamento. Para além do

tipo de epilepsia, a duração activa da epilepsia foi o preditor mais forte dos problemas intelectuais. Na avaliação das funções mnésicas, mais uma vez o grupo com ELF apresentou défices significativos na memória verbal e visual. Foi igualmente observada uma associação entre problemas mnésicos, e a idade de início da epilepsia mais precoce e maior duração activa da epilepsia. Na área da atenção e funções executivas, as crianças com ELF e ELT apresentaram resultados inferiores aos dos grupos de controlo na manutenção da atenção, atenção dividida e funções executivas. Por outro lado, neste domínio neurocognitivo, os participantes com EAC também evidenciaram dificuldades na atenção dividida e na capacidade de planeamento. Para além do tipo de epilepsia, a idade de início da epilepsia foi o melhor preditor dos desempenhos na atenção e funções executivas. Na área da linguagem, as crianças com ELF apresentaram um padrão de dificuldades generalizadas, diferindo do grupo de controlo em todas as tarefas aplicadas (fluência verbal, nomeação rápida, consciência fonológica). As crianças com EAC e com EBPCT também apresentaram dificuldades na compreensão, nomeação rápida e na consciência fonológica. Por outro lado, as crianças com uma duração activa da epilepsia maior apresentaram mais problemas no domínio da compreensão. A análise da situação escolar dos sujeitos estudados revelou que 30% destas crianças se encontrava abrangida pelo ensino especial e que 18% já tinham sido retidas pelo menos num ano de escolaridade. Por outro lado, este estudo demonstrou que as crianças com ELF e aquelas que apresentavam uma duração activa da epilepsia mais longa apresentaram resultados escolares inferiores.

Os resultados destas investigações empíricas constituem um elemento de validação adicional da Bateria de Avaliação Neuropsicológica de Coimbra. Por outro lado, evidenciam a necessidade de facilitar avaliações precoces às crianças e adolescentes com epilepsia em idade escolar, com protocolos de avaliação neuropsicológica compreensivos e extensos, de modo a estabelecer planos de intervenção psicológicos e escolares adequados e atempados, capazes de minimizar o impacto negativo dos problemas neurocognitivos no desempenho escolar e na qualidade de vida

ABSTRACT

This research studies focuses on the study of neurocognitive comorbidities of epilepsy in children and adolescents. First, we aim to describe neurocognitive functioning – including intellectual assessment, memory, attention, executive functions, language and school achievement – in well defined samples of children and adolescents with common types of childhood epilepsy [Temporal Lobe Epilepsy (TLE), Frontal Lobe Epilepsy (FLE), Childhood Absence Epilepsy (CAE) and Benign Epilepsy with Centro-Temporal Spikes (BECTS)]. In addition, the influence of following epilepsy related variables on neurocognitive functioning was investigated: type of epilepsy, age at epilepsy onset, duration of epilepsy, frequency of seizures and treatment.

Children with epilepsy were selected based on the following criteria: (i) children had to be between 6 and 15 years of age; (ii) diagnosis of TLE, FLE, CAE or BECTS; (iii) results on Full Scale IQ ≥70; and (iv) they were receiving no more than two antiepileptic medications. The assessment protocol included Wechsler Intelligence Scale for Children – Third Edition and Coimbra's Neuropsychological Assessment Battery. The preliminary study included 24 children with TLE and 24 controls. The second clinical sample includes 90 children with epilepsy (30 with FLE, 30 with CAE, 30 with BECTS), and 30 controls.

On intellectual functioning, participants with FLE scored significantly lower than controls on Verbal IQ, Full Scale IQ and Processing Speed Index. Besides type of epilepsy, active duration of epilepsy was the best indicator of intellectual functioning. Regarding, memory functioning, FLE was once more the type of epilepsy that was related to significant deficits on verbal and

visual memory. Furthermore, earlier age at onset and longer active duration of epilepsy were associated with memory problems. Attention and executive functions performances showed that both children with FLE and TLE performed significantly worse than controls on sustained attention, divided attention and executive functions. Also, children with CAE showed a worse performance compared to controls on divided attention and planning. Besides type of epilepsy, age at onset of epilepsy was the best predictor of attention and executive functions performance. Regarding language functioning, children with FLE showed significant and generalized deficits in all the investigated language domains (verbal fluency, rapid naming and phonemic awareness). In children with CAE and BECTS difficulties in comprehension, rapid naming and on phonemic awareness were also observed. In addition, a longer active duration of epilepsy was associated with verbal comprehension problems. The analysis of school status revealed that 30% of these children were receiving support from special education services and 18% had at least repeated one year at school. Also, this study revealed that children with FLE and those with a longer duration of active epilepsy had lower school results.

The results of these empirical studies are an additional element of validation of Coimbra's Neuropsychological Assessment Battery. Also, they highlight the need to provide early assessments to school-age children and adolescents with epilepsy, with extensive and comprehensive neuropsychological assessment protocols, in order to establish adequate and timely school intervention plans that are able to minimize the negative impact of neurocognitive problems on school achievement and on the quality of life of these children and adolescents.

INTRODUÇÃO

Introdução

O interesse pela avaliação neuropsicológica de crianças e adolescente com epilepsia tem vindo a aumentar de forma significativa nos últimos anos (Anderson et al., 2001; Clark & Christiansen, 2005; Deonna & Roulet-Perez, 2005; Helmstaedter et al., 2011; Jambaqué et al., 2001a; Lee, 2010; Riccio et al., 2010; Salpekare et al., 2011; Schachter et al., 2008; Seegmuller & Metz-Lutz, 2007; Westerveld, 2010; Youngman et al., 2010), assumindo um papel de destaque no tratamento deste grupo clínico. A avaliação neuropsicológica permite suportar decisões relativas ao tratamento farmacológico, bem como às intervenções psicológica e pedagógica. A presente investigação centra-se no estudo do funcionamento neurocognitivo de crianças e adolescentes com epilepsia. Numa caracterização breve é de referir que a epilepsia é uma doença crónica que se distingue pela repetição espontânea de crises epilépticas, que constituem descargas anómalas de um grupo ou da totalidade dos neurónios cerebrais (Lima, 2007). Esta condição neurológica encontra-se entre as mais frequentes no período da infância e adolescência (Anderson et al., 2001; Braun, 2000; Clark & Christiansen, 2005; Nieminen & Eriksson, 2008; Westerveld, 2010). Estudos epidemiológicos atestam que a epilepsia afecta 1 a 2% das crianças em idade escolar (Dreisbach et al., 2001). A epilepsia surge tipicamente durante a infância e adolescência, sendo que 75% dos indivíduos com epilepsia experienciam a primeira crise antes dos 20 anos de idade (Hauser & Banerjee, 2008). Além disso, a epilepsia é um termo que agrupa várias síndromes, com distintos perfis de semiologia clínica, etiologia, idade de início e características neurofisiológicas. Finalmente,

a epilepsia não é uma condição estática, sendo o seu aparecimento e manifestações influenciados por factores genéticos, fisiológicos e por variáveis relativas ao desenvolvimento (Lee, 2010).

As últimas décadas constituem um período de progressos notórios no domínio da epileptologia. A descoberta de novas síndromes, o aparecimento de novos fármacos anti-epilépticos, o desenvolvimento de novos métodos de neuro-imagem, publicações com melhores descrições e estudos de *follow-up* de diferentes epilepsias na idade pediátrica, vieram permitir diagnósticos mais precisos e precoces (Deonna & Roulet-Perez, 2005). No entanto, neuropediatras e epileptologistas centraram as suas preocupações na nosologia, electrofisiologia, tratamento farmacológico e no prognóstico das crises, deixando para segundo plano as comorbilidades neuropsicológicas. Nos finais da década de noventa dá-se uma mudança de perspectiva (Beckung & Uvebrant, 1997; Aicardi, 1999), passando a ser progressivamente mais valorizado o estudo das comorbilidades neurocognitivas no estudo da epilepsia. Esta alteração foi impulsionada, nomeadamente, pela evidência de que algumas crianças cuja epilepsia estava controlada com medicação mínima, ou que não tinham crises, ou que estavam mesmo sem medicação, apresentavam ainda assim dificuldades de natureza cognitiva, nomeadamente na velocidade de processamento e na atenção. Por outro lado, os progressos na cirurgia da epilepsia demonstraram que a resolução das crises não só promovia a qualidade de vida destes sujeitos, bem como algumas crianças rapidamente melhoravam o seu funcionamento neurocognitivo, factos que não poderiam ser explicados por uma diminuição do tratamento farmacológico ou por uma melhoria no funcionamento socioemocional.

Mais recentemente, desde os anos 2000 têm sido publicados estudos relevantes e convergentes (Austin et al., 2001; Berg et al., 2005; Bhise et al., 2010; Fastenau et al., 2009; Hermann et al., 2006, 2007a, 2008; Jackson et al., 2013; Oostrom et al., 2003), que comprovam que muitas das comorbilidades neurocomportamentais nas crianças com epilepsia, previamente

consideradas efeitos secundários da medicação anti-epiléptica, estão na verdade presentes num número considerável de crianças cuja epilepsia acaba de ser diagnosticada e que ainda não se encontram medicadas. Isto é, estes problemas parecem estar presentes mesmo antes da primeira convulsão, sugerindo que nalguns casos os défices cognitivos são um primeiro sintoma da perturbação fisiológica que dará origem à epilepsia, e não apenas um efeito secundário das convulsões ou dos fármacos. No estudo de base populacional do Connecticut (Berg et al., 2008), que avaliou o funcionamento intelectual numa amostra de 613 crianças com um diagnóstico recente de epilepsia, 26% das crianças apresentaram um funcionamento intelectual inferior aos parâmetros da normalidade. Fastenau et al. (2009) estudaram um grupo de 282 crianças entre os 6 e os 14 anos de idade, no momento da primeira crise reconhecida, verificando-se que 27% das crianças já manifestavam défices neurocognitivos. Hermann et al. (2007a) reportaram uma prevalência muito elevada (31% no grupo com epilepsia vs. 6% no grupo de controlo) de Perturbação de Hiperactividade com Défice de Atenção em crianças com um diagnóstico recente de epilepsia. Por outro lado, Jackson et al. (2013) concluíram que 50% das 94 crianças estudadas no momento do diagnóstico da sua epilepsia apresentavam dificuldades escolares. Finalmente, vários outros estudos sugerem que os problemas escolares (Berg et al., 2005; Hermann et al., 2006; Oostrom et al., 2003) e comportamentais (Austin et al., 2001; Hesdorffer et al., 2004; Jones et al., 2007) podem mesmo anteceder o diagnóstico de epilepsia e o reconhecimento da primeira convulsão.

As comorbilidades neuropsicológicas são um tópico importante, mas difícil de abordar tendo em conta que a relação entre epilepsia e funcionamento neuropsicológico parece ser multifactorial. Como aliás se podia ler em destaque no dia 17 de Maio de 2013 no site da Liga Internacional Contra a *Epilepsia Epilepsy is still a puzzle*. Vários factores dependentes entre si e por isso difíceis de estudar separadamente, contribuem para as comorbilidades neuropsicológicas. Várias variáveis clínicas relativas à

epilepsia parecem influenciar os défices neurocognitivos nas crianças com epilepsia, com destaque para a etiologia, o tipo de epilepsia, a idade de inicio da epilepsia, a duração activa da epilepsia, a frequência das crises, as descargas epilépticas subclínicas e o tratamento farmacológico.

No que diz respeito à *Etiologia*, as epilepsias podem ser classificadas da seguinte forma: idiopáticas, sintomáticas e criptogénicas ou de etiologia desconhecida (Berg et al., 2010; Commission on Classification and Terminology of the International League Against Epilepsy, 1989; Shorvon, 2011). As epilepsias idiopáticas têm uma origem predominantemente genética, não se verificando uma perturbação neuropatológica ou neuroanatómica importante. As epilepsias sintomáticas devem-se a um dano cerebral reconhecível (por ex., resultados de má formação, trauma, infecções do sistema nervoso central, tumor). Noutras situações, coloca-se a hipótese das epilepsias serem sintomáticas, apesar de tal não ser demonstrável; denominando-se estes casos por epilepsias criptogénicas ou de etiologia desconhecida. Vários estudos sugerem a existência de um impacto muito importante para a etiologia subjacente na explicação das comorbilidades neuropsicológicas, sendo descritas dificuldades mais acentuadas – nomeadamente no funcionamento intelectual (Bulteau et al., 2000), em funções cognitivas específicas (Fastenau et al., 2009), desempenho escolar (Berg et al., 2005; Aldenkamp et al., 2005) e a nível comportamental (Oostrom et al., 2003), – nas crianças cujas epilepsias têm como base uma disfunção ou dano cerebral (epilepsias relacionadas com a localização, maioritariamente de etiologia desconhecida e epilepsias generalizadas sintomáticas).

O *Tipo de Epilepsia* é outra variável clínica relativa à epilepsia que parece contribuir para a explicação das comorbilidades neuropsicológicas. Uma das principais distinções nos tipos de epilepsia é entre as crises parciais e crises generalizadas. As crises parciais começam numa área circunscrita das células nervosas (o foco epiléptico) num dos hemisférios e propagam-se a partir daí. Por outro lado, as crises generalizadas mobilizam

ambos os hemisférios desde o início da crise. A primeira classificação internacionalmente aceite centrou-se na definição do tipo de crise, com base na sintomatologia das crises e nos resultados dos exames electroencefalográficos (Commission on Classification and Terminology of the International League Against Epilepsy, 1981). Tendo em conta, que este sistema apresentava limitações significativas, um novo sistema centrado na síndrome epiléptica foi desenvolvido (Commission on Classification and Terminology of the International League Against Epilepsy, 1989), passando a contribuir para o processo de diagnóstico variáveis como a idade de início, o desenvolvimento intelectual, dados do exame neurológico e estudos de neuroimagem, para além da sintomatologia das crises e dos resultados dos exames electroencefalográficos (Fejerman, 2002).

Existem síndromes epilépticas com idade de início na infância, como a Síndrome de West e a Síndrome de Lennox-Gastaust (encefalopatias epilépticas) que têm um impacto muito negativo no desenvolvimento psicomotor, apresentando a maioria destas crianças um diagnóstico de deficiência mental (Besag, 2006; Guerrini & Marini, 2011; Jambaqué et al., 2001b; Kieffer-Renaux et al., 2001). No entanto, neste trabalho destacaremos apenas os três tipos de epilepsia que serão incluídos nos estudos empíricos que vamos apresentar nesta dissertação: Epilepsia do Lobo Temporal, Epilepsia do Lobo Frontal, Epilepsia de Ausências na Criança e Epilepsia Benigna da Infância com Pontas Centro-Temporais.

A *Epilepsia do Lobo* Temporal é a epilepsia focal mais prevalente nas crianças e nos adultos (Sauerwein et al., 2005). Este tipo de epilepsia apresenta variações, no que diz respeito à etiologia, idade de início, tipo de crises (crises parciais simples, parciais complexas e/ou secundariamente generalizadas), severidade e duração. Apesar da epilepsia do lobo temporal ser uma perturbação com início durante a idade escolar, só nos últimos anos começaram a surgir os primeiros estudos neuropsicológicos com crianças. As investigações publicadas demonstram que a epilepsia do lobo temporal produz défices neurocognitivos nestas crianças, incluindo défices mnésicos (Cormack et al. 2012; Culhane-Shelburne et al., 2002; Gonzalez et al., 2007;

Hermann et al., 2007b; Jambaqué et al., 1993), perturbações na linguagem (Cohen et al., 1990; Jambaqué, 2001; Jansky et al., 2005) e défices na atenção e funções executivas (Hernandez et al., 2002, 2003; Igarashi et al., 2002). Por outro lado, a epilepsia do lobo temporal parece também constituir um factor de risco para a ocorrência de dificuldades escolares e de problemas de comportamento (Jambaqué, 2001).

A *Epilepsia do Lobo Frontal* é considerada o segundo tipo mais frequente de epilepsia parcial da infância, sendo a sua prevalência de 20 a 30% entre as epilepsias parciais (Manford et al., 1992), situando-se a sua idade de início média entre os 4 e os 8 anos de idade (Sinclair et al., 2004). Este tipo de epilepsia pode associar-se a uma série de tipos de crises incluindo crises parciais simples, parciais complexas e secundariamente generalizadas, ou a uma combinação destas. Os lobos frontais têm um papel fundamental nas funções cognitivas e no comportamento, tendo em conta que estão envolvidos em funções importantes, incluindo as funções motoras, competências linguísticas, atenção e funções executivas, comportamento, competências sociais (Anderson et al., 2001; Braakman et al., 2011; Chieffo et al., 2011). Nos adultos com epilepsia do lobo frontal têm sido descritas perturbações ao nível do planeamento e da memória de trabalho, impulsividade, défices de atenção e dificuldades ao nível da coordenação motora. Estudos recentes apontam para a presença deste tipo de défices também em crianças e adolescentes com epilepsia do lobo frontal (Auclair et al., 2005; Braakman et al., 2011; Bulteau et al., 2000; Culhane-Shelburne et al., 2002; Hernandez et al., 2002, 2003; Luton et al., 2010; Prévost et al., 2006; Riva et al., 2002, 2005; Vanasse et al., 2005).

A *Epilepsia de Ausências na Criança* é uma forma bastante comum de epilepsia na idade pediátrica, com uma incidência entre 10-15% nas epilepsias diagnosticadas em idade escolar (Berg et al., 2000; Durón et al., 2005; Jallon et al., 2005). A idade de início varia entre os 3 e os 13 anos de idade, com maior incidência entre os 5 e os 7 anos de idade (Hirsch & Panayiotopoulos, 2005). Tem-se verificado que habitualmente cessa espontaneamente aos 12 anos de idade. A epilepsia de ausências na

criança é caracterizada por breves episódios de alteração da consciência, nos quais a criança pára subitamente uma actividade e olha fixamente durante um curto período de tempo, continuando depois a actividade que estava a realizar, sem qualquer evidência de um período pós–confusional. As ausências podem ocorrer várias vezes durante o dia, e são caracterizadas por um electroencefalograma com complexos de ponta-onda usualmente a 3 Hz (Bernard & Lowenstein, 2003; Browne & Holmes, 2004). Apesar de durante muito tempo a epilepsia de ausências na criança ter sido considerada uma forma de epilepsia benigna, estudos recentes associam-na a défices no funcionamento neurocognitivo, sobretudo nas funções da atenção e linguagem, que se relacionam com dificuldades escolares (Caplan et al., 2008;Chevalier et al., 2000; Connant et al., 2010; D'Agati et al., 2012; Hernandez et al., 2002, 2003; Jackson et al., 2013; Nolan et al., 2004; Oostrom et al., 2003; Pavone et al. 2001; Vanasse et al., 2005; Vega et al., 2010).

A *Epilepsia Benigna com Pontas Centro-Temporais,* também denominada epilepsia rolândica é a forma mais comum de epilepsia nas crianças, representando cerca de 20% das epilepsias em crianças com idade inferior a 15 anos (Arzimanoglou et al., 2004; Dalla Bernardina et al., 2005). O termo "benigna" refere-se ao facto da frequências das crises ser relativamente baixa, e pelo facto da remissão das crises ocorrer espontaneamente na adolescência (Goldberg-Stern et al., 2010). A idade de início varia entre os 2 e os 12 anos, sendo mais frequente entre os 5 e os 10 anos de idade (Browne & Holmes, 2004). Neste tipo de epilepsia, as crises são raras e ocorrem com mais frequência no sono (Pinton et al., 2006). Por outro lado, as crises são habitualmente crises hemifaciais clónicas, por vezes precedidas de disestesias, disartria e com manutenção da consciência, com duração inferior a 2 minutos (Gonçalves, 2007). As crianças com este tipo de epilepsia apresentam um funcionamento intelectual geral dentro dos parâmetros da normalidade (Croona et al., 1999; Deonna & Roulet-Perez, 2005; Northcott et al., 2005; Papavasiliou et al., 2005; Pinton et al., 2006; Tedrus et al., 2009). No entanto, estudos recentes demonstram que este grupo de sujeitos apresenta uma variedade de défices neurocognitivos – linguagem,

atenção, memória, aptidão visoperceptiva – que podem influenciar os seus desempenhos académicos de forma negativa (Chilosi et al., 2006; Clarke et al., 2007; Croona et al., 1999; Danielsson & Petermann, 2009; Giordani et al., 2006; Goldberg-Stern et al., 2010; Gülgönen et al., 2000; Miziara et al., 2012; Monjauze et al., 2005; Neri et al., 2012; Northcott et al., 2005, 2007; Piccinelli et al., 2008; Pinton et al., 2006; Sánchez-Carpintero & Neville, 2003; Vinayan et al., 2005; Völkl-Kernstock et al., 2009; Weglage et al., 1997).

A *Idade de Início da Epilepsia* na infância distingue-se daquela com idade de início na idade adulta, sobretudo por estarmos perante um cérebro em desenvolvimento. O início da epilepsia numa idade precoce pode ser altamente prejudicial para a aquisição de funções que se começam a desenvolver, podendo até precipitar a reorganização de algumas dessas funções no cérebro das crianças (Laurent & Arzimanoglou, 2006). A plasticidade neuronal nas crianças é superior à dos adultos; porém, maior plasticidade não implica necessariamente plasticidade adaptativa. Tendo em conta que menos redes estão funcionalmente especializadas nos primeiros anos de vida, sendo os constrangimentos entre redes mais fracos e, por isso, as interacções anómalas entre redes mais prováveis (Cazzulo et al., 1998). As investigações da equipa de Hermann (Hermann et al., 2002, 2003) demonstram que cérebros imaturos não aparentam beneficiar da plasticidade para a reorganização e protecção das funções cognitivas, tendo em conta que a presença de actividade epiléptica parece associar-se a efeitos adversos na estrutura e função cerebrais. Os estudos de Hermann demonstram que a idade de início durante a infância da epilepsia do lobo temporal se associa a um neurodesenvolvimento adverso – quer na estrutura cerebral, que nas funções cognitivas – que é especialmente evidente na redução do volume da substância branca (Hermann et al., 2002) e do corpo caloso (Hermann et al., 2003). De facto, a idade de início precoce parece ser um dos indicadores mais importantes do funcionamento intelectual das crianças com epilepsia. No estudo de Cormack et al. (2007) 82% das crianças cuja epilepsia tinha tido início no primeiro ano de vida

apresentavam um comprometimento cognitivo. Por outro lado, o estudo de base populacional do Connecticut (Berg et al., 2008), identifica a idade de início da epilepsia antes dos 5 anos de idade como o factor que mais contribui para resultados inferiores nas escalas de inteligência. Para além do funcionamento intelectual, a idade de início da epilepsia também se associa a dificuldades noutros domínios: memória (Helmstaedter et al., 2001; Kernan et al., 2012;Nolan et al., 2004; Riva et al., 2005), atenção e funções executivas (Hoie et al., 2006; Luton et al., 2010; Neri et al., 2012; Riva et al., 2005), linguagem (Schoenfeld et al., 1999), desempenho escolar (Fastenau et al., 2008; Piccinelli et al., 2008), problemas comportamentais (Hoie et al., 2006; Tanabe et al., 2013).

A *Duração Activa da Epilepsia* e a *Frequência das Crises* associam-se com frequência a défices no funcionamento intelectual (Bulteau et al. 2000; Caplan et al., 2004, 2008; Nolan et al., 2003; Singhi et al., 1992), bem como nas funções cognitivas mais específicas, nomeadamente, na memória (Nolan et al., 2004; Riva et al., 2002, 2005; Schoenfeld et al., 1999), linguagem (Caplan et al., 2004, 2006, 2008, 2009; Monjauze et al., 2005; Papavasiliou et al., 2005), atenção e funções executivas (Caplan et al., 2008; Hoie et al., 2006; Riva et al., 2005), funções motoras (Beckung & Uvebrant, 1997), velocidade de processamento (Aldenkamp et al., 2005). No entanto, importa realçar que estas variáveis clínicas, muitas vezes, não funcionam como variáveis independentes e correlacionam-se de forma significativa com o tipo de epilepsia (Aldenkamp et al., 2005) e com a idade de início da epilepsia (Nolan et al., 2003).

As *Descargas Epilépticas Subclínicas* ou *Défice Cognitivo Transitório* consistem na ocorrência de crises subclínicas, sem evidência clínica manifestada em simultâneo, que causam interrupções breves no processo de recepção da informação, e são muito difíceis de observar (Fowler, 1997). Os seus efeitos podem afectar de modo significativo o processamento cognitivo, nomeadamente, a atenção, a memória de trabalho e os tempos

de reacção (Fastenau, 2011; Holmes & Lenck-Santini, 2006; Lee, 2010; Svoboda, 2004). Esta actividade neuronal anómala, e que pode ser apenas evidenciada através de um electroencefalograma, pode ter consequências imediatas ou a longo-prazo no funcionamento cognitivo (Metz-Lutz et al., 2001). A ocorrência destes eventos na idade pediátrica, momento crítico para o desenvolvimento do funcionamento neurocognitivo e novas aquisições, poderá ter um efeito negativo no desempenho escolar destas crianças. Deste modo, quando se observam problemas de aprendizagem ou comportamentais, em crianças que apresentam um funcionamento cognitivo normal, que não são explicados por crises frequentes ou pelos efeitos da medicação, a presença de descargas epilépticas subclínicas deverá ser considerada.

A *Medicação Anti-Epiléptica* pode melhorar ou agravar o funcionamento cognitivo nalgumas crianças e adolescentes com epilepsia (Deonna & Roulet-Perez, 2005; Jokeit et al., 2011; Sirén et al., 2007). Idealmente o fármaco seleccionado deve ser utilizado em monoterapia e na dosagem mais baixa possível, o que é alcançado em 70-75% das crianças com epilepsia (Dulac, 2005). Estudos recentes sobre os efeitos neurocognitivos dos fármacos anti-epilépticos confirmam que a iniciação rápida da toma, a politerapia (utilização de mais de um fármaco) e as dosagens elevadas podem agravar os problemas cognitivos (Aldenkamp et al., 2005, Aldenkamp & Bootsma, 2005; Beckung & Uvebrant, 1997; Bulteau et al, 2000; Caplan et al., 2004; Hoie et al., 2006; Meador, 2002; Nolan et al., 2003; Pimentel & Robalo, 2007). A inatenção e a lentificação (mental ou motora) são os efeitos mais comuns dos fármacos anti-epilépticos no funcionamento neurocognitivo (Hessen et al., 2006; Lagae, 006; Mandelbaum et al., 2009; Meador, 2002; Mitchell et al., 1993; Williams et al., 1998). Consequentemente os efeitos secundários da medicação ocorrerão com mais frequência nos testes que avaliam a atenção, vigilância, aprendizagem, memória, velocidade de processamento, funções motoras e tempos de reacção. O grau de severidade dos efeitos secundários dos fármacos anti-epilépticos nas funções cognitivas é considerado leve a

moderado. No entanto, o seu impacto pode ser substancial, principalmente quando estão envolvidas funções críticas, como é o caso das aquisições escolares nas crianças e adolescentes. Contudo, a maioria das investigações acerca dos efeitos cognitivos dos fármacos anti-epilépticos são feitas com adultos (Lagae, 2006), o que introduz desde logo alguns problemas, uma vez que na maioria dos casos, os efeitos são mais graves nas crianças do que nos adultos (Dulac, 2005). A idade pediátrica constitui pois um grupo de risco acrescido, uma vez que mesmo os impactos cognitivos mais subtis se poderão tornar cumulativos ao longo do desenvolvimento.

A avaliação neuropsicológica assume um papel central na investigação e tratamento multidisciplinar das crianças com epilepsia, na medida em que possibilita: (i) a avaliação do nível cognitivo geral e a identificação de áreas fortes e de vulnerabilidade nas funções cognitivas específicas, bem como uma medida do desempenho escolar e funcionamento socioemocional, considerando a necessidade de estabelecer planos de intervenção; (ii) a avaliação do funcionamento actual, com o objectivo de o monitorizar e correlacionar directamente com a história da epilepsia, incluindo o regime de tratamento farmacológico; (iii) no âmbito da cirurgia da epilepsia, a avaliação neuropsicológica é um procedimento fundamental, na medida em que fornece informação valiosa relativamente à integridade de funções em regiões cerebrais específicas, avaliando o risco de défices cognitivos severos na sequência da cirurgia, e proporcionando uma caracterização do funcionamento neuropsicológico pré e pós cirurgia, que permite medir o sucesso da intervenção para além da ausência de crises (Boyer, 2010; Deonna & Roulet-Perez et al., 2005; Jones-Gotman et al., 2010; Lassonde et al., 2006; Lee, 2010; Smith et al., 2010; Rankin & Vargha-Khadem, 2007).

Uma vez que vários domínios do funcionamento neuropsicológico podem ser afectados pelo processo epiléptico, o processo de avaliação neuropsicológica deve ser extenso, incluir o recurso a distintos interlocutores (crianças e adolescentes, pais, professores), diversas técnicas e metodologias

(entrevistas, testes, observação), integrando o estudo de diferentes áreas, incluindo a avaliação do funcionamento intelectual, memória, atenção, funções executivas, linguagem, funções viso-perceptivas, funções motoras, comportamento adaptativo, desempenho escolar, qualidade de vida e a área socioemocional. Tendo em conta que os resultados da avaliação neuropsicológica podem ser influenciados por múltiplos factores – que incluem a etiologia e tipo de epilepsia, a idade de início, a frequência das crises, a duração activa da epilepsia, efeitos secundários da medicação anti-epiléptica – o processo de avaliação neuropsicológica deve ser complementado com a recolha detalhada da história de desenvolvimento, médica e escolar dos indivíduos. Por outro lado, esta informação deve ser integrada com os exames de neuroimagem (estruturais e funcionais) e estudos neurofisiológicos disponíveis (Baldweg & Liégeois, 2010; Lassonde et al., 2006; Rankin & Vargha-Khadem, 2007).

A presente investigação pretendeu dar continuidade ao estudo por nós realizado no âmbito da nossa dissertação de mestrado, que comprovou a utilidade clínica da Bateria de Avaliação Neuropsicológica de Coimbra na avaliação de crianças e adolescentes com epilepsia (Lopes, 2007). Este estudo constituiu o primeiro passo para a caracterização desta população clínica na idade pediátrica no nosso país. Na população adulta já haviam sido realizados importantes estudos nacionais (Baeta, 2002, 2003; Meneses, 2005). Nos últimos anos foram iniciados outros estudos no nosso país, com a população pediátrica com epilepsia que não podemos deixar de destacar. Após a validação portuguesa do questionário de qualidade de vida *Disabkids* (Carona et al., 2011; The European DISABKIDS Group, 2006), o grupo de Carlos Carona, e Maria Cristina Canavarro, com quem tivemos oportunidade de colaborar, demonstrou a validade deste questionário para crianças e adolescentes com epilepsia (Carona et al., 2013). No que diz respeito aos estudos com a Bateria de Avaliação Neuropsicológica de Coimbra, também destacamos o trabalho em curso de Ricardo Lopes, que pretende validar alguns testes desta bateria de testes em crianças

candidatas a cirurgia da epilepsia [Dissertação de Doutoramento com o título "Functional mapping and neuropsychological assessment in Epilepsy Surgery"; sob a orientação científica de Mário R. Simões, Alberto Leal e Mário Secca, com financiamento da Fundação para a Ciência e Tecnologia SFRH/BD/65617/2009]. Por último, o mais recente trabalho da Teresa Mendes que pretende estudar o ajustamento familiar ao diagnóstico de epilepsia na idade pediátrica [Dissertação de Doutoramento com o título "Adaptação psicológica e adesão ao tratamento na epilepsia pediátrica: Um estudo com díades de crianças/adolescentes e pais"; sob a orientação de Carla Crespo e Joan Kessner Austin, com financiamento da Fundação para a Ciência e Tecnologia SFRH/BD/86337/2012].

No início dos trabalhos desta dissertação de doutoramento em Neuropsicologia realizámos um estudo preliminar que avaliou as funções da atenção e funções executivas num grupo de 24 crianças e adolescentes com epilepsia do lobo temporal, considerando o impacto da idade de início da epilepsia e a evolução das crises nas funções cognitivas estudadas [Capítulo I; Lopes et al., 2010].

Seguindo posteriormente um plano mais sistemático, os restantes estudos empíricos que apresentaremos foram realizados também no âmbito da nossa Dissertação de Doutoramento em Neuropsicologia. Estas investigações pretendem, em primeiro lugar, caracterizar o funcionamento neurocognitivo – incluindo o funcionamento intelectual, memória, atenção, funções executivas, linguagem e rendimento escolar – em amostras bem definidas de crianças e adolescentes com três tipos de epilepsia comuns na idade pediátrica (Epilepsia do Lobo Frontal, Epilepsia de Ausências da Criança e Epilepsia Benigna com Pontas Centro-Temporais). Por outro lado, estes estudos pretendem investigar também a influência das variáveis relativas à epilepsia no funcionamento neurocognitivo deste grupo de crianças, incluindo o tipo de epilepsia, a idade de início da epilepsia, a duração activa da epilepsia, a frequência da epilepsia, e o tratamento.

Esta segunda amostra clínica inclui 90 crianças com epilepsia (30 com Epilepsia do Lobo Frontal, 30 com Epilepsia de Ausências na Criança,

30 com Epilepsia Benigna com Pontas Centro-Temporais), e 30 controlos. As crianças com epilepsia são utentes das consultas de epilepsia do Centro de Desenvolvimento da Criança Torrado da Silva do Hospital Garcia de Orta e do Centro de Desenvolvimento da Criança Luís Borges do Hospital Pediátrico de Coimbra. Neurologistas pediátricos classificaram os participantes com epilepsia tendo como base os critérios da Liga Internacional Contra a Epilepsia (Berg et al., 2010; Commission on Classification and Terminology of the International League Against Epilepsy, 1989) e forneceram informação clínica relativa à idade de início da epilepsia, data da última convulsão, frequência da crises e tratamento farmacológico. As crianças com epilepsia que participaram neste estudo cumpriam os seguintes critérios: (i) idade cronológica entre os 6 e os 15 anos de idade; (ii) diagnóstico de Epilepsia do Lobo Frontal, Epilepsia de Ausências da Criança ou Epilepsia Benigna com Pontas Centro-Temporais; (iii) resultados superiores ou iguais a 70 no QI de Escala Completa da Escala de Inteligência de Wechsler para Crianças – Terceira Edição (WISC-III; Wechsler et al., 2003); medicadas com um ou dois fármacos, ou cuja medicação já havia sido retirada.

O estudo foi aprovado pelas Comissões de Ética de ambas as instituições. As famílias e crianças deram o seu consentimento informado para participarem na presente pesquisa. Cada médico responsável identificou os participantes que cumpriam os critérios de inclusão no estudo, explicando de forma breve às famílias e crianças o objectivo e procedimento do estudo. Após o consentimento das famílias, abordámos as crianças e respectivas famílias explicando com mais detalhe os contornos do presente estudo, e agendámos o dia da avaliação. Antes da avaliação neuropsicológica formal, foi sempre conduzida uma entrevista com os pais da criança, tendo em vista a recolha da história de desenvolvimento e escolar do sujeito, bem como informação relativa à história da epilepsia. Complementarmente foram consultados os processos clínicos hospitalares de cada um dos participantes, e sempre que necessário conferenciámos com o médico responsável pelo caso. O protocolo de avaliação neuropsicológica foi aplicado em duas sessões, uma de manhã, seguida de uma pausa para almoço, e

outra à tarde. A cada família foi dedicada uma sessão de devolução de informação, bem como um relatório escrito e, sempre que necessário, foi realizada uma conversa telefónica com o respectivo professor responsável. O protocolo de avaliação contemplou a aplicação da Escala de Inteligência de Wechsler para Crianças – Terceira Edição (WISC-III; Wechsler, 2003) e da Bateria de Avaliação Neuropsicológica de Coimbra (BANC; Simões et al., *in press*). Os seguintes procedimentos de exame também foram incluídos – questionários de comportamento [Inventário de Competências Sociais e de Problemas de Comportamento em Crianças e Adolescentes (ICCP; Fonseca et al., 1994; Albuquerque et al., 1999a; Achenbach, 1991a) e Inventário de Comportamentos da Criança para Professores (ICCPR; Fonseca et al., 1995; Albuquerque et al., 1999b; Achenbach, 1991b)], inventários de qualidade de vida (DISABKIDS – Questionário para pais de crianças e adolescentes com problemas crónicos e Questionário para crianças e adolescentes com problemas crónicos; The European DISABKIDS Group, 2006), teste de leitura (O Rei – Teste de Avaliação da Fluência e Precisão da Leitura; Carvalho, 2008); teste de compreensão leitora (Provas de avaliação da Compreensão Leitora; Mendonça, 2008) e teste de expressão escrita (Teste de Expressão Escrita; Martins, 2005). Os resultados relativos a estes últimos instrumentos de avaliação serão reportados em investigações futuras.

De seguida apresentamos os estudos empíricos organizados em seis capítulos distintos:

Capítulo I: *Evaluación neuropsicológica en niños con epilepsia: Funciones ejecutivas y atención en epilepsia del lóbulo temporal* [Lopes, A. F., Simões, M. R., Robalo, C., Fineza, I, & Gonçalves, O. (2010). Evaluación neuropsicológica en niños con epilepsia: Funciones ejecutivas y atención en epilepsia del lóbulo temporal. *Revista de Neurología, 5*, 265-272.].

As investigações que estudam a atenção e funções executivas nas crianças e adolescentes com epilepsia têm caracterizado sobretudo os sujeitos com epilepsia do lobo frontal. No entanto, nos últimos anos alguns

estudos sinalizaram dificuldades nestas áreas em crianças e adolescentes com epilepsia do lobo temporal (Fabre et al., 2005; Fleck et al., 2002; Guimarães et al., 2007; Igarashi et al., 2002; Laurent & Arzimanoglou, 2006; Rzezak et al., 2007). O objectivo desta investigação é a caracterização da atenção e funções executivas (Barragem de Sinais, *Trail Making Test* – Parte A, *Trail Making Test* – Parte B, Torre de Londres e Fluência Verbal Fonémica) num grupo de crianças e adolescentes com epilepsia do lobo temporal, considerando a influência da idade de início e da evolução da epilepsia.

Capítulo II: *Intellectual functioning in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes* [Lopes, A. F., Simões, M. R., Monteiro, J. P., Fonseca, M. J., Martins, C., Ventosa, L., Lourenço, L., & Robalo, C. (*in press*). Intellectual Functioning in Children with Epilepsy: Frontal Lobe Epilepsy, Childhood Absence Epilepsy and Benign Epilepsy with Centro-Temporal Spikes. *Seizure,* n/a, 1-7.].

Investigações realizadas nos últimos anos demonstram que as crianças e adolescentes com epilepsia apresentam resultados nas escalas de inteligência que se situam no limite inferior da amplitude média, divergindo da população normal (Berg et al., 2008; Caplan et al., 2004; O'Leary et al., 2006). A utilização das escalas de inteligência constitui um passo fundamental no processo de avaliação neuropsicológica das crianças e adolescentes com epilepsia. Sendo um primeiro momento na avaliação do funcionamento neurocognitivo, que fornecerá suporte para interpretar os resultados noutros instrumentos de avaliação. Nesta medida pretende-se explorar as potencialidades da WISC-III na identificação de áreas de vulnerabilidade nos grupos em análise. Neste estudo é caracterizado o funcionamento intelectual (resultados compósitos e subtestes) das três síndromes epilépticas em estudo (Epilepsia do Lobo Frontal, Epilepsia de Ausências da Criança e Epilepsia Benigna com Pontas Centro-Temporais), em comparação com um grupo de controlo. Por outro lado examinamos a influência de variáveis relacionadas com a epilepsia (tipo de epilepsia, idade de início, duração

activa, frequência das crises e medicação anti-epiléptica) nos resultados.

Capítulo III: *Memory functioning in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes* [Lopes, A. F., Monteiro, J. P., Fonseca, M. J., Robalo, C., & Simões, M. R. (*submitted*). Memory functioning in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes.].

A memória tem um papel fundamental no desempenho escolar, na medida em que as crianças têm de aprender e integrar informação todos os dias. Os problemas mnésicos nas crianças e adolescentes com epilepsia têm sido sobretudo documentados na epilepsia do lobo temporal (Cormack et al., 2012; Gonzalez et al., 2007, Jambaqué et al., 2007). Assim permanece em aberto se noutros tipos de epilepsia também poderão surgir défices nesta área, na medida em que a literatura recente tem apontado para a possibilidade da presença de problemas mnésicos noutras epilepsias focais (Braakman et al., 2012; Northcott et al, 2007), bem como nas epilepsias generalizadas (Kernan et al., 2012). O objectivo deste terceiro estudo foi a caracterização do funcionamento mnésico, através de 3 provas de memória da BANC (Lista de Palavras, Figura Complexa de Rey e Tabuleiro de Corsi) nas síndromes epilépticas em estudo (Epilepsia do Lobo Frontal, Epilepsia de Ausências da Criança e Epilepsia da Infância com Pontas Centro-Temporais). Adicionalmente foi estudado o impacto das variáveis clínicas relativas à epilepsia (tipo de epilepsia, idade de início, duração activa, frequência das crises e medicação anti-epiléptica) nas provas de memória.

Capítulo IV: *Attention and executive functions in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes* [Lopes, A. F., Monteiro, J. P., Fonseca, M. J., Robalo, C., & Simões, M. R. (*submitted*). Attention and executive functions in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes.].

As dificuldades na atenção e funções executivas são frequentemente relatadas pelos diferentes agentes educativos (pais e professores) das crianças e adolescentes com epilepsia. Por outro lado, estas funções são fundamentais para o funcionamento de outros domínios cognitivos, nomeadamente a memória e a linguagem (Anderson et al., 2001; Baron, 2004). Este quarto estudo é dedicado ao exame da atenção e funções executivas, recorrendo às 4 provas da BANC que avaliam estes domínios (Barragem de Sinais, Trail Making Test – Parte A, Trail Making Test – Parte B e a Torre de Londres), nos grupos com epilepsia em análise (Epilepsia do Lobo Frontal, Epilepsia de Ausências da Criança e Epilepsia da Infância com Pontas Centro-Temporais). Por outro lado, também é estudada a influência das variáveis relativas à epilepsia (tipo de epilepsia, idade de início, duração activa, frequência das crises e medicação anti-epiléptica) nos domínios da atenção e funções executivas.

Capítulo V: *Language functions in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes* [Lopes, A. F., Monteiro, J. P., Fonseca, M. J., Robalo, C., & Simões, M. R. (*submitted*). Language functions in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes.].

Ao contrário de outras funções cognitivas – como a memória, atenção e funções executivas – apenas um número muito reduzido de estudos tem caracterizado as funções da linguagem nas crianças com epilepsia (Caplan et al., 2009; Selassie et al., 2008). No entanto, pensa-se que a prevalência de perturbações da fala e linguagem nas crianças com epilepsia em idade escolar é elevada, cerca de 25% (Overvliet et al., 2011; Sillanpää, 1992), justificando assim a análise de diferentes domínios da linguagem nas crianças com epilepsia. O propósito deste estudo é a caracterização de funções da linguagem, utilizando as provas da BANC (Fluência Verbal Semântica, Fluência Verbal Fonémica, Compreensão de Instruções, Nomeação Rápida de Cores e Formas, Nomeação Rápida de Números, Consciência Fonémica –

Eliminação; Consciência Fonémica – Substituição), nos grupos com epilepsia em estudo (Epilepsia do Lobo Frontal, Epilepsia de Ausências da Criança e Epilepsia da Infância com Pontas Centro-Temporais). Finalmente, é analisada a influência das variáveis relativas à epilepsia (tipo de epilepsia, idade de início, duração activa, frequência das crises e medicação anti-epiléptica) nas diferentes tarefas de avaliação da linguagem.

Capítulo VI: *Risk factors for school problems in children and adolescents with epilepsy* [Lopes, A. F., Monteiro, J. P., Fonseca, M. J., Robalo, C., & Simões, M. R. (*submitted*). Risk factors for school problems in children and adolescents with epilepsy.].

Os problemas escolares são comuns nas crianças e adolescentes com epilepsia, incluindo nos grupos de crianças com um funcionamento intelectual normal (Reilly & Neville, 2011). Os factores que contribuem para esta vulnerabilidade não estão completamente esclarecidos, sendo provavelmente multifactoriais. Neste trabalho descreve-se a situação escolar dos grupos de crianças e adolescentes com epilepsia em estudo (Epilepsia do Lobo Frontal, Epilepsia de Ausências da Criança e Epilepsia da Infância com Pontas Centro-Temporais), e é examinada a influência das diferentes variáveis relativas à epilepsia (tipo de epilepsia, idade de início, duração activa, frequência das crises e medicação anti-epiléptica) nos resultados escolares das disciplinas de Português e Matemática.

Finalmente é apresentada a **Discussão Geral e Conclusões Finais** destes trabalhos, que incluem os principais resultados da presente investigação, bem como as suas potencialidades e limites.

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CAPÍTULO I

Evaluación neuropsicológica en niños con epilepsia: Funciones ejecutivas y atención en epilepsia del lóbulo temporal

Evaluación neuropsicológica en niños con epilepsia: Funciones ejecutivas y atención en epilepsia del lóbulo temporal[1]

Resumen

La atención y las funciones ejecutivas (FE) se corresponden con áreas de funciones cognitivas asociadas al lóbulo frontal. El estudio de la atención y FE en niños con epilepsia se ha enfocado en caracterizar pacientes afectos de epilepsia del lóbulo frontal, aunque recientemente también se han identificado déficits en esas áreas en epilepsia del lóbulo temporal (ELT). Los objetivos del estudio se enfocan en investigar la atención y FE en niños con ELT, considerando también la influencia de variables clínicas (edad de comienzo, evolución de la epilepsia). Se estudió la atención y las FE en 24 niños afectos de ELT, de edad entre 7 y 15 años y se compararon con 24 niños controles. A todos ellos se les pasaron las siguientes pruebas: Test-Cancelación, Trail-Making-Test, Torre-Londres y Fluencia-Verbal-Fonémica. El grupo con ELT rendía sustancialmente por debajo tanto en atención sostenida y dividida como en fluencia verbal fonémica. En los marcadores que evaluaban omisiones y errores, no habían diferencias entre los diferentes grupos en ninguno de los test aplicados. Se comprobó también una lentificación de la capacidad de procesamiento. Además, los pacientes con mayor precocidad de inicio de la epilepsia presentaban mayores dificultades en el mantenimiento de la atención y en las capacidades de planificación. Estos resultados refuerzan la necesidad de evaluar y monitorizar el área de la atención, de las FE y de la velocidad de procesamiento en niños con ELT, sobre todo en los que tienen un comienzo precoz de la epilepsia.

[1] Lopes, A. F., Simões, M. R., Robalo, C., Fineza, I, & Gonçalves, O. (2010). Evaluación neuropsicológica en niños con epilepsia: Funciones ejecutivas y atención en epilepsia del lóbulo temporal. *Revista de Neurología*, *5*, 265-272.

Palabras clave

Atención, Epilepsia del lóbulo temporal, Evaluación neuropsicológica, Fluencia verbal fonémica, Funciones ejecutivas, Niños, Test de cancelación, Torre de londres, Trail making test.

Introducción

Una de las funciones que pueden alterarse en las personas con epilepsia es la atención (Alonso et al., 2001; Auclair et al., 2005; Culhane-Shelburne et al., 2002; Henkin et al., 2005), independientemente del nivel de las funciones intelectuales (Williams et al., 2003). También son frecuentes quejas por falta de atención por parte de padres y profesores de los pacientes con epilepsia (Lopes et al., 2007). Se calcula que la tercera parte de los niños epilépticos sufren problemas de atención (Dunn & Kronenberg, 2006). Probablemente, entre los factores que mas contribuyen a desarrollar problemas de atención, se encuentren la disfunción bioeléctrica, los tratamientos farmacológicos y la disfunción cerebral subyacente (Anderson et al., 2001; Deonna & Roulet-Perez, 2005; Hessen et al., 2006).

La atención es uno de los procesos básicos del funcionamiento cognitivo, siendo el que asegura la conexión entre la percepción y el procesamiento de la información (Alberto, 2003). Dentro de la palabra 'atención' se incluyen varios apartados: el estado de vigilancia (forma básica de la atención – el nivel de alerta ó de vigilancia – que expresa la disponibilidad fisiológica para procesar la información y su respuesta correspondiente), la atención selectiva (la capacidad de enfoque en un estímulo determinado), la atención dividida (la capacidad de prestar atención simultáneamente a mas de un estímulo) y la atención sostenida (la capacidad para mantener la atención durante un período de tiempo prolongado). La atención por su parte también influencia y modula la realización de otras funciones cognitivas, cooperando con algunas de ellas, generalmente con la percepción y con las funciones ejecutivas, con las que

a menudo es erróneamente confundida.

Se denominan funciones ejecutivas una serie de funciones heterogéneos que abarcan diversos aspectos del proceso cognitivo, tales como planificación, organización, autorregulación, inhibición y flexibilidad (Lezak, 2004; Linden et al., 2000; Papazian et al., 2009; Pereira et al., 2006), siendo su función principal la de guiar la adaptación individual a nuevas situaciones. Baron (2004) define las funciones ejecutivas como aptitudes metacognitivas que permiten al sujeto percibir los estímulos, responder de forma adaptada, cambiar direcciones con flexibilidad, anticipar objetivos futuros, considerar consecuencias y responder de forma conjunta para usar todas estas capacidades para conseguir un objetivo común.

Los déficits de atención y de funcionamiento ejecutivo son valiosos predictores del rendimiento escolar. Un estudio de Williams y col. (Williams et al., 2001) ha encontrado mas conexiones significativas entre atención y fracaso escolar que con otras variables (memoria y factores socioeconómicos). No obstante, en algunos niños pueden considerarse las dificultades de atención como la primera advertencia de que existe un déficit cognitivo causado por las convulsiones (Aldenkamp et al., 2005a).

Se consideran atención y las funciones ejecutivas como unas de las funciones principales asumidas por el cortex frontal (Martín-González-Pérez et al., 2008). No obstante, el estudio de la atención y sobre todo de las funciones ejecutivas en niños y adolescentes epilépticos se ha enfocado preferentemente en caracterizar a los pacientes con epilepsia del lóbulo frontal. Sin embargo, recientes estudios han registrado déficits de estas áreas en niños afectados de epilepsia del lóbulo temporal (Fabre et al., 2005; Fleck & Straskowski, 2002; García-Peñas, 2009; Guimarães et al., 2007; Henkin et al, 2005; Igarashi et al., 2002; Laurent & Arzimanoglou, 2006; Rzezak et al., 2007). Estas alteraciones pueden explicarse de dos maneras: (i) las funciones ejecutivas tienen una disfunción subyacente de las conexiones fronto-temporales (Laurent & Arzimanoglou, 2006); (ii) Los hipocampos pueden intervenir en algunas áreas de las funciones ejecutivas (Corcoran & Upton, 1993).

En los niños con epilepsia del lóbulo temporal la severidad de la disfunción de la atención y de las funciones ejecutivas parecen estar relacionadas con algunas variables propias de la epilepsia, tales como una edad precoz de comienzo, una mayor duración de la epilepsia y el uso de politerapia (García-Molina et al., 2009; Igarashi et al., 2002).

La finalidad de este trabajo es la investigación de la función neuropsicológica, especialmente de la atención y de las funciones ejecutivas en un grupo de niños y adolescentes con epilepsia del lóbulo temporal, considerando también la influencia de otras variables clínicas (edad de comienzo de la epilepsia y evolución de las crisis).

Material y Métodos

El presente estudio se realizó en el Centro Desarrollo Infantil Luís Borges en el Hospital Pediátrico de Coimbra. Se pidió a todos los padres completar un formulario de consentimiento informado para que los niños tomaran parte en el estudio.

El protocolo de evaluación incluía: (i) Entrevista con los padres del niño ó del adolescente para saber su nivel de rendimiento escolar y la marcha de su desarrollo así como información respecto al curso de la epilepsia (las historias clínicas de cada uno de ellos fueron también consultadas y se contactó con el neuropedíatra a su cargo siempre que se consideró necesario); (ii) Test de Inteligencia para Niños de Wechler – Tercera Edición (WISC-III; Wechsler, 2003) y (iii) Pruebas de atención y de funciones ejecutivas de la Batería de Evaluación Neuropsicológica de Coimbra (Bateria de Avaliação Neuropsicológica de Coimbra – BANC; Simões et al., 2008). Los instrumentos para atención y funciones ejecutivas fueron los siguientes- Test de Cancelación, Trail Making Test, Torre de Londres y Fluencia Verbal Fonémica.

El *Test de Cancelación* valora la atención sostenida. Consiste en dos folios A3 con 1600 cuadrados (40 líneas con cada una 40

cuadrados). De ellos, solo 10 (test de cancelación con 2 signos) o 15 (test de cancelación con 3 signos) cuadrados corresponden a uno de los modelos. La base de la prueba es trazar una línea sobre los cuadrados objetivos durante 10 minutos. Hay dos formas del test – una para niños entre 6 y 9 años (2 signos) y otra para adolescentes de 10 a 15 años (3 signos).

El *Trail Making Test* valora la atención selectiva (parte A), la atención dividida (parte B) y la velocidad de procesamiento motor. El test consta de dos partes diferentes, A y B. En la parte A el sujeto debe usar un lápiz pare dibujar una línea entre 25 círculos numerados,(distribuídos aletoriamente en una hoja de papel), siguiendo el orden correcto entre 1 y 25. En la parte B el sujeto debe dibujar una línea entre 25 círculos que contienen números o letras, también distribuídos aleatoriamente en orden alterno entre los números 1 y 13 alternando con letras (conectando 1 con A, A con 2, 2 con B, B con 3 etc.).

El Test de la *Torre de Londres* valora las funciones ejecutivas, tales como planificación, control, autorregulación y capacidades para resolver problemas. El niño tiene que replicar la torre en 12 a 14 modelos diferentes, moviendo tres esferas de colores, siguiendo tres reglas – Primera regla, cada eje de torre solo contiene un número determinado de esferas. Segunda regla, solo puede moverse una esfera de cada vez y tercera regla, cada problema permite un número de movimientos limitado para realizar el modelo presentado en la tarjeta correspondiente. Cuando se falta alguna de estas reglas, se considera que el sujeto ha cometido errores de tipo 1, de tipo 2 y de tipo 3.

La *Fluencia Verbal Fonémica* valora la capacidad para producir palabras de acuerdo a una categoría fonémica y el sujeto

debe decir un máximo de palabras comenzado por una letra determinada ("P", "M" y "R") en un minuto para cada letra.

El grupo clínico consiste en 24 sujetos afectos de epilepsia del lóbulo temporal (14 niños y 10 niñas). Todos los niños con epilepsia que entraron en el estudio reunían los siguientes criterios: (1) Resultados iguales ó superiores a 70 en al menos uno de los CI del WISC-III; (2) Estar entre 7 y 15 años de edad; (3) No diagnóstico previo de encefalitis ni meningitis; (4) Tomar uno o dos fármacos ó haber suspendido la medicación; (5) Haber sido diagnosticado de epilepsia del lóbulo temporal. El grupo de control comporta el mismo número de pacientes que se adecuaron al grupo clínico en edad, género, zona de residencia y nivel escolar de sus padres. La Tabla 1 resume las características demográficas de ambos grupos.

Tabla 1. Datos demográficos del grupo clínico y del grupo control

	Grupo con epilepsia del lóbulo temporal (N=24)	Grupo control (N=24)	*p*
Edad	M=11.21; DP=2.13	M=11.21; DP=2.13	n.s.[1]
Género	58% ninõs (N=14); 42% ninãs (N=10)	58% ninõs (N=14); 42% ninãs (N=10)	n.s.[2]
Región geográfica	Litoral: 79% (N=19); Interior: 21% (N=5)	Litoral: 79% (N=19); Interior: 21% (N=5)	n.s.[2]
Area geográfica[3]	APU: 50% (N=12); AMU: 25% (N=6); APR: 25% (N=6)	APU: 50% (N=12); AMU: 29% (N=7); APR: 21% (N=5)	n.s.[2]
Education formal materna	M=8.50; DP=3.98 (Rango: 3 – 17 years)	M=8.21; DP=3.27 (Rango: 4 – 14 years)	n.s.[1]
Education formal paterna	M=7.26; DP=3.49 (Rango: 4 – 17 years)	M=8.21; DP=3.20 (Rango: 4 – 14 years)	n.s.[1]

[1] Mann-Whitney Test.
[2] Chi-square Test.
[3] APU, Área Predominantemente Urbana; AMU, Área Moderadamente Urbana; APR, Área Predominantemente Rural.

Se recogió de cada niño la información clínica siguiente: etiología, tipos de crisis, edad de comienzo, evolución de la epilepsia y medicación (Tabla 2 y Tabla 3). La clasificación tanto de las crisis como del tipo de epilepsia se hizo de acuerdo al sistema de clasificación de la Liga Internacional Contra la Epilepsia (Commission on Classification and Terminology of the International League Against Epilepsy, 1981; Commission on Classification and Terminology of the International League Against Epilepsy, 1989). Así, el diagnóstico de crisis epiléptica se basa en la historia clínica (todos los niños tienen clínica compatible con la semiologia de las crisis del lóbulo temporal)

Tabla 2. Datos clínicos y funcionamiento Intelectual del grupo con Epilepsia del Lóbulo Temporal

Etiología	Idiopática: 13% (N=3); Sintomática: 29% (N=7); Criptogénica: 58% (N=14)
Tipo de crisis	Parcial simple: 8% (N=2); Parcial compleja: 42% (N=10); Parcial secundar. generaliz.: 50% (N=12)
Edad comienzo	≤ 5 años: 42% (N=10); ≥ 6 años: 58% (N=14)
Evolución	Sin crisis: 54% (N=13); Con crisis: 46% (N=11)
Medicación	Sin medicación: 4% (N=1); Monoterapia: 88% (N=21); Politerapia: 8% (N=2)
WISC-III	CI Verbal: M=86.58; DP=14.74
	CI Manipulativo: M=86.87; DP=13.78
	CI Total: M=83,75; DP=15,33
	Indice de Comprensión Verbal: M=87.63; DP=14.15
	Indice de Organización Perceptiva: M=92.00; DP=14.11
	Indice de Rapidez de Procesamiento: M=81.00; DP=14.01

Tabla 3. Medicación y Dosis del grupo con Epilepsia del Lóbulo Temporal

Pacientes	Edad	Medicación y Dosis
1	7	Ácido Valproico (800 mg / día)
2	7	Lamotrigina (200 mg / día)
3	8	Ácido Valproico (600 mg / día)
4	9	Ácido Valproico (1000 mg / día); Levetiracetam (1500 mg / día)
5	10	Ácido Valproico (500 mg / día)
6	10	Ácido Valproico (1000 mg / día)
7	10	Ácido Valproico (300 mg / día)
8	11	Ácido Valproico (1000 mg / día)
9	11	Sin Medicación
10	11	Ácido Valproico (1000 mg / día)
11	11	Ácido Valproico (500 mg / día)
12	11	Ácido Valproico (1000 mg / día)
13	11	Ácido Valproico (1600 mg / día); Carbamacepina (200 mg / día)
14	11	Ácido Valproico (600 mg / día)
15	12	Carbamacepina (400 mg / día)
16	12	Ácido Valproico (1000 mg / día)
17	12	Ácido Valproico (800 mg / día)
18	12	Ácido Valproico (1000 mg / día)
19	13	Topiramato (175 mg / día)
20	13	Carbamacepina (600 mg / día)
21	13	Ácido Valproico (1100 mg / día)
22	14	Ácido Valproico (1500 mg / día)
23	15	Ácido Valproico (1000 mg / día)
24	15	Ácido Valproico (1000 mg / día)

y en el Vídeo-EEG intercrítico (con actividad paroxística localizada en el lóbulo temporal). Todos los sujetos tienen estudio de imagen.

En la Tabla 2 presentamos los resultados obtenidos con el WISC-III. En primer lugar queremos subrayar un valor por debajo del promedio

del CI en la escala total (M=83.75; DP=15.33), considerando el valor de la media en alguna parte entre 90 y 109. Estos resultados son consistentes con los encontrados en otros estudios (Aldenkamp et al., 2005b; Auclair et al., 2005; Hernandez et al., 2002; Williams et al., 1998). Queremos destacar las dificultades registradas en la velocidad de procesamiento, teniendo en cuenta que el rendimiento en el Indice de Velocidad de Procesamiento es el resultado compuesto del WISC-III con puntuaciones mas bajas.

Respecto a la situación académica del grupo de niños con epilepsia, pudimos comprobar que 8 niños (33 por ciento) habían tenido que repetir un año en la escuela y que 11 (46 por ciento), precisaban educación especial.

Resultados

En la Tabla 4 comparamos resultados obtenidos por los dos grupos (epilepsia de lóbulo temporal y grupo control) en tareas de atención y de funciones ejecutivas. En la prueba de cancelación (evaluación de la atención sostenida) encontramos diferencias entre grupos en la forma de 3 signos (10 a 15 años) tanto en el resultado global (*U*=86.500, *p*=.002) como en el número de símbolos que fueron cancelados correctamente (*U*=100.000, *p*=.007). En la prueba asignada a niños mas pequeños de 2 signos, encontramos la misma tendencia (resultado global: *U*=2.000, *p*=.081; signos correctos: *U*=2.000, *p*=.083), aunque sin significancia estadística. Los resultados para la evaluación de la atención selectiva (Trail Making Test – Parte A) están significativamente por debajo en el grupo con epilepsia del lóbulo temporal (*U*=115.500, *p*=.002) y lo mismo en la Parte B de esta prueba que intenta evaluar la atención dividida (*U*=127.000, *p*=.002). En los resultados relativos a omisiones y errores, no hay diferencias entre los grupos en ninguno de estos test (Test de Cancelación y Trail Making Test). Esto nos lleva a preguntarnos si los resultados mas bajos obtenidos no fueran consecuencia de un rendimiento inferior mas que a un déficit de atención real. En la prueba que intenta valorar las funciones ejecutivas (Torre de Londres), el

Tabla 4. Resultados en Atención y Tareas de Funciones Ejecutivas
Comparación entre grupos de Epilepsia del Lóbulo Temporal y grupo Control

	Epilepsia del Lóbulo Temporal (N=24)			Control (N=24)				
	M	DP	Rango	M	DP	Rango	U	*p*
Test de Cancelación								
2 Señales (7 - 9 años)[1]	6.25	4.57	1 - 12	10.75	3.20	8 - 14	2.000	.081
2 Señales: Signos Correctos[1,2]	63.00	30.41	25 - 95	107.25	31.40	80 - 152	2.000	.083
2 Señales: Omisiones[1,2]	11.00	6.83	2 - 18	18.00	9.13	7 - 29	4.000	.248
2 Señales: Errores[1,2]	3.00	4.69	0 - 10	.25	.50	0 - 1	3.500	.155
3 Señales (10 - 15 years)[3]	7.55	4.44	1 - 18	11.55	2.80	7 - 17	86.500	.002
3 Señales: Signos Correctos[2,3]	160.60	57.22	66 - 300	205.30	50.09	132 - 325	100.000	.007
3 Señales: Omisiones[2,3]	17.95	21.35	1 - 88	15.20	9.25	1 - 41	175.000	.498
3 Señales: Errores[2,3]	.70	.92	0 - 3	.45	.83	0 - 3	168.000	.316
Trail Making Test								
Trail A: Tiempo	7.13	3.38	1 - 13	10.79	3.26	1 - 17	115.500	.002
Trail A: Errores[2]	.08	.28	0 - 1	.08	.28	0 - 1	288.000	.137
Trail B: Tiempo[4]	6.68	4.02	1 - 13	10.45	2.61	4 - 14	127.000	.002
Trail B: Errores[2,4]	.86	1.52	0 - 5	.18	.39	0 - 1	210.500	.137
Torre de Londres								
1º Ensayo	8.83	3.84	3 - 16	9.75	2.74	5 - 15	232.500	.249
Total	8.92	3.17	1 - 11	10.17	2.08	3 - 12	217.500	.094
Numero de Ensayos	8.29	4.01	1 - 16	9.88	3.25	5 - 15	219.000	.153
Errores de Tipo I	.17	.48	0 - 2	-	-	-	252.000	.077
Errores de Tipo II	1.29	2.53	0 - 9	.17	.56	0 - 2	214.000	.032
Errores de Tipo III	7.33	3.87	1 - 14	6.29	2.90	2 - 11	242.000	.341
Fluencia Verbal Fonémica	7.75	2.88	3 - 16	9.71	3.20	4 - 15	184.000	.031

[1] Grupo de Epilepsia del Lóbuto Temporal: N=4; Grupo de Control: N=4.
[2] Para estos resultados se consideran resultados brutos.
[3] Grupo de Epilepsia del Lóbulo Temporal: N=20; Grupo de Control: N=20.
[4] Grupo de Epilepsia del Lóbulo Temporal: N=22; Grupo de Control: N=22 (porque dos niños no conocían el alfabeto).

análisis estadístico solamente encuentra diferencias significativas en errores de tipo II (U=214.000, p=.032). En la prueba de Fluencia Verbal Fonémica, el análisis estadístico muestra una diferencia significativa entre ambos grupos (U=184.000, p=.031).

Comprobamos en la literatura revisada la tendencia a un mayor riesgo de presentar deficiencias cognitivas en aquellos pacientes cuya edad de comienzo de la epilepsia es precoz, (Beckung & Uvebrant, 1997; Cormack et al., 2007; Riva et al., 2002; Sillanpää, 2004). Esto nos ha llevado a valorar si existen diferencias de rendimiento en las pruebas

neuropsicológicas analizadas entre dos grupos: (i) grupo con epilepsia de lóbulo temporal con comienzo precoz (5 años de edad ó inferior); y (ii) grupo de epilepsia con comienzo mas tardío (6 años de edad o superior). Como regla general, observamos una tendencia a un rendimiento mas pobre en niños y adolescentes cuya edad de comienzo de su epilepsia es inferior a 6, comparados con los resultados obtenidos con edades superiores. De todos modos, estas diferencias solo tenían significación estadística en el test de la Torre de Londres (problemas correctos en lo 1º ensayo: U=28.000; p=.013; número de ensayos: U=34.000; p=.036) y Test de Cancelación de 3 señales (puntuación total: U=7.000; p=.001; signos correctos: U=12.500; p=.006).

Por último, cuando comparamos los grupos de niños con crisis con el grupo libre de ellas durante al menos 6 meses, el primero presenta resultados promedios inferiores en la mayoría de las pruebas. De todas formas, esta diferencia tan solo fue estadísticamente significativa en la prueba de Fluencia Verbal Fonémica (U=21.500; p=.002).

Conclusiones

En el área de la atención se observaron déficits en las tareas de atención sostenida, atención selectiva y atención dividida, pese a que el rendimiento de los sujetos con epilepsia del lóbulo temporal solo diferían significativamente de los del grupo control en los valores relacionados con el tiempo necesario para completar las tareas y no en la realización de omisiones u errores. Esto puede ser consecuencia de un déficit de la velocidad de procesamiento, posiblemente anteriores a los déficits en el área de la atención (Hernandez et al., 2003). Este proceso de enlentecimiento puede afectar las capacidades de atención de estos niños y adolescentes. Por otra parte, las dificultades mostradas en el Indice de Velocidad de Procesamiento del WISC-III (ver apartado de material y métodos) añaden peso a la hipótesis de que los niños y adolescentes con epilepsia del lóbulo temporal tienen problemas de la velocidad de procesamiento. Por otro lado, debemos

considerar el efecto de los fármacos anti-epilépticos en la velocidad de procesamiento (Aldenkamp, 2001; Vermeulen et al., 1994). En un estudio de Hessen y col. (2006), los niños con epilepsia fueron evaluados en tareas neuropsicológicas antes y después de la interrupción de la medicación antiepiléptica, observándose que después de la interrupción el desempeño de los sujetos mejoró significativamente en las tareas más exigentes desde el punto de vista de la velocidad de procesamiento.

Por tanto, la explicación de las dificultades mostradas en la prueba de Fluencia Verbal Fonémica, puede no ser debida a un trastorno de las funciones ejecutivas sino a alteraciones de la velocidad de procesamiento así como del lenguaje (Sauerwein et al., 2005). Debemos resaltar el hecho de que un test no valora solamente funciones primarias, sino también áreas secundarias. Por ejemplo los problemas de memoria valorados mediante problemas de evaluación de memoria, pueden ser secundarios a déficits de otros campos tales como la atención, las funciones ejecutivas, el lenguaje, las capacidades visuoperceptivas e incluso factores emocionales. De ahí la necesidad de ampliar los protocolos de evaluación neuropsicológica a cada dimensión de la función neurocognitiva, debemos tener en cuenta que ningún test valora una sola función. Primero, la misma clasificación de los instrumentos para valorar cada área todavía genera controversia. Como por ejemplo la prueba de Fluencia Verbal Fonémica que puede clasificarse como un test de lenguaje (Lezak et al. 2004) ó como un test de funciones ejecutivas (Baron, 2004). Segundo, mas allá de esta categorización, la tarea en sí pude exigir, como ya se ha mencionado, la movilización de diferentes funciones. Este aspecto debe tenerse en consideración cuando se interpreten los resultados.

Desde el punto de vista del comienzo de la epilepsia, los niños que la inician precozmente muestran mayor dificultad en el mantenimiento de la atención y en la capacidad de planificación. Por ello los déficits de atención y de control ejecutivo en este grupo de niños con epilepsia del lóbulo temporal, parecen estar asociados con epilepsias cuyo inicio tiene lugar antes de los 6 años de edad.

La existencia de déficits de la atención y de las funciones ejecutivas generan dificultades de funcionamiento en estos niños – que van desde las actividades rutinarias básicas a los procesos complejos del aprendizaje – debido al impacto que tienen sobre las capacidades metacognitivas, básicas para el control de la actividad cognitiva (Riva et al., 2005). A consecuencia de ello, tienen un efecto desfavorable sobre la calidad de vida, afectando principalmente al bienestar psicológico, social y educativo. Estos resultados indican la necesidad de valorar y monitorizar las áreas de atención, de las funciones ejecutivas y de la velocidad de procesamiento de la información en los niños y adolescentes con epilepsia del lóbulo temporal, especialmente en aquellos en que la edad de comienzo de la epilepsia es precoz. Estas dificultades parecen contribuir significativamente en el fracaso escolar. Por ello, una intervención enfocada a paliar estos problemas puede ser de gran trascendencia. El tratamiento puede incluir terapia cognitivo conductual (por ejemplo, entrenamiento de los padres, intervención en la escuela para facilitar estructura y retroalimentación frecuente e inmediata) y terapia farmacológica (psicoestimulantes).

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CAPÍTULO II

Intellectual functioning in children with epilepsy: Frontal lobe epilepsy, childhood absence Epilepsy and benign epilepsy with centro-temporal spikes

Intellectual functioning in children with epilepsy: Frontal lobe epilepsy, childhood absence Epilepsy and benign epilepsy with centro-temporal spikes[1]

Abstract

The purpose of our study is to describe intellectual functioning in three common childhood epilepsy syndromes – Frontal Lobe Epilepsy (FLE), Childhood Absence Epilepsy (CAE) and Benign Epilepsy with Centro-Temporal Spikes (BECTS). And also to determine the influence of epilepsy related variables, type of epilepsy, age at epilepsy onset, duration and frequency of epilepsy, and treatment on the scores. Intellectual functioning was examined in a group of 90 children with epilepsy (30 FLE, 30 CAE, 30 BECTS), aged 6–15 years, and compared with a control group (30). All subjects obtained a Full Scale IQ ≥ 70 and they were receiving no more than two antiepileptic medications. Participants completed the Wechsler Intelligence Scale for Children – Third Edition. The impact of epilepsy related variables (type of epilepsy, age at epilepsy onset, duration of epilepsy, seizure frequency and anti-epileptic drugs) on intellectual functioning was examined. Children with FLE scored significantly worse than controls on WISC-III Verbal IQ, Full Scale IQ and Processing Speed Index. There was a trend for children with FLE to have lower intelligence scores than CAE and BECTS groups. Linear regression analysis showed no effect for age at onset, frequency of seizures and treatment. Type of epilepsy and duration of epilepsy were the best indicators of intellectual functioning. It is crucial that children with FLE and those with a longer active duration of epilepsy are closely monitored to allow the early identification and evaluation of cognitive problems, in order to establish adequate and timely school intervention plans.

[1] Lopes, A. F., Simões, M. R., Monteiro, J. P., Fonseca, M. J., Martins, C., Ventosa, L., Lourenço, L., & Robalo, C. (*in press*). Intellectual Functioning in Children with Epilepsy: Frontal Lobe Epilepsy, Childhood Absence Epilepsy and Benign Epilepsy with Centro-Temporal Spikes. *Seizure*, n/a, 1-7 .

Keywords

Frontal lobe epilepsy, Childhood absence epilepsy, Benign epilepsy with centro-temporal spikes, Intelligence quotient, Children, WISC-III, Processing speed, Duration of epilepsy.

1. Introduction

Many children and adolescents with epilepsy have normal general intellectual functioning (Gülgnönen et al., 2000; Jeong et al., 2011; Northcott et al., 2005), however a lowered intelligence quotient (IQ) is a main consequence of epilepsy in some cases. In a representative community-based study by Anne Berg's team (2008a) 26% of the children identified when first diagnosed with epilepsy had a subnormal cognitive function. Most studies using intelligence scales have documented low average range IQ's (Caplan et al., 2004; O'Leary et al., 2006; Singhi et al., 1992).

The cause of cognitive problems in epilepsy seems to be multifactorial, that is several intercorrelated factors contribute for deficits in intellectual functioning. Such epilepsy related variables include: type of epilepsy and underlying aetiology, age at onset, frequency of seizures, duration of epilepsy and treatment (anti-epileptic drugs). The type of epilepsy is considered an important predictor of intellectual functioning. Studies have described below average performances for partial epilepsies and in idiopathic generalized epilepsies (Aldenkamp et al., 2005; Braakman et al., 2012; Caplan et al., 2008; Cormack et al., 2007; Prévost et al., 2006). It is well known that children with generalized symptomatic epilepsy are at a higher risk for lower intellectual functioning (Bulteau et al., 2000; Fastenau et al., 2009; Nolan et al., 2003). In fact in severe epilepsies, like Lennox-Gastaut and West syndromes, mental retardation is seen as part of the syndrome. Age at seizure onset seems to be one of the most important predictors of cognitive outcome. Several studies have identified an increased risk of cognitive dysfunction on children that had an early onset of epilepsy. The study by Cormack et al. (2007) identified

82% of intellectual impairment in children with epilepsy onset in the first year of life. In the community-based sample of Berg et al. (2008a) the most significant factor contributing to IQ impairment was seizure onset before 5 years of age. The negative impact of a longer duration of epilepsy on intellectual performance has been described in several types of epilepsy (Bulteau et al., 2000; Caplan et al., 2008; Singhi et al., 1992). Frequency of seizures is also an important factor that can influence intellectual functioning as several authors have described that children with a history of higher seizure frequency tend to present lower IQ scores (Braakman et al., 2012; Caplan et al., 2004; Nolan et al., 2003; Prévost et al., 2006). Finally, polytherapy (taking more than one anti-epileptic drug) seems to have a significant impact on IQ (Aldenkamp et al., 2005; Hoie et al., 2005; Nolan et al., 2003; Selassie et al., 2008).

Intelligence scales, such as the Wechsler Scales gives us a global measure of intellectual abilities, and at the same time they cover different aspects of cognitive functioning (namely, verbal, visuospatial, processing speed, attention tasks). Using an intelligence scale may be the first step on neuropsychological assessment of children with epilepsy. The information coming from these scales can help neuropsychologists to identify the cognitive domains which needs further assessment (i.e. language, memory, attention, executive functions, motor functions). Also performance on intelligence scales may facilitate the understanding of academic and behavioural problems (Deonna & Roulet-Perez, 2005; Oxbury, 1997) and can be used as a baseline for later comparison, depending on the evolution of the epileptic syndrome.

The intelligence scales are probably the instrument most often included in neuropsychological studies of children with epilepsy, but most times their scores are merely used as exclusion/inclusion criteria and only global cognitive measures are reported. The purpose of our study is to compare the WISC-III performance in children with Frontal Lobe Epilepsy (FLE), usually considered to cause problems on cognitive functioning, and children with Childhood Absence Epilepsy (CAE) and Benign Epilepsy with Centro-Temporal Spikes (BECTS), often considered as benign disorders. We also investigated the influence of epilepsy related variables on intellectual

functioning, including type of epilepsy, age at epilepsy onset, duration and frequency of epilepsy, and treatment.

2. Methods

2.1 *Participants*

The clinical sample included 90 children with epilepsy [30 with Frontal Lobe Epilepsy (FLE); 30 with Childhood Absence Epilepsy (CAE); 30 with Benign Epilepsy with Centro-Temporal Spikes (BECTS)] and 30 controls. Children with epilepsy were recruited from neuropaediatric units of the Hospital Garcia de Orta and Coimbra's Paediatric Hospital. All children with epilepsy from these geographic areas are referred to these tertiary care paediatric epilepsy outpatient clinics for neurological and neuropsychological care, and therefore they seem representative samples of children and adolescents with FLE, CAE and BECTS.

The child neurologists (i) classified the participants with epilepsy based on the International League Against Epilepsy criteria (Berg et al., 2010; Commission on Classification and Terminology of the International League Against Epilepsy, 1989) and (ii) provided for each child information regarding age at epilepsy onset, date of last seizure, frequency of seizures and present treatment. Children with epilepsy were selected based on the following inclusionary criteria: (1) children had to be between 6 and 15 years of age; (2) diagnosis of FLE, CAE or BECTS; (3) they were administered the Wechsler Intelligence Scale for Children – Third Edition (WISC-III; Wechsler, 2003) to obtain a Full Scale IQ ≥ 70 (WISC-III); and (4) they were receiving no more than two antiepileptic medications.

The group of healthy control children was chosen, from the group that was previously used to standardise the Portuguese version of the WISC-III, to match the experimental group for socioeconomic level, age and gender.

2.2 *Intelligence assessment*

Intellectual functioning was assessed using the Portuguese version of the Wechsler Intelligence Scale for Children – Third Edition (WISC-III; Wechsler, 2003). The Portuguese version of the WISC-III was normed on 1354 children aged 6 to 16 years of age. The sample was stratified according to gender, age, years of education and geographic regions. Geographic regions were based on the 1998 Portuguese Census. This scale allows the calculation

Table 1. Description of WISC-III composite scores and subtests

COMPOSITE SCORES	DESCRIPTION
Verbal IQ	Verbal IQ reflects the child's verbal ability and is a good predictor of school achievement. The Information, Similarities, Arithmetic, Vocabulary and Comprehension subtests comprises the Verbal IQ.
Performance IQ	Performance IQ is not as good a predictor of school achievement as the VIQ. This composite score provides a better estimate of fluid activity and is not as loaded with verbal and cultural content as the Verbal IQ. The Picture Completion, Coding, Picture Arrangement, Block Design and Object Assembly subtests comprises the Performance IQ.
Full Scale IQ	Full Scale IQ is a measure of general intellectual functioning. The Information, Similarities, Arithmetic, Vocabulary, Comprehension, Picture Completion, Coding, Picture Arrangement, Block Design and Object Assembly subtests comprises the Full Scale IQ.
Verbal Comprehension Index	Verbal Comprehension Index assesses verbal knowledge and comprehension. The Information, Similarities, Vocabulary and Comprehension subtests comprises the Verbal Comprehension Index.
Perceptual Organization Index	Perceptual Organization Index is a measure of perceptual and organizational dimension. The Picture Completion, Picture Arrangement, Block Design and Object Assembly subtests comprises the Perceptual Organization Index.
Processing Speed Index	Processing Speed Index is a measure of processing speed of nonverbal information. The coding and Symbol Search subtests comprises the Processing Speed Index.
VERBAL SUBTESTS	
Information	Information assesses the general cultural knowledge and acquired facts.
Similarities	Similarities is a measure of logical abstract thinking and reasoning.
Arithmetic	Arithmetic is a measure of mental arithmetic ability and problem solving.
Vocabulary	Vocabulary assesses verbal fluency, word knowledge and language development.
Comprehension	Comprehension is a measure of social knowledge and practical judgement in social situations.
Digit Span	Digit Span assesses short-term verbal memory and attention.
PERFORMANCE SUBTESTS	
Picture Completion	Picture Completion assesses visual alertness and visual long-term memory.
Coding	Coding is a measure of visual-motor dexterity, associative nonverbal learning and speed.
Picture Arrangement	Picture Arrangement assesses visual comprehension, planning and social intelligence.
Block Design	Block Design is a measure of spatial analysis and nonverbal reasoning.
Object Assembly	Object Assembly assesses perception, assembly skills and flexibility.
Symbol Search	Symbol Search is a measure of perception, speed, attention and concentration.

of six composite scores: Verbal IQ (VIQ), Performance IQ (PIQ), Full Scale IQ (FSIQ), Verbal Comprehension Index (VCI), Perceptual Organization Index (POI), Processing Speed Index (PSI) (see Table 1); each with a mean of 100 and a standard deviation of 15. There are 13 subtests (10 core and 3 supplemental) that are transformed in scaled scores with a mean of 10 and standard deviation of 3. Information, Similarities, Arithmetic, Vocabulary, Comprehension, Picture Completion, Coding, Picture Arrangement Block Design, Object Assembly are the 10 core subtests. Digit Span, Symbol Search and Mazes are the 3 supplemental tests. In the present study the Mazes subtest was not administered.

2.3 *Procedure*

This study was approved by the institutional review boards of both institutions. Also families and children gave their consent to participate. Children and adolescents that met the inclusion criteria were identified by the responsible neuropediatrician or paediatrician, and during the medical appointment they would briefly explain the aim and procedures of the study. After the consent of the families, we approached children and their families, and with more detail explained the goals and procedures of the study, and scheduled the day of the assessment. Each participant was assessed individually by the one of the investigators of this study (AFL). Prior to the assessment an interview with the parents was conducted, to acquire information regarding the developmental history, children's behaviour and school performance. Children had two neuropsychological assessment sessions – one in the morning, followed by a lunch break, and another on the afternoon. A feedback session was provided for each family, as well as a written report and whenever necessary a telephone conversation was held with the responsible teacher.

2.4 *Statistical analysis*

The statistical analysis was performed with the assistance of the program *Statistical Package for the Social Sciences* (SPSS, Chicago, IL, USA – Version 17.0). Associations between categorical variables were analysed using Chi-Square Test. Analysis of variance (ANOVA) was used to test mean differences in demographic and clinical variables, and in intelligence scores across the three types of epilepsy (FLE, CAE, BECTS), with post-hoc analysis using *Tukey HSD*. To analyze the effects of epilepsy related clinical variables (type of epilepsy, age at onset, active duration, frequency of seizures and treatment) on intellectual functioning (WISC-III composite scores and subtests) simple regression analysis was used. In all analysis results were judged statistically significant if the *p*-value was identical to or smaller than .05.

3. Results

We assessed 90 children and adolescents with epilepsy and 30 controls, between the ages of 6 and 15 years old. The main demographic (age at testing, gender and parental education) and clinical characteristics (age at epilepsy onset, seizure frequency, active duration – i.e. time interval between age at onset of epilepsy and the last episode of seizure –, and treatment) for the 3 experimental groups and control group are presented in Table 2. There were no significant differences between the clinical groups and controls for age at testing and parental education. However for the variable gender the FLE group differed from the CAE, BECTS and control groups. These can be explained by the fact that FLE seems to be more frequent on male gender (Braakman et al., 2012). We tested for gender differences on the intelligence scale results, and no differences were found between boys and girls. On the neurological characteristics of the experimental samples no significant differences were observed between the groups for any of the epilepsy-related variables (age at onset of epilepsy, active duration of epilepsy, seizure frequency and treatment). The FLE group consisted of 7

participants with structural aetiology and 23 with unknown aetiology. The analysis revealed no differences on WISC-III performance between FLE with structural and unknown aetiology.

Table 2: Demographic and neurological features

	FLE (N=30)	CAE (N=30)	BECTS (N=30)	Control (N=30)	*p*-Value
Age	M=10.13 (SD=2.73)	M=9.93 (SD=2.54)	M=9.77 (SD=2.43)	M=10.13 (SD=2.73)	.937
Gender					
Boys	77% (N=23)	30% (N=9)	33% (N=10)	50% (N=15)	.001
Girls	23% (N=7)*	70% (N=21)	67% (N=20)	50% (N=15)	
Years of education (mother)					
Up to 9th grade	17% (N=5)	23% (N=7)	20% (N=6)	10% (N=3)	
9th grade	30% (N=9)	30% (N=9)	47% (N=14)	43%(N=13)	
12th grade	30% (N=9)	20% (N=6)	20% (N=6)	30% (N=9)	.702
Superior	23% (N=7)	27%(N=8)	13% (N=4)	17% (N=5)	
Age at onset (years)	M= 6.40 (SD=3.10)	M=6.83 (SD=2.32)	M=6.77 (SD=2.43)		.792
Seizure frequency					
No seizures (last 6 months)	57% (N=17)	70 % (N=21)	60% (N=18)		.177
< 1 a month	30% (N=9)	13% (N=4)	37% (N=11)		
≥ 1 a month	13% (N=4)	17% (N=5)	3% (N=1)		
Active duration (months)	M=27.57 (SD=36.24)	M=22.63 (SD=17.95)	M=20.90 (SD=26.44)		.632
Treatment					
No medication	7% (N=2)	13% (N=4)	27% (N=8)		
Monotherapy	80% (N=24)	73% (N=22)	73% (N=22)		.087
Duotherapy	13% (N=4)	13% (N=4)	–		

* Differs from Control (*p*=.032), from CAE (*p*=.000) and from BECTS (*p*=.001).

3.1 *WISC-III composite scores results*

Global intellectual functioning was normal (FSIQ scores ≥ 90) for 53% (N=48) of the clinical sample [FLE 47% (N=14); CAE 43% (N=13), BECTS 70% (N=21)], and for 88% (N=24) of the control group. 28% (N=25) of the children and adolescents with epilepsy presented a low average (FSIQ scores between 80 and 89) FSIQ [FLE 30% (N=9), CAE 37% (N=11), BECTS 17% (N=5)] and 19%

(N=17) borderline (FSIQ scores between 70 and 79) [FLE 23% (N=7), CAE 20% (N=6), BECTS 13% (N=4)], whereas in the control group 13% (N=4) had a low average FSIQ and 7% (N=2) borderline (see Figure 1).

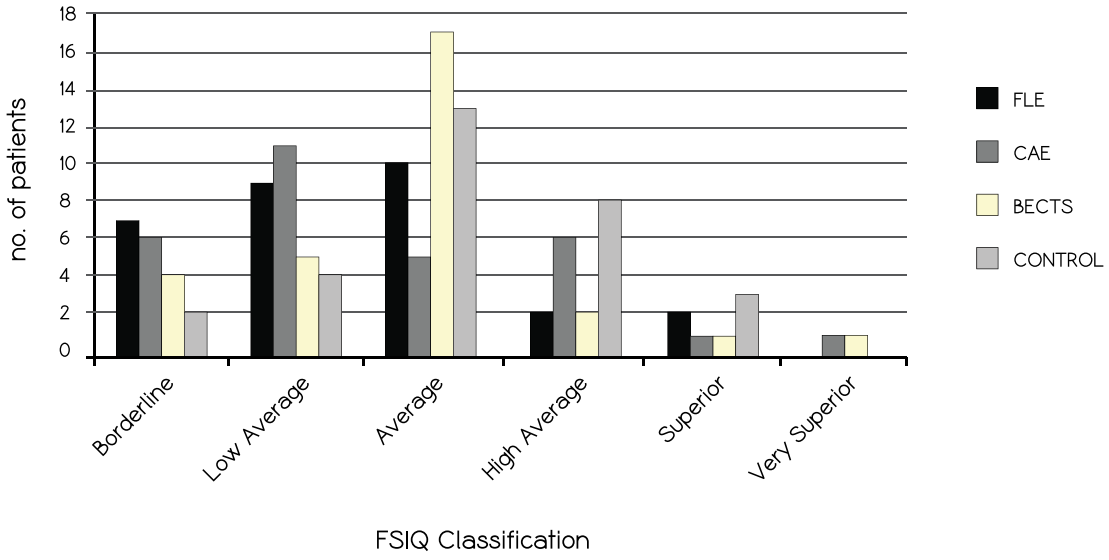

Figure 1. The distribution of Full Scale IQ on the four samples studied.

The results of the comparison between the 3 groups of children with epilepsy and the control group are presented in Table 3. We found significant differences for VIQ [$F(3,116) = 3.600$, $p=.016$], FSIQ [$F(3,116) = 3.256$, $p=.024$] and PSI [$F(3,116) = 4.768$, $p=.004$]. Post hoc analysis indicated that children with FLE scored significantly worse than controls on the following WISC-III composite scores: VIQ ($p=.014$), FSIQ ($p=.016$) and PSI ($p=.001$). There was no significant difference in the PIQ, VCI and POI.

Given the fact that 7 children from the FLE group had structural lesions, a second analysis including only the other 23 cases with unknown cause was performed. Significant differences were still found for VIQ [$F(3,109) = 3.242$, $p=.025$] and PSI [$F(3,109) = 3.681$, $p=.014$]. A tendency towards statistical significance was observed for FSIQ results [$F(3,109) = 2.558$, $p=.059$]. Post-hoc

analysis revealed that children with FLE performed worse than controls on the VIQ (p=.033) and PSI (p=.007).

Although the other two clinical groups (CAE and BECTS) did not differ statistically from controls, their mean results on the six composite scores were systematically lower compared to the controls' scores.

Table 3: WISC-III composite and subtest scores

	FLE (N=30)	CAE (N=30)	BECTS (N=30)	CONTROL (N=30)	F	df	p-Value
	M (SD)	M (SD)	M (SD)	M (SD)			(ANOVA)
COMPOSITE SCORES							
Verbal IQ	92.97 (14.29)**	94.83 (15.71)	97.97 (12.28)	103.90 (12.75)	3.600	3, 116	.016
Performance IQ	92.40 (14.26)	95.10 (16.34)	95.30 (13.45)	101.30 (15.19)	1.921	3, 116	.130
Full Scale IQ	90.40 (14.22)**	93.63 (17.47)	95.10 (13.24)	101.97 (13.89)	3.256	3, 116	.024
Verbal Comprehension	95.93 (15.54)	95.93 (15.50)	99.37 (13.21)	104.63 (12.52)	2.494	3, 116	.063
Perceptual Organization	95.70 (14.66)	95.63 (17.20)	96.27 (14.51)	101.20 (14.64)	.922	3, 116	.432
Processing Speed	88.30 (11.19)***	95.27 (17.80)	96.30 (11.87)	102.57 (15.88)	4.768	3, 116	.004
VERBAL SUBTESTS							
Information	8.90 (2.87)***	8.70 (2.74)***	9.20 (2.93)**	11.50 (3.10)	5.966	3, 116	.001
Similarities	10.43 (2.75)	9.87 (3.59)	10.37 (2.71)	10.33 (2.50)	.236	3, 116	.871
Arithmetic	7.47 (2.65)***	8.87 (3.43)	9.07 (2.73)	10.17 (2.60)	4.470	3, 116	.005
Vocabulary	9.43 (3.13)	10.20 (3.04)	10.20 (2.86)	10.83 (2.63)	1.155	3, 116	.330
Comprehension	9.10 (3.18)	8.97 (2.14)	10.13 (2.64)	10.63 (2.87)	2.620	3, 116	.054
Digit Span	7.67 (2.28)***	7.93 (2.39)***	8.30 (2.61)**	10.79 (2.96)	9.149	3, 116	.000
PERFORMANCE SUBTESTS							
Picture Completion	10.70 (3.13)	9.90 (2.90)	10.73 (3.14)	10.23 (2.96)	.496	3, 116	.686
Coding	7.83 (2.51)***	8.87 (2.84)	9.27 (2.78)	10.47 (2.69)	4.856	3, 116	.003
Picture Arrangement	8.80 (2.86)	8.90 (3.86)	9.33 (2.66)	10.27 (3.44)	1.279	3, 116	.285
Block Design	9.03 (2.33)	9.77 (2.62)	9.03 (2.71)	10.40 (3.78)	1.535	3, 116	.209
Object Assembly	9.23 (3.55)	9.47 (2.69)	9.23 (2.94)	10.03 (2.09)	.520	3, 116	.669
Symbol Search	8.00 (2.49)	9.50 (4.12)	9.23 (2.98)	10.25 (3.44)	2.335	3, 116	.078

** Differs from Control ($p \leq .01$)
*** Differs from Control ($p \leq .001$)

3.2 *WISC-III subtests results*

The results for the 12 WISC-III subtests are shown in Table 3. Significant differences were observed for the following subtests: Information [F(3,116) = 5.966, p=.001], Arithmetic [F(3,116) = 4.470, p=.005], Digit Span [F(3,116) = 9.149,

p=.000] and Coding [*F*(3,116) = 4.856, *p*=.003]. For the Information and Digit Span subtests all the three clinical groups differed from the control group, presenting significantly lower results: Information [FLE (*p*=.004), CAE (*p*=.002), BECTS (*p*=.015)]; Digit Span [FLE (*p*=.000), CAE (*p*=.000), BECTS (*p*=.002)]. FLE children also differed from the Control group on Arithmetic (*p*=.002) and Coding subtests (*p*=.001).

The analysis without the 7 children with FLE with structural lesions revealed significant differences for the same subtests: Information [*F*(3,109) = 6.391, *p*<.001], Arithmetic [*F*(3,109) = 5.480, *p*=.002], Digit Span [*F*(3,109) = 8.973, *p*<.001] and Coding [*F*(3,109) = 4.099, *p*=.008]. For the Information and Digit Span subtests all the three clinical groups showed an inferior performance compared to the control group: Information [FLE (*p*=.004), CAE (*p*=.001), BECTS (*p*=.011)]; Digit Span [FLE (*p*<.001), CAE (*p*<.001), BECTS (*p*=.002)]. FLE children also performed worse than controls on Arithmetic (*p*=.001) and Coding subtests (*p*=.005).

3.3 *Results related to epilepsy variables (Regression)*

In the linear regression analysis (Table 4), intelligence scores were correlated to type of epilepsy and active duration of epilepsy. There was no significant effect for age at onset of epilepsy, frequency of seizures and treatment (*p*-values > than .053). Lower scores on VIQ (*p*=.022), on FSIQ (*p*= .018) and VCI (*p*=.009) were all associated with a longer active duration of epilepsy. Lower results on PSI were associated with a longer active duration of epilepsy (*p*=.005) and type of epilepsy: PSI was higher for children with BECTS when compared with FLE (*p*=.032). A lower result on the subtest Similarities was associated to a longer active duration of epilepsy (*p*=.008), as well as a lower result on Vocabulary (*p*=.016) and Symbol Search (*p*=.003). Lower results on the subtest Arithmetic were related to type of epilepsy: BECTS showed a better performance than FLE (*p*=.030) on the Arithmetic.

Table 4: WISC-III composite scores and subtests: linear regression analysis

Dependent variables	Independent variables included in the model: FLE vs CAE		FLE vs BECTS		CAE vs BECTS		Age at onset		Active duration		Frequency of seizures		Treatment		r2	F
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*		
VIQ	1.725	.637	5.225	.171	3.499	.350	-.835	.179	-.147	.022	.561	.802	2.463	.464	.086	1.296
PIQ	2.461	.522	2.544	.524	.083	.983	-.368	.571	-.124	.063	2.000	.395	.211	.952	.055	.803
FSIQ	2.975	.444	4.471	.269	1.497	.706	-.752	.254	-.161	.018	1.302	.584	1.184	.740	.085	1.282
VCI	-.150	.968	3.453	.380	3.603	.351	-1.019	.113	-.173	.009	1.366	.554	1.844	.596	.095	1.460
POI	-.321	.937	.114	.978	.435	.916	-.097	.887	-.112	.109	2.809	.257	-.340	.927	.045	.658
PSI	6.812	.057	7.979	.032	1.167	.747	-.994	.099	-.174	.005	1.621	.454	1.681	.606	.153	2.502
INF	-.267	.718	.369	.632	.637	.402	.055	.659	-.021	.104	.190	.675	.611	.372	.053	.778
SIM	-.596	.441	-.052	.948	.544	.491	-.256	.053	-.036	.008	.079	.867	.454	.523	.102	1.578
ARIT	1.421	.072	1.786	.030	.365	.648	-.063	.632	-.004	.759	-.324	.498	.701	.331	.075	1.117
VOC	.782	.307	.731	.358	-.051	.948	-.235	.071	-.032	.016	.745	.114	-.016	.982	.108	1.675
COMP	-.156	.824	.976	.181	1.132	.116	-.176	.140	-.019	.114	-.072	.866	.047	.942	.083	1.245
DS	.210	.745	.616	.358	.407	.537	.054	.622	-.007	.541	-.135	.732	.198	.739	.026	.369
PC	-.868	.296	-.005	.995	.863	.310	.115	.414	-.013	.375	.367	.469	.118	.877	.047	.676
COD	1.001	.161	1.425	.056	.424	.559	-.131	.277	-.017	.162	-.222	.609	.262	.688	.084	1.261
PA	-.013	.987	.148	.862	.161	.848	-.064	.647	-.018	.218	.054	.915	-.896	.239	.056	.826
BD	.684	.308	-.036	.959	-.720	.294	.059	.602	-.014	.213	.423	.302	.077	.900	.058	.852
OA	.316	.692	.218	.793	-.098	.905	-.184	.175	-.023	.091	.774	.115	.610	.407	.059	.874
SS	1.485	.073	1.217	.155	-.268	.749	-.237	.090	-.043	.003	.792	.117	.233	.757	.151	2.468

VIQ Verbal IQ; **PIQ** Performance IQ; FSIQ Full Scale IQ; **VCI** Verbal Comprehension Index; **POI** Perceptual Organization Index; **PSI** Processing Speed Index; **INF** Information; **SIM** Similarities; **ARIT** Arithmetic; **VOC** Vocabulary; **COMP** Comprehension; **DS** Digit Span; **PC** Picture Completion; **COD** Coding; PA Picture Arrangement; **BD** Block Design; **OA** Object Assembly; **SS** Symbol Search.

4. Discussion

The aim of our study was to describe the intellectual performance in three common groups of childhood epilepsies [Frontal Lobe Epilepsy (FLE), Childhood Absence Epilepsy (CAE) and Benign Epilepsy with Centro-Temporal Spikes (BECTS)] and to determine the influence of epilepsy related variables (type of epilepsy, age at onset, duration of epilepsy, frequency of seizures and treatment).

Following results were observed: first, children with FLE did significantly less well than controls with respect to the following WISC-III Composite Scores: Full Scale IQ (FSIQ), Verbal Comprehension Index (VCI), Processing

Speed Index (PSI), as well as on the subtests related to school performance (Information, Arithmetic, Digit Span and Coding). Excluding children with structural lesions from the FLE group did not change these results. Second, children with CAE and BECTS performed significantly lower than controls on Information and Digit Span subtests. Third, linear regression analysis revealed that type and duration of epilepsy were the best indicators of intellectual functioning. Finally results showed no effect for age at onset, frequency of seizures and treatment.

In this study we did not include more severe syndromes of infancy and early childhood, also children with IQ's below 70 were excluded, and in spite of that we still found that 28% of the children with epilepsy had a low average FSIQ and 19% borderline. More specifically, our results show that FLE group exhibited lower FSIQ scores, when compared with the control group. Also there was a trend for children with FLE to have lower intelligence scores than CAE and BECTS groups. The impact of FLE on intelligence is still controversially discussed in the literature, as some authors report impairments on IQ scores (Braakman et al., 2012; Nolan et al., 2003) and others do not (Riva et al., 2002, 2005). Our results, together with recent studies (Braakman et al., 2012; Bulteau et al., 2000; Nolan et al., 2003) shows that children with FLE have lower IQ scores than the general population. Future studies, with large samples, are needed to specify which specific subgroups of children with FLE are at risk, considering aetiology, age at onset, duration of epilepsy, frequency of seizures and treatment.

In this study, for the children with FLE differences were more marked on processing speed tasks and in subtests that are thought to influence school performance – Information, Arithmetic, Digit Span and Coding –, which compose the so called ACID pattern previously identified in children with learning problems (Daley & Nagle, 1996; Prifitera & Dersh, 1993; Watkins et al., 1997). Gottlieb's group (2012) recent work considered working memory and processing speed tasks together as an integrated component of mental ability called Cognitive Proficiency. In this study 90 patients with paediatric epilepsy were examined and the relationship between cognitive proficiency

and general ability and seizure focus was analysed. The authors concluded that deficits in cognitive proficiency are a neurocognitive marker of paediatric epilepsy, as children presented more problems on cognitive proficiency than in general ability. When seizure focus was analysed, deficits on cognitive proficiency were especially noted if patients presented frontal lobe epilepsy or right temporal lobe epilepsy. Also, in a recent validity study of WISC-IV for the paediatric population with epilepsy, children with epilepsy scored lower on Processing Speed and Working Memory Indexes than on Verbal Comprehension and Perceptual Organization Indexes (Sherman et al., 2012). Other investigations have outlined that children with FLE have impaired results on processing speed tasks (Auclair et al., 2005; Braakman et al., 2012; Bulteau et al., 2000; Hernandez et al., 2003). Difficulties in processing speed are relevant, especially in school aged children, as they may impact on general cognition. In fact, some authors (Deary et al., 2010; Madden, 2001; Salthouse, 1996) describe processing speed as a fundamental property of the central nervous system that provides a foundation for the efficient implementation of other cognitive functions, supporting learning and classroom performance. This way cognitive performance and school achievement may be impaired when processing is slow. The classroom setting tasks may not be successfully completed as there is a limited time, and this way simultaneity may be hard to achieve as early processing may no longer be available when late processes are complete. More rapid processing seems to increase working memory capacity, which impacts on inductive reasoning and mathematical problem solving (Kail & Ferrer, 2007).

A lot has been said about the effect of treatment on intellectual functions in children, specially regarding processing speed tasks (Aldenkamp, 2001; Fastenau et al., 2009; Hessen et al., 2006; Mandelbaum et al., 2009; Mitchell et al., 1993; Northcott et al., 2005). However in our study no considerable difference was noted between intelligence scores of children in monotherapy, duotherapy, or with no medication. However, note that participants were not equally distributed over the groups, with most subjects on monotherapy (75%) and only 9% on duotheraphy and 16% with

no medication. This result was corroborated by other studies that also found no effects for treatment. Berg and colleagues (2008b) demonstrated that processing speed was slower even in a group of children with epilepsy with 5 years seizure free and off anti-epileptic drugs. In addition, recent studies have demonstrated that these deficits may precede seizure onset. Fastenau et al. (2009) identified several neuropsychological deficits, including on processing speed, in a sample of children assessed at the time of the first recognized seizure. As Kwan and Brodie (2001) have noted it seems that the negative effects of anti-epileptic drugs on neuropsychological functioning may have been over-rated in the past. However, our study was not designed to address this aspect, so results need to be interpreted with caution.

The children with CAE and BECTS showed difficulties on Information and Digit Span subtests. So although their global intellectual functioning was intact, they can have specific cognitive deficits that may impact on their school performance. In fact, several studies reported that children with CAE (Jackson et al., 2013; Oostrom et al., 2003) and BECTS (Clarke et al., 2007; Piccinelli et al., 2008; Tedrus et al., 2009) show school problems. More specifically, neuropsychological deficits in the domains of attention for CAE (Connant et al., 2010; D'Agati et al., 2012; Vega et al., 2010) and language functions for BECTS (Goldberg-Stern et al., 2010; Pinton et al., 2006; Völk-Kernstock et al., 2009) seems to be associated to academic achievement problems, that intelligence scales are not able to capture.

In this study age at epilepsy onset, frequency of seizures and treatment did not affect intellectual functioning. We highlight that the mean age at onset of the sample studied was 6 years of age, which can explain the absence of impact of this epilepsy-related variable on intellectual functioning. As some authors have shown that onset of epilepsy in the first three years of life is the most significant risk factor for intellectual disabilities (Arzimanoglou et al., 2004; Cormack et al., 2007; Vasconcelos et al., 2001).

Active duration of epilepsy was the strongest predictor of intellectual problems. A longer active duration of epilepsy was associated with lower scores on four composite scores (FSIQ, VIQ, VCI and PSI) and three subtests

(Similarities, Vocabulary and Symbol Search). The adverse effect of a longer duration of epilepsy on intellectual functioning has been reported on adults (Jokeit & Ebner, 2002) and children with epilepsy (Bulteau et al., 2000; Caplan et al., 2008; Sherman et al., 2012; Singhi et al., 1992). This data captures our attention towards the risk of cognitive decline. There are only a few longitudinal studies that addressed the investigation of cognitive change in epilepsy. In a review of cognitive longitudinal studies in children and adults, Dodrill (2004) reported a mild but real relationship between seizures and mental decline, and these seems to be more evident on children than on adults (Bjornaes et al., 2001). In addition in the last ten years several studies have documented that cognitive problems may be present at the beginning of the epilepsy (Austin et al., 2001; Berg et al., 2005; Bhise et al., 2010; Fastenau et al., 2009; Hermann et al., 2006; Oostrom et al., 2003).

Future research work needs to analyze longitudinally the performance of these patients (starting their follow-up at time of diagnosis and grouping patients in specific epilepsy syndromes), especially those that have a longer duration of epilepsy, in order to establish the stability of their IQ's. But one must keep in mind that intellectual deterioration may be real or apparent (Brown, 2006; Neyens et al., 1999; Seidenberg & Hermann, 2010). The intelligence scores are related to age-related norms, this way a child with slow progressing or stagnation will show a decline of IQ, but in fact there is no real decline or regression. The best way to distinguish these situations is to analyse raw subtests results, rather than the scaled scores.

Intelligence tests are widely used to assess cognitive problems in children as they help to guide diagnosis, treatment and educational intervention. But IQ measures were not designed to investigate brain-behaviour relationships and sometimes can be relatively insensitive, as a normal IQ does not exclude other specific cognitive deficits. Many children with normal IQ still experience difficulties at school. The present study results demonstrate the strengths and limitations of Wechsler Scales, as IQ results do not reflect all domains of cognitive functioning. If other cognitive functions, such as attention or language, had been tested then children with CAE

and BECTS may have presented different results. For this reason assessments must be more comprehensive, a complete analysis of specific cognitive functions (memory, language, attention, executive functions, visuospatial and visuoconstructional functions, motor functions), complemented with the assessment of academic achievement and socio-emotional status is necessary to identify which factors are contributing for academic vulnerability and to better understand how each child perceives and processes information.

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CAPÍTULO III

Memory functioning in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes

Memory functioning in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes[1]

Abstract

Specific cognitive deficits have been identified in children with epilepsy irrespective of results on intelligence tests. Memory deficits are traditionally attributed to temporal lobe epilepsy, whereas the impact of Frontal Lobe Epilepsy on memory functions has remained controversial. The aim of this study was the examination of memory abilities in other childhood common epilepsy syndromes [Frontal Lobe Epilepsy (FLE), Childhood Absence Epilepsy (CAE) and Benign Epilepsy with Centro-Temporal Spikes (BECTS)] and the influence of epilepsy-related variables. Memory was examined in 90 children with epilepsy (each epilepsy group consisted of 30 children), aged 6-15 and compared with 30 control children. Children with FLE showed significant deficits in verbal and visual memory. In addition, type of epilepsy, earlier age at epilepsy onset and longer active duration of epilepsy were associated with memory problems. Seizure frequency and treatment, however, did not influence memory performance. This study indicates that children with FLE show greater risk of developing memory deficits, than children with CAE or BECTS, thus highlighting the importance of assessing also memory functions in Frontal Lobe Epilepsy.

Keywords

Frontal lobe epilepsy, Childhood absence epilepsy, Benign epilepsy with centro-temporal spikes, Memory, Duration of epilepsy, Age at onset.

[1] Lopes, A. F., Monteiro, J. P., Fonseca, M. J., Robalo, C., & Simões, M. R. (*submitted*). Memory functioning in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes.

1. Introduction

Memory plays an important role on school performance, as school age children have to learn and integrate new information everyday. Memory problems are common in patients with epilepsy and may be differently affected by the cause, course or treatment of epilepsy. Memory deficits have been documented especially in children with temporal lobe epilepsy (Cohen, 1992; Cormack et al., 2012; Gonzalez et al., 2007; Guimarães et al., 2007; Helmstaedter, 2005; Jambaqué et al., 2007; Nolan et al., 2004). But several studies have shown that memory problems may be present in other epilepsy syndromes, such as frontal lobe epilepsy (Braakman et al., 2012; Hernandez et al., 2003; Jambaqué et al., 1993; Lendt et al., 2002; Nolan et al., 2004; Prévost et al., 2006), idiopathic generalized epilepsy including childhood absence epilepsy (Henkin et al., 2005; Nolan et al., 2004; Pavone et al., 2001) and benign epilepsy with centro-temporal spikes (Croona et al., 1999; Northcott et al., 2005; Pinton et al., 2006).

The study of memory combines the characterization of the phases of encoding, storage and retrieval of information, which has been associated with temporal, as well as frontal networks. Whereas children with temporal lobe epilepsy seem to reveal most of all difficulties with recalling, those with frontal lobe epilepsy seem to be more prone to interference and show difficulties organizing the material to be learned and finding mnemonic strategies (Hernandez et al., 2003; Jambaqué et al., 1993; Riva et al., 2005). Children with frontal lobe epilepsy experience memory difficulties that have been attributed to primary attention problems and difficulties to apply successful encoding strategies. However this association between memory deficits and frontal lobe epilepsy is still controversial, as some authors have reported no memory difficulties (Culhane-Shelburne et al., 2002; Hoie et al., 2006).

Although memory deficits are more often present in focal epilepsies, some studies have also found memory problems – especially in visual memory – in children with childhood absence epilepsy (Henkin et al., 2005; Jambaqué

et al., 1993; Kernan et al., 2012; Pavone et al., 2001), while others have not found significant differences in memory functioning in these epileptic syndrome (Hommet et al., 2001; Williams et al., 2001). However these children are usually integrated in a miscellanea group that includes not only children with childhood absence epilepsy, but also juvenile absence seizures, juvenile myoclonic epilepsy and grand mal seizures on awakening, integrating several generalized idiopathic epileptic syndromes.

There is also an extensive literature on the neuropsychological functioning of children and adolescents with benign epilepsy with centro-temporal spikes that includes the study of memory functions. Some studies with this population have identified deficits on verbal memory tasks (Goldberg-Stern et al., 2010; Northcott et al., 2005; Vago et al., 2008). Other studies found no memory deficits in this subgroup (Hommet et al., 2001; Völk-Kernstock et al., 2009). In this group of children with epilepsy, memory problems seem secondary to problems on the language domain, as children with benign epilepsy with centro-temporal spikes show deficits that involve most of all verbal functioning (Goldberg-Stern et al., 2010; Pinton et al., 2006; Völk-Kernstock et al., 2009).

Besides type of epilepsy there are multiple factors that may contribute to memory problems in children with epilepsy. These include age at epilepsy onset (Helmstaedter & Lendt, 2001; Kernan et al., 2012; Nolan et al., 2004; Riva et al., 2005;), duration of active epilepsy (Nolan et al., 2004; Riva et al., 2005), seizure frequency (Jocic-Jakubi & Jovic, 2006; Kernan et al., 2012; Kramer et al., 2006) and treatment (Aldenkamp, 2001; Fastenau et al., 2009). However, only few studies in the paediatric population have studied the impact of these epilepsy-related variables on memory. Moreover, often the evaluation protocols do not include measures of memory.

The aim of this study was to examine memory abilities in children with common childhood epilepsy syndromes [Frontal Lobe Epilepsy (FLE), Childhood Absence Epilepsy (CAE) and Benign Epilepsy with Centro-Temporal Spikes (BECTS)] and compare them with matched controls. We hypothesize that children with FLE will present worse performances on memory

tasks, especially on verbal memory. Finally, we will examine the influence of epilepsy-related variables (type of epilepsy, age at epilepsy onset, duration of active epilepsy, frequency of seizures and treatment) on memory functions.

2. Material and methods

2.1 *Participants*

Memory was examined in 90 children with epilepsy [30 with Frontal Lobe Epilepsy (FLE), 30 with Childhood Absence Epilepsy (CAE), 30 with Benign Epilepsy with Centro-Temporal Spikes (BECTS)] and 30 controls. Children with epilepsy were recruited from neuropaediatric units of the Hospital Garcia de Orta and Coimbra's Paediatric Hospital. This study was approved by the institutional review boards of both institutions, and families and children gave their consent to participate. The healthy control children were chosen from the group that was previously used to standardize Coimbra's Neuropsychological Assessment Battery, to match the experimental group for socio-economic level, age and gender.

The participants with epilepsy were classified by child neurologists using the International League Against Epilepsy criteria (Berg et al., 2010; Commission on Classification and Terminology of the International League Against Epilepsy, 1989). Children with epilepsy were selected based on the following inclusionary criteria: (i) they were between 6 and 15 years of age; (ii) they were diagnosed with FLE, CAE or BECTS; (iii) they were administered the Wechsler Intelligence Scale for Children – Third Edition (Wechsler, 2003) and obtained a Full Scale IQ ≥ 70 (Lopes et al., *in press*); and (iv) they were receiving no more than two antiepileptic medications.

2.2 *Measures*

Memory functioning was evaluated using memory tests from Coimbra´s Neuropsychological Battery Assessment (Simões et al., *in press*). Coimbra's Neuropsychological Assessment Battery is a comprehensive assessment instrument, directed towards the assessment of Portuguese children's neuropsychological development and functioning. It contains a diversified group of subtests which address the domains of attention, executive functions, memory, language and motor functions (Albuquerque & Simões, 2010). The different subtests are transformed in scaled scores with a mean of 10 and a standard deviation of 3. The following memory tests were administered.

2.2.1 *List Learning.*

This test assesses the child's ability to learn and evoke a list of words. Children must learn a list of 15 words over four consecutive learning trials (*Learning*). After learning an interference list that is repeated only once, the child is asked to recall the first list of words (*Immediate Recall Trial*). After an interval of 20 to 30 minutes, the child must recall once more the learning list (*Delayed Recall Trial*). Finally, 45 words are presented and the child must identify which words belong to the learning list (*Recognition Trial*).

2.2.2 Rey *Complex Figure Test.*

This is a classic measure of visual memory, visuospatial constructional ability and planning. Children are instructed to copy a complex geometric figure and then reproduce it from memory after three minutes (*Immediate Recall*) and then 30 minutes (*Delayed Recall*). Given the fact that this article aims to study memory functioning, the copy results won't be described.

2.2.3 *Corsi Block Tapping Test.*

This is a test of visual working memory. Children have to remember blocks that were tapped in sequence by the examiner. Immediately after children

repeat the sequence demonstrated by the examiner. These sequences are presented on a wooden board with 9 blocks numbered on the side of the examiner (children do not have visual access to the blocks numeration). At each difficulty level (starting at two blocks) two different trials are presented.

2.3 *Statistical analysis*

Statistical analysis was performed using the *Statistical Package for the Social Sciences* (SPSS, Chicago, IL, USA – Version 17.0). Associations between categorical variables were analysed using Chi-Square Test. To test mean differences in demographic and clinical variables, and in memory scores across the three types of epilepsy (FLE, CAE, BECTS), analysis of variance (ANOVA) was used with post-hoc analysis using *Tukey HSD*. Simple regression analysis was used to analyse the effects of epilepsy related clinical variables (type of epilepsy, age at epilepsy onset, active duration, frequency of seizures and treatment). Results were judged statistically significant if the *p*-value was identical to or smaller than .05.

3. Results

Table 1 summarizes the demographic (age at testing, gender, parental education) and clinical characteristics (age at epilepsy onset, seizure frequency, active duration of epilepsy and treatment) of the participants, 90 children and adolescents with epilepsy (30 FLE; 30 CAE; 30 BECTS) and 30 controls, between the ages of 6 and 15 years old. No significant differences were found between the clinical groups and the control group for age at testing and parental education. However for the variable gender the group with FLE differed from the CAE, BECTS and control groups. These can be explained by the fact that FLE is more frequent in male children (Braakman et al., 2012; Hernandez et al., 2003). We tested for gender differences on the memory tests performed, and no differences were found between boys and girls. On the neurological characteristics of the experimental samples

no significant differences were observed between the groups for any of the epilepsy-related variables in analysis (age at epilepsy onset, seizure frequency, active duration of epilepsy and treatment). The group with FLE was composed of 7 children with structural aetiology and 23 with unknown aetiology.

Table 1: Demographic and neurological features

	FLE (N=30)	CAE (N=30)	BECTS (N=30)	Control (N=30)	*p*-Value
Age	M=10.13 (SD=2.73)	M=9.93 (SD=2.54)	M=9.77 (SD=2.43)	M=10.13 (SD=2.73)	.937
Gender					
Boys	77% (N=23)	30% (N=9)	33% (N=10)	50% (N=15)	
Girls	23% (N=7)*	70% (N=21)	67% (N=20)	50% (N=15)	.001
Years of education (mother)					
Up to 9th grade	17% (N=5)	23% (N=7)	20% (N=6)	14% (N=4)	
9th grade	30% (N=9)	30% (N=9)	47% (N=14)	30%(N=9)	
12th grade	30% (N=9)	20% (N=6)	20% (N=6)	33% (N=10)	
Superior	23% (N=7)	27%(N=8)	13% (N=4)	23% (N=7)	.736
Age at onset (years)	M= 6.40 (SD=3.10)	M=6.83 (SD=2.32)	M=6.77 (SD=2.43)		.792
Seizure frequency					
No seizures (last 6 months)	57% (N=17)	70 % (N=21)	60% (N=18)		
< 1 a month	30% (N=9)	13% (N=4)	37% (N=11)		.177
≥ 1 a month	13% (N=4)	17% (N=5)	3% (N=1)		
Active duration (months)	M=27.57 (SD=36.24)	M=22.63 (SD=17.95)	M=20.90 (SD=26.44)		.632
Treatment					
No medication	7% (N=2)	13% (N=4)	27% (N=8)		.087
Monotherapy	80% (N=24)	73% (N=22)	73% (N=22)		
Duotherapy	13% (N=4)	13% (N=4)	_		

* Differs from Control (*p*=.032), from CAE (*p*=.000) and from BECTS (*p*=.001).

3.1 *Differences between groups*

As can be see in Table 2, significant differences were observed for the following List Learning Test trials: Learning [$F(3,116) = 5.039$, $p=.003$], Immediate Recall [$F(3,116) = 3.322$, $p=.022$] and Recognition [$F(3,116) = 5.191$, $p=.002$]; and

also for the Corsi Block Tapping Test [$F(3,116) = 3.098$, p=.030]. Post-hoc analysis revealed a consistent pattern in which children with FLE showed the worst performance on memory testing: compared to controls, FLE performed worse on the List Learning-Learning trial (p=.001); on the List Learning-Immediate Recall trial (p=.023); on the List Learning-Recognition trial (p=.005) and on the Corsi Block Tapping Test (p=.017). The group with BECTS scored significantly lower than Controls on the Recognition Trial of the List Learning Task (p=.004). For the Rey Complex Figure Test (immediate and delayed recall trials) the differences between the clinical groups and the control group did not reach statistical significance.

Given the fact that 7 children from the FLE group had structural lesions, a second analysis including only the other 23 cases with unknown cause was performed. Significant differences were still found for List Learning trials – Learning [$F(3,109) = 5.770$, p=.001], Immediate Recall [$F(3,109) = 4.434$, p=.006] and Recognition [$F(3,109) = 6.779$, p=.000] – and for the Corsi Block Tapping Test [$F(3,109) = 3.057$, p=.031]. Post-hoc analysis revealed that children with FLE performed worse than controls on the same 4 trials: List Learning-

Table 2: Memory tests scores

	FLE (N=30)	CAE (N=30)	BECTS (N=30)	CONTROL (N=30)	F	df	*p*-Value
	M (SD)	M (SD)	M (SD)	M (SD)			(ANOVA)
LIST LEARNING							
Learning	6.33 (3.45)***	8.13 (3.28)	8.47 (2.90)	9.39 (2.82)	5.039	3,116	.003
Immediate Recall	7.17 (3.06) *	8.70 (3.38)	7.73 (3.08)	9.38 (2.20)	3.322	3,116	.022
Delayed Recall	7.83 (2.60)	8.90 (3.07)	8.40 (3.05)	9.39 (2.27)	1.744	3,116	.162
Recognition	7.13 (3.79) **	8.20 (3.63)	7.07 (3.85) **	10.25 (2.72)	5.191	3,116	.002
REY COMPLEX FIGURE TEST							
Immediate Recall	8.33 (3.27)	9.00 (3.27)	8.87 (2.85)	9.57 (2.67)	.757	3,116	.521
Delayed Recall	8.50 (3.26)	8.63 (3.73)	8.47 (3.09)	9.59 (2.84)	.810	3,116	.491
CORSI BLOCK TAPPING TEST	7.40 (3.14) *	8.97 (3.44)	8.77 (3.27)	9.85 (2.74)	3.098	3,116	.030

* Differs from Control ($p \leq .05$)
** Differs from Control ($p \leq .01$)
*** Differs from Control ($p \leq .001$)

Learning trial (p=.001); on the List Learning-Immediate Recall trial (p=.005); on the List Learning-Recognition trial (p=.000) and on the Corsi Block Tapping Test (p=.017). Also on Learning trial of the List Learning test the group with FLE had significantly lower scores than CAE (p=.047) and BECTS (p=.017).

3.2 *Risk factors related to epilepsy*

Table 3 shows the results for the linear regression analysis. Regression coefficients were not significant for frequency of seizures and treatment. Lower scores on the List Learning Test - Learning trial (FLE vs. AE: p=.042; FLE vs. BECTS: p=.021) were associated to the type of epilepsy. Also lower scores on the List Learning Test - Learning trial (p=.055) were related to a longer duration of epilepsy. Finally, lower scores on the Corsi Block Tapping Test (p=.002) were associated to younger age at epilepsy onset.

Table 3: Memory tests: linear regression analysis

	Independent variables included in the model															
Dependent variables	FLE vs CAE		FLE vs BECTS		CAE vs BECTS		Age at onset		Active duration		Frequency of seizures		Treatment		r2	F
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*		
List L	1.720	.042	2.042	.021	.322	.707	-.100	.481	-.028	.055	.041	.936	.159	.836	.125	1.972
List IR	1.389	.096	.245	.776	-1.145	.178	-.038	.788	-.015	.291	-.530	.296	-.494	.517	.086	1.309
List DR	1.012	.189	.442	.579	-.570	.468	-.088	.496	-.016	.233	-.057	.903	-.132	.852	.047	.678
List R	.903	.359	-.345	.736	-1.248	.216	.068	.681	-.021	.225	-.125	.835	-.296	.743	.057	.832
Rey IR	.667	.448	.778	.395	.110	.902	.152	.309	.000	.980	.069	.898	.865	.286	.037	.538
Rey DR	.071	.936	.103	.910	.033	.971	.232	.121	-.003	.840	.059	.912	.703	.386	.046	.663
Corsi	1.407	.090	1.261	.142	-.146	.863	.435	.002	.020	.170	-.718	.156	.059	.938	.157	2.584

List L List Learning – Learning; **List IR** List Learning – Immediate Recall; **List DR** List Learning – Delayed Recall; **List R** List Learning – Recognition; **Rey IR** Rey Complex Figure Test – Immediate Recall; **Rey DR** Rey Complex Figure Test – Delayed Recall; **Corsi** Corsi Block Tapping Test.

4. Discussion

Mnemonic deficits are traditionally considered characteristic of temporal lobe epilepsy. If the same scenario applies to FLE is a question still

open in the literature. Results of the present study confirm that children with FLE demonstrate a higher risk of developing memory problems, than children with CAE or with BECTS, highlighting the importance of assessing memory functions especially in FLE. Age at epilepsy onset and duration of active epilepsy were the other epilepsy-related variables that were associated with lower memory scores.

4.1 *Type of epilepsy*

Our study indicates that children with FLE show greater risk of developing memory problems. Memory deficits occurred mainly during the learning phase of the verbal learning task (List Learning Test), and the impairment on the immediate recall and recognition trials seems to be the consequence of problems during the initial encoding of information. Verche et al. (2011) identified similar verbal memory deficits using the same task, where children with FLE applied encoding and recall strategies less effectively than those of control children. The authors suggest that the deficits found could be explained by the executive functioning deficits commonly detected in patients with FLE. These results appear to be consistent with those of Jambaqué et al. (1993) and Lendt et al. (2002), who both demonstrated memory impairment did not just occur in participants with temporal lobe epilepsy, but also in children suffering from FLE. These FLE samples showed particularly poor performances in verbal memory tasks that required planning and organizational strategies. Visual memory has been less well studied in children with FLE. Contrary to previous studies (Hernandez et al., 2003), we did not found deficits on visual memory, as assessed by the recall trials of Rey Complex Figure Test. On the visual working memory test (Corsi Block Tapping Test) results of children with FLE were lower than the control group, which suggests visuospatial working memory problems. The frontal lobes play an important role on the performance of these tasks, as several studies have demonstrated the activation of the pre-frontal cortex for the performance of working memory tasks (Baddeley & Logie, 1999; Smith & Jonides, 1997).

Regarding aetiology of epilepsy, our FLE sample is mainly constituted by an unknown aetiology (77%). And in fact, authors argue that children with FLE rarely show macro-structural brain abnormalities (Braakman et al., 2012). The recent work of Braakmann et al. (2012, 2013) hypothesized that neuronal injury associated with epilepsy could be expressed as a micro-structural or functional abnormality. That simultaneously results in neurobehavioral comorbidities. 32 children with cryptogenic FLE underwent neuropsychological assessment and structural and functional Magnetic Resonance Imaging and decreased functional frontal lobe connectivity was associated with cognitive impairment in FLE.

The existing literature suggests that most children with BECTS show intact memory skills (Goldberg-Stern et al., 2010; Hommet et al., 2001; Pinton et al., 2006; Völk-Kernstock et al., 2009). Our study only identified difficulties in the recalling phase (Recognition) of the List Learning Task, presenting mean normal scores during learning and recall on all of the other memory tasks. Attention problems that have been previously reported in children with BECTS (Deltour et al., 2007; Giordani et al., 2006; Kavros et al., 2008; Pinton et al., 2006) may justify the difficulties with recognition of items previously learned and failure to resist to interference.

It is very important to consider memory problems in the context of other cognitive pathology, namely in the domains of attention, executive functions and language. As memory deficits in children seem to be a part of a much more diffuse impairment (Helmstaedter & Lendt, 2001; Rijckevorsel, 2006). Clinically, the memory profile of each child should be analysed in the context of other neurocognitive abilities, and this is only possible when conducting extensive and comprehensive neuropsychological assessment protocols.

4.2 *Age at epilepsy onset and duration of active epilepsy*

Concerning the impact of the clinical variables related to epilepsy, besides type of epilepsy, age at epilepsy onset and duration of active

epilepsy were the most significant risk factors for memory difficulties in our study. Seizure frequency and the number of antiepileptic drugs were not associated with memory functioning.

In the present study younger age at epilepsy onset was associated with poorer performance on the Corsi Block Tapping Test, that assesses visual working memory. The negative impact of an earlier age at epilepsy onset on cognitive functions has been largely documented, including on memory functions (Hommet et al., 2001; Prévost et al., 2006; Riva et al., 2005). In our study, an earlier age at epilepsy onset was related to a lower performance on a task that assesses visual working memory, but that is also sensitive to attention and executive functions deficits. This is a common finding on other studies. Kernan et al. (2012) studied a group of children with CAE and found a significant effect for age at epilepsy onset on a Digit Span task testing verbal working memory abilities. And Riva et al. (2005) documented a significant correlation between age at epilepsy onset of epilepsy and performance on a list learning test, these children had difficulties on learning and using clusters, and these impaired their scores on recall tasks. In our study earlier age at epilepsy onset only influenced results on the task that is sensitive to executive functions performance (Corsi Block Tapping Test). Executive functions is a heterogeneous construct that includes several subdomains (such as, planning, organization, working memory, inhibition, problem solving, fluency, initiative, anticipation), that are difficult to dissociate from other constructs, such as memory, attention or processing speed. Executive functions are subserved by the frontal lobes, and these are the latest brain regions to develop, as maturation continues throughout adolescence (Hernandez et al., 2001). For this reason early age at epilepsy onset is a major risk factor for difficulties on executive functions related skills.

A longer duration of active epilepsy predicted memory difficulties on the learning phase of the List Learning Task. That is, children and adolescents with more years of active epilepsy were more likely to have problems on the acquisition and consolidation of knowledge, which will probably impact on their school results. A few studies have documented the impact of active

duration of epilepsy on memory functions. Schoenfeld et al. (Schoenfeld et al., 1999) investigated a group of children with complex partial seizures and observed an association of a longer duration of active epilepsy with lower scores on visual memory. Nolan's group (2004) studied memory functions in three childhood epilepsy syndromes (temporal lobe epilepsy, FLE and CAE) and found that duration of epilepsy correlated negatively with memory function, and thus was the most significant risk factor for memory problems. This was confirmed by another study that included only children with FLE: Riva et al. (2005) found that performance on a list learning task (number of correct answers, short and long-term recall) correlated with the duration of the disorder.

4.3 *Limitations*

One of the limitations of our study was the fact that regarding verbal memory assessment we only included the List Learning Test, which is considered a representative task to assess memory (verbal memory). List Learning is a task that includes repeated presentations of test material, and is very susceptible to attention and executive functions problems.

It is frequently reported by parents and teachers that children with epilepsy experience memory deficits impairing their everyday life. Traditional memory tests may not capture all the real memory capabilities of children with epilepsy. Everyday memory might be influenced much more by attention problems, than standard memory testing (Kadis et al., 2004; Smith & Vriezen, 1997). Therefore future studies should include measures of everyday memory on neuropsychological assessment protocols, as well as other memory tests (Story Recall, Paired Word Learning, Sentence Memory, Visual Recall, Memory for Faces).

4.4 *Conclusions*

The present study demonstrates that children with FLE show significant deficits in verbal and visual memory. In addition, type of epilepsy, earlier age at epilepsy onset and longer active duration of epilepsy were associated with memory problems. Our research findings underline the importance of offering early assessments, especially for children with FLE, with a longer duration and an early age at epilepsy onset, with extensive neuropsychological assessment protocols that include several measures of memory. Knowing the outcome of these groups of children with epilepsy in memory tests gives clinicians the possibility to establish adequate and timely school intervention plans to diminish the negative influence that this memory problems might have on their academic achievement.

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CAPÍTULO IV

Attention and executive functions in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes

Attention and executive functions in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes[1]

Abstract

The aim of our study is to describe attention and executive functions in children with three common childhood epilepsy syndromes – Frontal Lobe Epilepsy (FLE), Childhood Absence Epilepsy (CAE) and Benign Epilepsy with Centro-Temporal Spikes (BECTS). In addition, we intended to investigate the influence of epilepsy related variables, type of epilepsy, age at epilepsy onset, duration and frequency of epilepsy, and treatment on the scores. Attention and executive functions were assessed in a group of 90 children with epilepsy (30 in each group, N=90), aged 6–15 years, and compared with a control group (N=30). All participants were receiving no more than two antiepileptic medications and the obtained Full Scale IQ was equal or more than 70. The impact of epilepsy related variables (type of epilepsy, age at epilepsy onset, duration of epilepsy, seizure frequency and anti-epileptic drugs) was examined. Children with FLE did significantly less well than controls on sustained attention, divided attention, planning and problem solving. Children with CAE performed significantly lower than controls on the divided attention and planning. Linear regression analysis revealed that type and age at onset of epilepsy were the best indicators of attention and executive functions performance. Finally, results showed no effect for duration of active epilepsy, frequency of seizures and treatment. Our study shows that children with FLE, CAE and those with an earlier age at onset of epilepsy have impairments in their attention and executive functioning. Therefore,

[1] Lopes, A. F., Monteiro, J. P., Fonseca, M. J., Robalo, C., & Simões, M. R. (*submitted*). Attention and executive functions in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes.

these results alert clinicians to the need for early assessment and treatment of attention and executive functioning deficits in these groups of children with epilepsy.

Keywords

Frontal lobe epilepsy, Childhood absence epilepsy, Benign epilepsy with centro-temporal spikes, Sustained attention, Divided attention, Executive functions, Children, Age at onset of epilepsy

1. Introduction

Attention and executive functions deficits have frequently been associated with childhood epilepsy (Auclair et al., 2005; Baglietto et al., 2001; Braakman et al., 2012; Caplan et al., 2008; Chavalier et al., 2000; Conant et al., 2010; Culhane-Shelburne et al., 2002; D'Agati et al., 2012; Deltour et al., 2007; Giordani et al., 2006; Henkin et al., 2005; Hernandez et al., 2002; Hernandez et al., 2003; Hoie et al., 2006 ; Lopes et al., 2010; Luton et al., 2010 ; Pinton et al., 2006 ; Prévost et al., 2006 ; Vega et al., 2010). Parents, teachers and children often complain about impaired vigilance, difficulties focusing and sustaining their effort along time, and problems with organization. These neurocognitive functions are essential for academic achievement and cognitive development, as they are fundamental for other cognitive functions, namely memory performance and language functions (Anderson et al., 2001; Andrewes, 2001; Baron, 2004).

Attentional problems, with or without the presence of hyperactivity, are very frequent in children with epilepsy. Children with epilepsy are at higher risk of meeting diagnostic criteria for Attention-deficit hyperactivity disorder (ADHD), as recent clinical studies suggest a prevalence rate of 30 to 40% (Dunn & Kronenberg, 2005; Hermann et al., 2007; Williams et al., 2002). Also most studies report that the inattentive subtype of ADHD is more common in

children with epilepsy (Dunn et al., 2003; Hermann et al., 2007; Koneski et al., 2011).

Attention is a construct of many subdomains (Sánchez-Carpintero & Neville, 2003; van Zomeren, 1994), referring to alertness, selective, sustained and divided attention. Alertness allows the initial reception of the stimuli. Selective attention refers to the ability to focus on target information, in detriment of other stimuli. Sustained attention is the ability to sustain attention over a period of time. Divided attention is the aptitude to alternate our attention to two stimuli at the same time.

On the other hand, Executive Functions are considered as the central executive component of the information-processing system, directing attention, monitoring activity, and coordinating and integrating information and activity (Anderson et al., 2001). Thus this central executive component includes abilities such as planning, mental flexibility, fluency, flexibility, inhibition, problem solving, self-regulation.

The cause of attention and executive functions deficits reported in children with epilepsy are multifactorial, and include type of epilepsy, age at onset of epilepsy, duration of active epilepsy, frequency of seizures, and effects of antiepileptic drugs. In focal epilepsies, deficits on attention and executive functions are more frequently reported in children with frontal lobe epilepsy, as they show problems with planning and problem solving (Culhane-Shelburne et al., 2002; Hernandez et al., 2002; Luton et al., 2010), sustained attention (Hernandez et al., 2003), alertness (Braakman et al., 2012). Although attention and executive problems are more likely to occur in children with frontal lobe seizures, similar deficits have also been reported in other types of epilepsy, namely in patients with childhood absence epilepsy (Conant et al., 2010; D'Agati et al., 2012; Killory et al., 2011) and benign epilepsy with centro-temporal spikes (Giordani et al., 2006; Kavros et al., 2008; Pinton et al., 2008). Besides type of epilepsy, an earlier age at onset of epilepsy is another epilepsy-related variable that as been identified as a strong predictor of attention and executive functions performance in children with epilepsy (Hoie et al., 2006; Luton et al., 2010; Neri et al., 2012; Riva et al., 2005). In addition, deficits in

attention and executive functions tasks are related to a longer duration of active epilepsy and (Caplan et al., 2008; Riva et al., 2005) a higher frequency of seizures (Caplan et al., 2008; Hoie et al., 2006). Attention and executive functions problems are often considered a consequence of medication side effects, and are, along with processing speed, the most vulnerable cognitive skills to the side effects of anti-epileptic drugs (Hoie et al., 2006; Hessen et al., 2006; Lagae, 2006; Meador, 2002). This negative impact is increased by rapid initiation, higher dosages and polytherapy. Also, children seem to be at a higher risk for these adverse effects due to the cumulative effect over time during neurodevelopment (Meador, 2001).

The aim of our study was to compare attention and executive functions performance in children with epilepsy Frontal lobe epilepsy (FLE), Childhood absence epilepsy (CAE) and Childhood absence epilepsy (BECTS) and matched controls. In addition, we studied the influence of epilepsy related variables on attention and executive functions, including type of epilepsy, age at epilepsy onset, duration and frequency of epilepsy, and treatment.

2. Methods

2.1 *Participants*

In this clinical study, we included 90 children with epilepsy (30 with FLE, 30 with CAE; 30 with BECTS) and 30 controls (matched for age at testing, gender and parental education). Children with epilepsy were recruited from neuropaediatric units of the Hospital Garcia de Orta and Coimbra's Paediatric Hospital (tertiary centres to where all children with epilepsy from these geographic areas are referred to). This study was approved by the institutional review boards of both institutions, and families and children gave their informed consent to participate.

The child neurologists (i) classified the participants with epilepsy

based on the International League Against Epilepsy criteria (Berg et al., 2010; Commission on Classification and Terminology of the International League Against Epilepsy, 1989) and (ii) provided for each child information regarding age at epilepsy onset, date of last seizure, frequency of seizures and treatment. Following inclusionary criteria were applied: Children (1) had to be between 6 and 15 years of age; (2) were diagnosed with FLE, CAE or BECTS; (3) obtained a Full Scale IQ of 70 or more (Wechsler Intelligence Scale for Children – Third Edition (WISC-III) (Wechsler, 2003; Lopes et al., *in press*); and (4) were receiving no more than two antiepileptic medications.

2.2 *Measures*

Attention and executive functions were evaluated using tests from Coimbra´s Neuropsychological Battery Assessment (Simões et al., *in press*). Coimbra's Neuropsychological Assessment Battery is a comprehensive assessment instrument, directed towards the assessment of Portuguese children's neuropsychological development and functioning. It contains a diversified group of subtests which address the domains of attention, executive functions, memory, language and motor functions (Albuquerque & Simões, 2010). The different subtests are transformed in scaled scores with a mean of 10 and a standard deviation of 3. The following tests were administered.

2.2.1 *Cancellation Task.*

This test assesses selective and sustained attention, visual perception and visuomotor speed. The 2 Signs Cancellation Test is administered to children aged from 6 to 9 and the 3 Signs Cancellation Test to children aged from 10 to 15 years of age. The material comprises an A3 sheet with squares arranged in lines and 2 or 3 model squares placed at the top of the sheet (according to whether it is the 2 or the 3 Signs Cancellation Test). During 10 minutes the child has to cross out the squares that are equal to the model squares. The score is determined through a formula that includes the number of squares correctly crossed, omitted and incorrectly crossed.

2.2.2 *Trail Making Test – Parts A and B.*

This test assesses attention, speed of visual search, cognitive flexibility and visuospatial sequencing. It consists of two parts, Trail A (selective attention) and Trail B (divided attention). Trail A requires the child to draw a line connecting 25 encircled numbers randomly distributed on a sheet of paper, sequentially from 1 to 25. Trail B is a more complex task, demanding greater requirements in terms of motor speed, planning, cognitive shifting and flexibility. It requires the child to draw a line while alternating between numbers (1 through 13) and letters (A through M) in sequence (e. g., 1, A, 2, B, 3, C, etc.). The score of both parts corresponds to the time required to complete each task correctly. Children with 6 years of age only complete part A of the Trail Making Test.

2.2.3 *Tower of London.*

This test is a measure of planning and problem solving ability. The material comprises 14 models (of increasing difficulty), presented in photographs that the child has to reproduce with a wooden tower using 3 balls of different colours (red, green and blue). Children have 4 attempts to solve each model. Also children have to follow three rules: (i) they can not place more than one ball on the smallest post or more than two balls on middle post; (ii) children can only pick one ball at a time; (iii) for each problem there is a limited number of moves to match the model (from one to five movements). Scores achieved include number of problems solved in the first trial (*Tower of London – 1st Trial*), total number of problems solved (*Tower of London – Total*) and the total number of trials required to reproduce the 14 problems (*Tower of London – Total trials*).

2.3 *Statistical Analysis*

Data were analysed using the *Statistical Package for the Social Sciences* (SPSS, Chicago, IL, USA – Version 17.0). Categorical variables were compared using Chi-Square Test. Analysis of variance (ANOVA) was used to explore mean differences in demographic and clinical variables, and in

attention and executive functions scores across the three types of epilepsy (FLE, CAE, BECTS), with post-hoc analysis using *Tukey HSD*. To explore the effects of epilepsy related clinical variables (type of epilepsy, age at epilepsy onset, active duration, frequency of seizures and treatment) on attention and executive functions tasks simple regression analysis was used. For all these analysis, results were judged statistically significant if the *p*-value was identical to or smaller than .05.

3. Results

The demographic (age at testing, gender, parental education) and clinical characteristics (age at epilepsy onset, seizure frequency, active duration of epilepsy and treatment) of the participants, 90 children and adolescents with epilepsy (30 FLE; 30 CAE; 30 BECTS) and 30 controls, between the ages of 6 and 15 years old are shown in Table 1. No significant differences were observed between the clinical groups and the control group for age at testing and parental education. For the variable gender the group with FLE differed from the CAE, BECTS and control groups. These results can be explained because FLE is more frequent in male children (Braakman et al., 2012; Hernandez et al., 2003). We tested for gender differences on the attention and executive functions tests performed, and found no differences between boys and girls. On the neurological characteristics of the experimental samples no significant differences were observed between the groups for any of the epilepsy-related variables in analysis (age at epilepsy onset, seizure frequency, active duration of epilepsy and treatment). The group with FLE was composed of 7 children with structural aetiology and 23 with unknown aetiology.

Table 1: Demographic and neurological features

	FLE (N=30)	CAE (N=30)	BECTS (N=30)	Control (N=30)	*p*-Value
Age	M=10.13 (SD=2.73)	M=9.93 (SD=2.54)	M=9.77 (SD=2.43)	M=10.13 (SD=2.73)	.937
Gender					
Boys	77% (N=23)	30% (N=9)	33% (N=10)	50% (N=15)	
Girls	23% (N=7)*	70% (N=21)	67% (N=20)	50% (N=15)	.001
Years of education (mother)					
Up to 9th grade	17% (N=5)	23% (N=7)	20% (N=6)	14% (N=4)	
9th grade	30% (N=9)	30% (N=9)	47% (N=14)	30%(N=9)	
12th grade	30% (N=9)	20% (N=6)	20% (N=6)	33% (N=10)	
Superior	23% (N=7)	27%(N=8)	13% (N=4)	23% (N=7)	.736
Age at onset (years)	M= 6.40 (SD=3.10)	M=6.83 (SD=2.32)	M=6.77 (SD=2.43)		.792
Seizure frequency					
No seizures (last 6 months)	57% (N=17)	70 % (N=21)	60% (N=18)		
< 1 a month	30% (N=9)	13% (N=4)	37% (N=11)		.177
≥ 1 a month	13% (N=4)	17% (N=5)	3% (N=1)		
Active duration (months)	M=27.57 (SD=36.24)	M=22.63 (SD=17.95)	M=20.90 (SD=26.44)		.632
Treatment					
No medication	7% (N=2)	13% (N=4)	27% (N=8)		.087
Monotherapy	80% (N=24)	73% (N=22)	73% (N=22)		
Duotherapy	13% (N=4)	13% (N=4)	_		

* Differs from Control (*p*=.032), from CAE (*p*=.000) and from BECTS (*p*=.001).

3.1 *Differences between groups*

The results of the comparison between the 3 groups of children with epilepsy and the control group are presented in Table 2. Significant differences were observed for the following tasks: Cancellation Task [$F(3,116) = 5.015$, $p=.003$], Trail Making Test Part B [$F(3,100) = 7.045$, $p<.001$], Tower of London – 1st trial [$F(3,116) = 5.037$, $p=.003$], Tower of London – Total trials [$F(3,116) = 2.652$, $p=.052$]. Post-hoc analysis revealed a consistent pattern in which children with FLE showed the worst performance on testing: compared to controls, children with FLE performed worse on the Cancellation Task ($p=.001$); on the

Trail Making Test Part B (p<.001); Tower of London – 1st trial (p=.001) and on the Tower of London – Total trials (p=.032). The group with CAE scored significantly lower than controls on the Trail Making Test Part B (p=.032) and on the Tower of London – 1st trial (p=.042). For the Trail Making Test Part A and for the Tower of London – Total the differences between the clinical groups and the control group did not reach statistical significance.

Table 2: Attention and executive functions tests scores

	FLE (N=30)	CAE (N=30)	BECTS (N=30)	CONTROL (N=30)	F	df	p-Value
	M (SD)	M (SD)	M (SD)	M (SD)			(ANOVA)
Cancellation Task	7.37 (3.56)***	8.43 (2.58)	8.40 (3.32)	10.51 (3.36)	5.015	3, 116	.003
Trail Making Test Part A	8.48 (2.58)	8.48 (3.31)	9.34 (3.27)	9.75 (2.11)	1.124	3, 112	.342
Trail Making Test Part B	5.65 (3.10)***	7.36 (3.40)*	7.71 (2.99)	9.72 (2.79)	7.045	3, 100	.000
Tower of London _ 1st Trial	7.77 (3.79)**	8.63 (2.75)*	9.27 (3.18)	10.76 (2.43)	5.037	3, 116	.003
Tower of London _ Total	8.47 (2.65)	8.40 (3.17)	8.47 (3.10)	9.62 (2.34)	1.285	3, 116	283
Tower of London _ Total trials	7.60 (3.67)*	8.50 (3.45)	8.87 (3.44)	10.04 (3.02)	2.652	3, 116	.052

* Differs from Control (p≤.05)
** Differs from Control (p≤.01)
*** Differs from Control (p≤.001)

Given the fact that 7 children from the FLE group had structural lesions, a second analysis including only the other 23 cases with unknown cause was performed. Significant differences were still found for the Cancellation Task [F(3,109) = 6.838, p<.001], the Trail Making Test Part B [F(3,93) = 6.183, p=.001], the Tower of London – 1st trial [F(3,109) = 4.419, p=.006], the Tower of London – Total trials [F(3,109) = 2.650, p=.052]. Post-hoc analysis revealed that children with FLE performed worse than controls on the Cancellation Task (p<.001); on the Trail Making Test Part B (p<.001); Tower of London – 1st trial (p=.005) and on the Tower of London – Total trials (p=.033). Also, compared to controls children with CAE had significantly lower scores on the Trail Making Test Part B (p=.033) and on the Tower of London – 1st trial (p=.034).

3.2 *Risk Factors Related to Epilepsy*

Table 3 shows the results for the linear regression analysis. Regression coefficients were not significant for active duration of epilepsy, frequency of seizures and treatment. Lower scores on the Trail Making Test Part B (FLE vs. BECTS: *p*=.021) were associated to the type of epilepsy. Also lower scores on the Tower of London, for the 1st Trial (*p*=.006) and the Total trials (*p*=.037) were related to an earlier age at onset of epilepsy.

Table 3: Attention and executive functions tests: linear regression analysis

	Independent variables included in the model															
Dependent variables	FLE vs CAE		FLE vs BECTS		CAE vs BECTS		Age at onset		Active duration		Frequency of seizures		Treatment		r2	F
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*		
CT	.929	.259	1.054	.218	.125	.881	.169	.224	−.018	.200	−.206	.681	.695	.358	.088	1.331
TMTA	.261	.751	.914	.295	.653	.431	−.213	.140	−.024	.093	.733	.157	.386	.611	.068	.957
TMTB	1.734	.057	2.207	.021	.473	.581	.248	.127	−.010	.517	.519	.341	.353	.667	.142	1.986
TOL_1st	.702	.393	1.104	.198	.402	.632	.389	.006	.008	.565	.347	.490	−1.060	.163	145	2.345
TOL_t	−.172	.824	−.298	.711	−.126	.874	.198	.134	.001	.951	.301	.526	−.814	.255	.051	.746
TOL_tt	1.059	.274	.650	.517	−.409	.679	.345	.037	.008	.621	.145	.806	−1.692	.060	.113	1.756

CT Cancellation Task; TMTA Trail Making Test Part A; TMTB Trail Making Test Part B; TOL_1st Tower of London – 1st Trial; TOL_t Tower of London – Total; TOL_tt Tower of London – Total trials.

4. Discussion

This study was aimed at describing the attention and executive functions performance in three common groups of childhood epilepsies (FLE, CAE and BECTS) and to analyse the influence of epilepsy related variables (type of epilepsy, age at onset, duration of epilepsy, frequency of seizures and treatment).

Following results were observed: first, children with FLE did significantly less well than controls on the following attention and executive functions tests: Cancellation Task (sustained attention), Trail Making Test – Part B (divided attention) and Tower of London (planning and problem solving). Excluding

children with structural lesions from the FLE group did not alter results. Second, children with CAE performed significantly lower than controls on the Trail Making Test – Part B and Tower of London. Third, performance of children with BECTS did not differ from controls. Forth, type and age at onset of epilepsy were the best indicators of attention and executive functions performance. Finally, results showed no effect for duration of active epilepsy, frequency of seizures and treatment.

The results obtained by the group with FLE confirm that children with this type of epilepsy show difficulties in sustained attention, divided attention, planning and problem solving when compared to the control group. It is well known that frontal lobes are essential for cognitive functioning and behaviour, among others they are responsible for the mediation of attention and executive functions (Braakman et al., 2011), therefore structural and functional lesions can interfere with a variety of these functions. Our results are supported by previous results that indicate that the presence of FLE in children affects the capacity to resist to interference (Auclair et al., 2005; Culhane-Shelburne et al., 2002; Hernandez et al., 2003), to pay attention and control impulses (Culhane-Shelburne et al., 2002; Hernandez et al., 2003; Prévost et al., 2006), to plan and organize (Luton et al., 2010). These problems are corroborated by parents who rate them as being easily distracted, absentminded, impulsive, and disorganized (Hernandez et al., 2003; Lassonde et al., 2000; Sinclair et al., 2004).

Our study also supports previous studies (Caplan et al., 2008; Chevalier et al., 2000; Henkin et al., 2005; Kernan et al., 2012; Pavone et al., 2001; Vega et al., 2010) that suggest that children with CAE show deficits in attention and executive functions. In fact, attention and executive functioning problems have been the cognitive constructs most often and consistently described in this population of children with epilepsy. Our study identified specific problems in divided attention and planning. It has previously been showed that children with CAE exhibit difficulties in problem solving (Conant et al., 2008; D'Agati et al., 2012), scoring lower on tasks that are sensitive to cognitive flexibility and planning abilities. Contrary to previous studies (D'Agati et al.,

2012; Hernandez et al., 2003; Killory et al., 2011; Vega et al., 2010), the CAE group did not significantly differ on measures of selective and sustained attention. However it should be considered that most of these studies have used smaller samples than the group we studied. Also, some studies have used checklists completed by parents or teachers, and attentional difficulties may become more evident in more distracting environments, such as the classroom or at home. Some recent studies have shown that absence seizures are not truly generalized, but rather have selective cortical networks, namely in the pre-frontal cortex (Blumenfeld et al., 2003; Clemens et al., 2007; Hughes, 2009; Tucker et al., 2007). This can explain the deficits shown by this population of children with epilepsy in attention and executive functions, considering that the pre-frontal cortical circuits have been implicated in these cognitive domains (van Zomeren & Brouwer, 1994).

Concerning the group of children with BECTS the study of attention and executive functions revealed normal results. But other studies, with this population have shown that these children can present deficits in some tasks that aim to assess attention and executive functions (Croona et al., 1999; Giordani et al., 2006; Neri et al., 2012; Pinton et al., 2006). Deltour et al. (2007) studied a group of 29 children with BECTS, and similar to our study their results did not reveal deficits on the tasks identical to the Tower of London and Cancellation Task that we have used. However their group did show difficulties in high attention control demand tasks requiring inhibitory processes or cognitive flexibility. It is crucial that future studies on children with BECTS integrate a more extensive battery of attention and executive tests, which also include auditory attention tests, to capture which specific sub-domains of these multi-component constructs are at risk.

Besides type of epilepsy, the other risk factor identified in our study was age at onset of epilepsy. In the literature, age at onset of epilepsy has been identified as a strong predictor of cognitive ability (Berg et al., 2008; Cormack et al., 2007). We found that children with an early age at epilepsy onset presented more difficulties with planning and problem solving. Luton et al. (2010) also reported that children with FLE whose seizures emerge before

age 7 had more difficulties in efficiency and maintenance of effort, working memory, cognitive flexibility and self-monitoring, than children with later age at epilepsy onset. In Kernan et al. study (2012), children with CAE and an earlier age at onset of their epilepsy presented more problems in attention. Studying children with BECTS, Neri et al. (2012) reported that children with earlier onset of epilepsy showed more problems performing executive functions tasks. The maturation of the frontal lobes is progressive and results from a combination of myelination and synaptogenesis (Anderson et al., 2001; Hernandez et al., 2001; Huttenlocher & Dabholkar, 1997; Klinberg et al., 1999). Developmental neuropsychological studies have demonstrated that attentional control appears to emerge in infancy and develop in early childhood, and executive abilities have a developmental peak between 7 and 9 years of age and are relatively mature by 12 years of age (Anderson, 2002; Levin et al., 1996). These findings support the idea that the earlier is the onset of seizures, the more critical are the cognitive consequences.

Duration of active epilepsy, seizure frequency and treatment did not affect attention and executive functions outcome. Although in our study anti-epileptic medication was not related to deficits in attention and executive functioning, we highlight that our clinical samples were mainly composed by subjects in monotherapy which can explain why this variable was not related to attention and executive functions. As some authors have reported that concentration, vigilance and working memory are the cognitive domains more vulnerable to the adverse effects of pharmacological treatment (Hoie et al., 2006; Meador, 2001). It is difficult to disentangle the impact of the several epilepsy related variables. But recent studies show that attention deficits may be sometimes erroneously ascribed to medication, as these studies found attention and executive functions problems in several groups of children with new onset epilepsy, even before starting anti-epileptic medication (Bhise et al., 2010; Hermann et al., 2006).

The limitations of our study include the fact that neuropsychological instruments are only indirect measures of central nervous system functioning. Future studies should use simultaneously neuropsychological instruments and

advanced neuroimaging techniques (including diffusion tensor imaging and functional magnetic resonance imaging) that are able to assess the integrity of functional networks and its relation to cognitive impairment. It is also important to note that the adverse effects of medication cannot be completely ruled out as contributing to attention and executive functions. In the future, longitudinal studies should be performed, in which attention and executive functions are examined prior to the initiation of medication, while on medication and after medication withdrawal. Finally, as attention and executive functions are both constructs that include many subdomains, therefore additional tests (such as, visual and verbal span tests, auditory sustained attention, continuous performance tests, fluency tests, estimation tests, behavioural questionnaires) should be included in future studies in order to obtain a more comprehensive assessment of these specific functions.

The strength of the current study is that he is one of the few that compares performance on attention and executive functions of children with FLE with samples of children with different types of epilepsy, and also with matched controls. Most studies compare performance of children with FLE with matched controls (Cerminara et al., 2013; D'Agati et al., 2010; Killory et al., 2011; Luton et al., 2010) or with other types of epilepsy (Auclair et al., 2005; Culhane-Shelburne et al., 2002; Hernandez et al., 2002, 2003), and not both cases simultaneously.

Problems in attention and executive functions may be devastating for school-aged children, as they interfere with the learning of new information and with retrieving and generating spontaneous answers. These problems frequently result in educational problems and the need for educational intervention plans (Berg et al., 2005; Braakman et al., 2012; Williams et al., 2001). Future studies should test the utility of interventions designed to improve attention and executive functions in children with epilepsy, as these as only been tested with adults (Engelberts et al., 2002; Helmstaedter et al., 2008). The reeducation of attention and executive functions deficits requires a multidisciplinary approach, that includes pharmacological management, tutoring and psychological support (Hernandez et al., 2001). Treatment

with stimulant medication in children with epilepsy was initially considered with concern, as it was thought that it could provoke seizures in vulnerable children. But recent reports support the use of stimulants with this population, as children do not show an increase risk of seizures and an improvement in attention functions is found (Gross-Tsur et al., 1997; Koneski et al., 2011; Parisi et al., 2010). Suggestions for teachers to manage attention and executive problems can include: establishing eye contact with pupils while delivering instructions; directions should be clear, simply stated given one at a time; information should be presented step-by-step; minimize distractions in the classroom; provide consistency and structure through daily schedules; supply organizational checklists; give extra time. At home, the environment should be structured and they may need frequent attentional cueing and extra instruction in organization (Hernandez et al., 2001; Hale et al., 2010; Zaccariello et al., 2008).

In conclusion, the results of the present study suggest that attention and executive functioning are areas of weakness in FLE, CAE and in epilepsies with an earlier age at onset. The early detection of these problems and intervention could prevent the long-term consequences for children with these problems, therefore neuropsychological assessments and appropriate interventions should be considered at the time of diagnosis.

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CAPÍTULO V

Language functions in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes

Language functions in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes[1]

Abstract

The aim of this study was the examination of language functions (verbal fluency, comprehension, rapid naming and phonemic awareness) in common childhood common epilepsy syndromes [Frontal Lobe Epilepsy (FLE), Childhood Absence Epilepsy (CAE) and Benign Epilepsy with Centro-Temporal Spikes (BECTS)] and the influence of epilepsy-related variables. Language tests (verbal fluency, rapid naming, comprehension and phonemic awareness) were administered to 90 children with epilepsy (each epilepsy group consisted of 30 children), aged 6-15 and compared with 30 control children. Children with FLE showed significant and generalized deficits in the language domains studied, differing from controls on all the tasks administered. Children with CAE and BECTS also showed difficulties in comprehension, rapid naming and on phonemic awareness (only on the substitution of phonemes). In addition, a longer active duration of epilepsy was associated with comprehension problems. Age at epilepsy onset, seizure frequency and treatment did not influence results in language tasks. Results of the present study suggest that these groups of children with epilepsy have specific deficits in language, which are likely to influence their academic performance, especially in areas of reading and writing.

[1] Lopes, A. F., Monteiro, J. P., Fonseca, M. J., Robalo, C., & Simões, M. R. (*submitted*). Language functions in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes.

Keywords

Frontal lobe epilepsy, Childhood absence epilepsy, Benign epilepsy with centro-temporal spikes, Active duration of epilepsy, Verbal fluency, Comprehension, Rapid naming, Phonemic awareness, Children

1. Introduction

Contrary to other cognitive domains (like, memory, attention and executive functions) few studies have focused on examining language performance in children with epilepsy with normal intellectual functioning (Caplan et al., 2009; Selassie et al., 2008). However the presumed prevalence of speech and language disorders justifies further studies with school-aged children with epilepsy, as one population-based study identified 28% of children with language problems (Sillanpää, 1992). Also these difficulties have been found in children with a recent onset of epilepsy (Fastenau et al., 2009; Hermann et al., 2006, 2007).

The more frequently reported language difficulties are verbal fluency (D'Agati et al, 2012; Hernandez et al., 2002; Neri et al., 2012), comprehension (Danielsson et al., 2009; Riva et al., 2007; Schoenfeld et al., 1999), phonological awareness (Clarke et al., 2007; Northcott et al., 2007; Riva et al., 2007; Vanasse et al., 2005) and naming (Chaix et al., 2006; Hermann et al., 2001; Jackson et al., 2013). There is also evidence that reading and writing are consequently affected (Ay et al., 2009; Ebus et al., 2011; Monjauze et al., 2005; Vanasse et al., 2005).

Language deficits are more frequent in partial epilepsies than in generalized epilepsies (Parkinson, 2002). In temporal lobe epilepsy, language problems are common. Fluency and word-finding difficulties have been reported (Chaix et al., 2006; Hamberger & Tamy, 1999; Hermann et al., 2001), as well as phonological awareness deficits (Chaix et al., 2006; Vanasse et al., 2005). Frontal lobe epilepsy can cause problems on language development, impacting on verbal fluency (Hernandez et al., 2002; Riva et

al., 2005) and metaphonological tasks (Vanasse et al., 2005). In the field of epilepsy research, some of the most recent studies on language have been conducted with children with benign epilepsy with centro-temporal spikes. Speech and language problems in this population of children with epilepsy are above expected, considering that they have normal intellectual functioning. Overvliet et al. (2011) have reported that 23% of a group of 28 children with benign epilepsy with centro-temporal spikes had speech therapy. Different areas of vulnerability have been identified: articulation (Danielsson et al., 2009), grammar (Croona et al., 1999; Monjauze et al., 2005), verbal fluency (Croona et al., 1999; Neri et al., 2012) and phonological awareness (Northcott et al., 2005).

Problems in verbal fluency and phonemic segmentation have also been found in children with idiopathic generalized epilepsy, childhood absence epilepsy included (Conant et al., 2010; D'Agati et al., 2012; Vanasse et al., 2005). Caplan et al. (2008) observed in a relative large sample of children with childhood absence epilepsy found that 43% had linguistic difficulties as expressed the results of the spoken language quotient.

Nevertheless the effect of clinical epilepsy variables on language has not been fully addressed. The few available studies suggest that language impairment is associated with age at epilepsy onset (Schoenfeld et al., 1999), duration of active epilepsy (Caplan et al., 2006), frequency of seizure (Caplan et al., 2004), epileptiform activity (Ebus et al., 2011), and medication (Selassie et al., 2008). However, these associations are still controversial, as other studies found no relation between language functions (more specifically, verbal fluency and phonological awareness) and epilepsy related variables (Hernandez et al., 2002; Northcott et al., 2005; Riva et al., 2005). More studies, that assess multiple domains of language functioning and include larger and more well-defined samples can help us determine the influence of the clinical variables related to epilepsy on language functions.

The present study aims to compare language performance, by looking at verbal fluency, oral comprehension, rapid naming and phonemic awareness, in children with frontal lobe epilepsy (FLE), childhood absence

epilepsy (CAE) and benign epilepsy with centro-temporal spikes (BECTS) and matched controls. In addition, we studied the influence of epilepsy related variables on language, including type of epilepsy, age at epilepsy onset, duration and frequency of epilepsy, and treatment.

2. Methods

2.1 *Participants*

In this clinical study, the experimental group consisted of 90 children with epilepsy (30 with FLE, 30 with CAE; 30 with BECTS) and 30 controls which were matched for age at testing, gender and parental education. Children with epilepsy were recruited from the neuropaediatric units of the Hospital Garcia de Orta and Coimbra's Paediatric Hospital. This study was approved by the institutional review boards of both institutions, and families and children gave their informed consent to participate.

The child neurologists (i) classified the participants with epilepsy based on the International League Against Epilepsy criteria (Berg et al., 2010; Commission on Classification and Terminology of the International League Against Epilepsy, 1989) and (ii) provided for each child information regarding age at epilepsy onset, date of last seizure, frequency of seizures and treatment. Following inclusionary criteria were applied: Children (1) had to be between 6 and 15 years of age; (2) were diagnosed with FLE, CAE or BECTS; (3) obtained a Full Scale IQ of 70 or more (Wechsler Intelligence Scale for Children – Third Edition (WISC-III; Wechsler, 2003; Lopes et al., *in press*); and (4) were receiving no more than two antiepileptic medications.

2.2 *Measures*

Language functions were evaluated using tests from Coimbra´s Neuropsychological Battery Assessment (Simões et al., *in press*). Coimbra's Neuropsychological Assessment Battery is a comprehensive assessment

instrument, directed towards the assessment of Portuguese children's neuropsychological development and functioning. It contains a diversified group of subtests addressing the domains of attention, executive functions, memory, language and motor functions (Albuquerque & Simões, 2010). The different subtests are transformed in scaled scores with a mean of 10 and a standard deviation of 3. The following tests were administered.

2.2.1 *Semantic Verbal Fluency.*

This test evaluates the mobilisation of verbal skills, memory and executive functions. In this task children must generate as many different words as possible, according to three semantic categories (animals, names and food). The score corresponds to the number of correct words generated over the 3 trials of one minute each.

2.2.2 *Phonemic Verbal Fluency.*

This test assesses the same skills as Semantic Verbal Fluency, as well as phonological knowledge. In these task children are instructed to verbalize as many words as possible beginning with a given phoneme (P, M and R), having one minute for each phoneme. Children were asked not to use names of people and places. The total score is the total number of correct words generated over the 3 trials of one minute each.

2.2.3 *Comprehension of Instructions.*

This test assesses receptive language through 27 oral instructions that express several concepts: quantity, sequence, temporal or spatial relationships. The instructions are arranged in 3 parts, with increasing conceptual complexity and different materials: in the first part, one or more puppies that differ in colour, size and expression; in the second part, one or more geometrical shapes with different colours and shapes; and in the third part, one or more geometrical shapes that differ in colour, size and shape. The child identifies pictures in response to orally presented directions by the examiner. The total score is the number of instructions correctly performed.

2.2.4 *Rapid Naming of Shapes and Colours.*

This test assesses the ability to access and produce familiar words rapidly. The child should name as quickly as possible the shape and colour of 50 visual stimuli, displayed on a card (5 rows with 10 stimuli each). The score corresponds to the time required to complete the task.

2.2.5 *Rapid Naming of Numbers.*

The child must rapidly name the numbers (again 50 visual stimuli displayed on a card). The score corresponds to the time required to complete the task.

2.2.6 *Phonemic Awareness: Elision*

This test assesses phonological awareness. The child must say 19 familiar words without a particular phoneme. The score is the number of words correctly pronounced.

2.2.7 *Phonemic Awareness: Substitution*

This test also assesses phonological awareness. The child is asked to say familiar words after replacing one or more phonemes for others. The score is the number of words correctly pronounced.

2.3 *Statistical Analysis*

The statistical analysis was performed using the program *Statistical Package for the Social Sciences* (SPSS, Chicago, IL, USA – Version 17.0). Associations between categorical variables were analysed using Chi-Square Test. Analysis of variance (ANOVA) was used to test mean differences in demographic and clinical variables, and in language scores across the three types of epilepsy (FLE, CAE, BECTS), with post-hoc analysis using *Tukey HSD*. To analyze the effects of epilepsy related clinical variables (type of epilepsy, age at epilepsy onset, active duration, frequency of seizures and treatment) on language tests simple regression analysis was used. In all analysis results were judged statistically significant if the *p*-value was identical to or smaller than .05.

3. Results

Table 1 summarizes the demographic (age at testing, gender, parental education) and clinical characteristics (age at epilepsy onset, seizure frequency, active duration of epilepsy and treatment) of the participants, 90 children and adolescents with epilepsy (30 FLE; 30 CAE; 30 BECTS) and 30 controls, between the ages of 6 and 15 years old. No significant differences were found between the clinical groups and the control group for age at testing and parental education. However for the variable gender the group with FLE differed from the CAE, BECTS and control groups. This might be due to the fact that FLE is more frequent in male children (Braakman et al., 2012;

Table 1: Demographic and neurological features

	FLE (N=30)	CAE (N=30)	BECTS (N=30)	Control (N=30)	*p*-Value
Age	M=10.13 (SD=2.73)	M=9.93 (SD=2.54)	M=9.77 (SD=2.43)	M=10.13 (SD=2.73)	.937
Gender					
Boys	77% (N=23)	30% (N=9)	33% (N=10)	50% (N=15)	
Girls	23% (N=7)*	70% (N=21)	67% (N=20)	50% (N=15)	.001
Years of education (mother)					
Up to 9th grade	17% (N=5)	23% (N=7)	20% (N=6)	14% (N=4)	
9th grade	30% (N=9)	30% (N=9)	47% (N=14)	30%(N=9)	
12th grade	30% (N=9)	20% (N=6)	20% (N=6)	33% (N=10)	
Superior	23% (N=7)	27%(N=8)	13% (N=4)	23% (N=7)	.736
Age at onset (years)	M= 6.40 (SD=3.10)	M=6.83 (SD=2.32)	M=6.77 (SD=2.43)		.792
Seizure frequency					
No seizures (last 6 months)	57% (N=17)	70 % (N=21)	60% (N=18)		
< 1 a month	30% (N=9)	13% (N=4)	37% (N=11)		.177
≥ 1 a month	13% (N=4)	17% (N=5)	3% (N=1)		
Active duration (months)	M=27.57 (SD=36.24)	M=22.63 (SD=17.95)	M=20.90 (SD=26.44)		.632
Treatment					
No medication	7% (N=2)	13% (N=4)	27% (N=8)		.087
Monotherapy	80% (N=24)	73% (N=22)	73% (N=22)		
Duotherapy	13% (N=4)	13% (N=4)	–		

* Differs from Control (*p*=.032), from CAE (*p*=.000) and from BECTS (*p*=.001).

Hernandez et al., 2002). We tested for gender differences on the attention and executive functions tests performed, and no differences were found between boys and girls. On the neurological characteristics of the experimental samples no significant differences were observed between the groups for any of the epilepsy-related variables in analysis (age at epilepsy onset, seizure frequency, active duration of epilepsy and treatment). The group with FLE was composed of 7 children with structural aetiology and 23 with unknown aetiology.

3.1 *Differences between groups*

The results of the comparison between the 3 groups of children with epilepsy and the control group are presented in Table 2. Significant differences were observed for all the administered tasks: Semantic Verbal Fluency [$F(3,116) = 3.442$, $p=.019$], Phonemic Verbal Fluency [$F(3,102) = 3.466$, $p=.019$], Comprehension of Instructions [$F(3,116) = 15.153$, $p<.001$], Rapid Naming of Shapes and Colours [$F(3,102) = 13.379$, $p<.001$] Rapid Naming of Numbers [$F(3,102) = 7.679$, $p<.001$], Phonemic Awareness – Elision [$F(3,116) = 8.827$, $p<.001$] and Phonemic Awareness – Substitution [$F(3,116) = 12.926$, $p<.001$]. Post-hoc analysis revealed significant differences between the three epilepsy groups and the control group. Compared to controls, children with FLE performed worse on the following Tasks: Semantic Verbal Fluency ($p=.028$); Phonemic Verbal Fluency ($p<.026$); Comprehension of Instructions ($p<.001$), Rapid Naming of Shapes and Colours ($p<.001$), Rapid Naming of Numbers ($p<.001$), Phonemic Awareness – Elision ($p<.001$), Phonemic Awareness – Substitution ($p<.001$). The group with CAE scored significantly lower than controls on these tasks: Phonemic Verbal Fluency ($p=.038$); Comprehension of Instructions ($p<.001$), Rapid Naming of Shapes and Colours ($p<.001$), Rapid Naming of Numbers ($p=.004$), Phonemic Awareness – Substitution ($p<.001$). Children with BECTS also differed from the controls on the following language tasks: Comprehension of Instructions ($p<.001$), Rapid Naming of Shapes and Colours ($p=.001$), Rapid Naming of Numbers ($p=.002$), Phonemic Awareness –

Substitution (p=.001).

Given the fact that 7 children from the FLE group had structural lesions, a second analysis including only the other 23 cases with unknown cause was performed. Significant differences were still observed for the same language tasks: Semantic Verbal Fluency [F(3,109) = 3.476, p=.019], Phonemic Verbal Fluency [F(3,95) = 3.062, p=.032], Comprehension of Instructions [F(3,109) = 16.019, p<.001], Rapid Naming of Shapes and Colours [F(3,95) = 12.286, p<.001] Rapid Naming of Numbers [F(3,95) = 6.944, p<.001], Phonemic Awareness – Elision [F(3,109) = 7.486, p<.001] and Phonemic Awareness – Substitution [F(3,109) = 10.989, p<.001]. Post-hoc analysis revealed similar differences between the

Table 2: Language tests scores

	FLE (N=30)	CAE (N=30)	BECTS (N=30)	CONTROL (N=30)	F	df	p-Value
	M (SD)	M (SD)	M (SD)	M (SD)			(ANOVA)
Semantic Verbal Fluency	7.77 (2.81)*	9.17 (2.90)	8.07 (2.48)	9.88 (3.34)	3.442	3, 116	.019
Phonemic Verbal Fluency	8.00 (2.65)*	8.18 (3.06)*	8.64 (3.43)	10.42 (2.68)	3.466	3, 102	.019
Comprehension of Instructions	5.83 (3.02)***	6.27 (4.20)***	7.07 (3.31)***	10.96 (2.38)	15.153	3, 116	.000
Rapid Naming – Shapes and Colours	5.28 (3.45)***	7.00 (3.77)***	7.43 (3.35)***	11.08 (2.63)	13.379	3, 102	.000
Rapid Naming – Numbers	5.68 (3.01)***	6.68 (4.00)**	6.50 (4.05)***	10.08 (2.71)	7.679	3, 102	.000
Phonological Awareness – Elision	5.60 (3.19)***	7.90 (3.93)	7.83 (3.69)	10.12 (2.65)	8.827	3, 116	.000
Phonological Awareness – Substitution	5.23 (2.98)***	6.63 (4.21)***	7.20 (3.38)***	10.54 (2.99)	12.926	3, 116	.000

* Differs from Control (p≤.05)
** Differs from Control (p≤.01)
*** Differs from Control (p≤.001)

three epilepsy groups and the control group. Compared to controls, children with FLE performed worse on the following Tasks: Semantic Verbal Fluency (p=.029); Comprehension of Instructions (p<.001), Rapid Naming of Shapes and Colours (p<.001), Rapid Naming of Numbers (p=.001), Phonemic Awareness – Elision (p<.001), Phonemic Awareness – Substitution (p<.001). The group with CAE scored significantly lower than Controls on these tasks: Phonemic Verbal Fluency (p=.038); Comprehension of Instructions (p<.001), Rapid Naming of Shapes and Colours (p<.001), Rapid Naming of Numbers (p=.004), Phonemic Awareness – Substitution (p<.001). Children with BECTS also differed from the

Controls on the following language tasks: Comprehension of Instructions (p<.001), Rapid Naming of Shapes and Colours (p<.001), Rapid Naming of Numbers (p=.002), Phonemic Awareness – Substitution (p=.001).

3.2 *Risk Factors Related to Epilepsy*

Table 3 shows the results for the linear regression analysis. Regression coefficients were not significant for age at epilepsy onset, frequency of seizures and treatment. Lower scores on the Comprehension of Instructions (p=.048) were related to a longer active duration of epilepsy. Also lower scores on the Rapid Naming of Shapes and Colours (FLE vs. BECTS: p=.028), Phonemic Awareness – Elision (FLE vs. CAE: p=.020; FLE vs. BECTS: p=.012) and on the Phonemic Awareness – Substitution (FLE vs. BECTS: p=.022) were associated with type of epilepsy.

Table 3: Language tests: linear regression analysis

	Independent variables included in the model															
Dependent variables	FLE vs CAE		FLE vs BECTS		CAE vs BECTS		Age at onset		Active duration		Frequency of seizures		Treatment		r2	F
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*		
SVF	1.322	.060	-.006	.993	-1.328	.064	-.201	.090	-.022	.066	-.129	.762	-.644	.316	.135	2.165
PVF	.041	.963	.305	.736	.265	.756	-.064	.680	-.003	.829	-.409	.446	-.680	.405	.037	.469
CI	.291	.748	1.188	.208	.897	.333	.146	.341	-.031	.048	.435	.432	.475	.569	.104	1.606
RNSC	1.637	.090	2.222	.028	.586	.531	.232	.179	-.028	.086	-.006	.992	1.020	.255	.171	2.541
RNN	.944	.369	.856	.433	-.088	.931	.210	.266	-.011	.548	.631	.328	.192	.844	.063	.828
PAE	2.210	.020	2.491	.012	.281	.768	.117	.458	-.020	.226	-.398	.486	1.450	.094	.142	2.296
PAS	1.348	.146	2.221	.022	.874	.355	.086	.582	-.025	.111	.265	.638	1.262	.139	.109	1.699

SVF Semantic Verbal Fluency; **PVF** Phonemic Verbal Fluency; **CI** Comprehension of Instructions; **RNSC** Rapid Naming – Shapes and Colours; **RNN** Rapid Naming – Numbers; **PAE** Phonological Awareness – Elision; **PAS** Phonological Awareness – Substitution.

4. Discussion

In this study we aimed to describe language performance in three common groups of childhood epilepsies [Frontal Lobe Epilepsy (FLE), Childhood Absence Epilepsy (CAE) and Benign Epilepsy with Centro-Temporal Spikes (BECTS)] and to determine the influence of epilepsy related variables (type of epilepsy, age at onset, duration of epilepsy, frequency of seizures and treatment).

The following results were observed: first, children with FLE did significantly less well than controls on all the tasks administered (verbal fluency, comprehension, rapid naming and phonemic awareness). Second, children with CAE showed problems on verbal fluency (phonemic), comprehension, rapid naming and phonemic awareness, compared to controls. Third, children with BECTS performed significantly lower than controls on comprehension, rapid naming and phonemic awareness. Forth, linear regression analysis revealed that type and duration of epilepsy were the best indicators of language functioning. Finally, results showed no effect for age at onset, frequency of seizures and treatment. This study underlies the importance of assessing language functions on these populations with epilepsy, as all the clinical groups (FLE, CAE and BECTS) showed difficulties in this neurocognitive domain.

Most neuropsychological studies of children with FLE have described memory, attention and executive functions, and language tasks are not so often included in the research protocols. Our study illustrates that children with FLE show greater risk of developing language problems, as they had the lowest results in all the administered tasks. The results are in agreement with the few studies published observing that children with FLE perform lower than controls on semantic and phonemic verbal fluency (Hernandez et al., 2002; Riva et al., 2005) and on phonemic awareness (Vanasse et al., 2005) tasks. Neuroimaging studies have described that frontal lobes are involved in the performance of phonological awareness tasks (Price, 1998, 2010). Considering that deficits in phonological awareness (Shaywitz, 2003;

Snowling, 2000; Vellutino et al., 2004) and also rapid naming (Albuquerque et al., 2012) are underlying deficits of reading and spelling abilities, future studies should examine school achievement in school-age children with FLE, as these group of children may be at risk of showing specific learning disabilities.

We also observed that children with CAE showed language problems, more specifically on phonemic verbal fluency, comprehension, rapid naming and phonemic awareness (substitution task). Linguistic comorbidities in CAE have been previously described (Caplan et al., 2008; Conant et al., 2010; D'Agati et al., 2012; Vanasse et al., 2005). These difficulties are of great importance, as language problems in CAE have been linked with poor academic achievement (Vanasse et al., 2005) and psychopathology (Caplan et al., 2005, 2009). This link between linguistic deficits and the presence of a psychiatric diagnosis underlies the clinical importance of testing language functions in CAE. One possible explanation for language difficulties in CAE is the hypothesis that suggests that absence seizures may not be truly generalized, as seizures begin with discrete spikes in the dorsolateral frontal and orbital frontal regions (Holmes et al., 2004; Tucker et al., 2007).

Our findings also show that children with BECTS scored significantly lower than controls on measures of language, such as comprehension, rapid naming and phonemic awareness (substitution task). These findings are congruent with other studies that use similar tasks (Clarke et al., 2007; Danielsson et al., 2009; Neri et al., 2012; Northcott et al., 2005, 2007; Riva et al., 2007;) and report language deficits in BECTS in these same areas. Moreover reading and writing difficulties have been systematically found in BECTS (Miziara et al., 2012; Monjauze et al., 2005; Piccinelli et al., 2008; Pinton et al., 2006; Vinayan et al., 2005). Difficulties on language, reading and spelling performance in this group of children with epilepsy have been correlated with the amount of paroxysmal EEG activity (Deonna et al., 2000; Riva et al., 2007; Tedrus et al., 2009), specially nocturnal epileptiform activity (Ebus et al., 2011; Overvliet et al., 2011; Piccinelli et al., 2008). The relationship between interictal activity and linguistic problems raises questions regarding the use of anti epileptic drugs. Since treatment indications are usually restricted to

the frequency of seizures, and do not consider the presence of paroxysmal abnormalities (Pinton et al., 2006). Future studies should address this question, to confirm if treatment of interictal activity can improve linguistic functions and school achievement.

In this study age at epilepsy onset, frequency of seizures and treatment did not affect language functioning. We found that longer active duration of epilepsy was associated with receptive language problems (Comprehension of Instructions test). Previously we have described intellectual functioning with the same populations of children with epilepsy of the present study, and we reported the same adverse effect of duration of epilepsy on the verbal composite scores (Verbal IQ and Verbal Comprehension Index) of the Wechsler Intelligence Scale for Children (Lopes et al., in press). Caplan and colleagues (Caplan et al., 2006, 2008, 2009) have also show that there is a wider range of linguistic deficits in subjects with a longer duration of illness. Also, reading and spelling performance has been linked with the duration of epileptic activity (Monjauze et al., 2005; Papavasiliou et al., 2005).

Our study is one of the few that compare language functioning in relatively large samples of children with different common childhood epilepsy syndromes (FLE, CAE, BECTS) with comparable demographic and neurologic variables. Moreover we were able to cover different domains of language functioning in our protocol, including phonological processing, naming and receptive language. However we did not include the assessment of expressive language and written language.

Future studies should analyze in detail language functions longitudinally in childhood epilepsy, as it is not clear if they improve (Deonna et al., 2000; Northcott et al., 2006) or if negative long-term consequences are shown (Ay et al., 2009; Monjauze et al., 2005, Papavasiliou et al., 2005) when epilepsy is in remission. In addition, the incidence of dyslexia in childhood epilepsy also needs to be examined. So far, few studies with small populations have described a higher incidence of dyslexic type-errors in children with BECTS (Canavese et al., 2007; Papavasiliou et al., 2005). But larger population based studies are needed, in order to identify which specific groups of

children with epilepsy are in risk, considering the impact of the clinical variables related to epilepsy.

In conclusion, our study indicates that FLE, CAE, BECTS and a longer duration of epilepsy constitutes risk factors for language development in the subdomains of verbal fluency, comprehension, rapid naming and phonemic awareness. Some of these problems, especially phonemic awareness difficulties, can impact on school performance, most of all on reading and writing abilities. Therefore comprehensive neuropsychological assessments, that include several measures of language and school achievement, should be offered to these children. These children should go through regular clinical investigations as some difficulties might be permanent or may emerge later in life. And whenever necessary, school intervention plans should be established, as well as a specialized intervention with a speech therapist.

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CAPÍTULO VI

Risk factors for school problems in children and adolescents with epilepsy

Risk factors for school problems in children and adolescents with epilepsy[1]

Abstract

The purpose of the present study was to describe the school achievement, assessed by teacher ratings, of children and adolescents with common childhood epilepsy syndromes. In addition, the influence of epilepsy related variables, like type of epilepsy [Frontal Lobe Epilepsy (FLE); Childhood Absence Epilepsy (CAE); Benign Epilepsy with Centro-Temporal Spikes (BECTS)], age at epilepsy onset, duration of active epilepsy, frequency of seizures and treatment on school results was investigated. School status and school results for Portuguese and Maths as reported by teachers were examined in 90 children with epilepsy (30 FLE, 30, CAE, 30 BECTS). 30% of these children were receiving support from special education services and 18% had at least repeated one year at school. Children with a longer duration of active epilepsy were more likely to be receiving support from special education services or to have at least repeated one year at school. Linear regression analysis showed that type of epilepsy (FLE) and a longer duration of active epilepsy were the best predictors for lower scores in Portuguese. For school results in Maths there was no significant effect for the epilepsy-related variables. It is important that children with FLE or with a longer duration of active epilepsy are targeted as soon as possible for neuropsychological assessment in order to establish effective remedial education plans.

[1] Lopes, A. F., Monteiro, J. P., Fonseca, M. J., Robalo, C., & Simões, M. R. (*submitted*). Risk factors for school problems in children and adolescents with epilepsy.

Keywords

Frontal lobe epilepsy, Childhood absence epilepsy, Benign epilepsy with centro-temporal spikes, School performance

1. Introduction

Academic achievement problems are common in children and adolescents with epilepsy, even in those with normal or near average intellectual functioning (Fastenau et al., 2008; Piccinelli et al., 2008; Reilly & Neville, 2011; Vinayan et al., 2005).

A considerable percentage of children with epilepsy are supported by special education services, even if neurologically normal. The community based Connecticut Study of Epilepsy (Berg et al., 2005, 2011) reported that 49% of children with idiopathic or cryptogenic epilepsy benefited from special education services. Also, it has been described that for a large percentage of children the initiation of special education measures (Berg et al., 2005) or repetition of years at school (Schouten et al., 2001) precedes the diagnosis of epilepsy. These data suggests that cognitive and behavioural comorbidities may precede the onset of epilepsy.

The factors underlying academic vulnerability are not well understood, and are likely to be multi-factorial. Type of epilepsy (Aldenkamp et al., 2005; Berg et al., 2005), age at epilepsy onset (Fastenau et al., 2008; Piccinelli et al., 2008), duration of epilepsy (Adewuya et al., 2006), frequency of seizures (McNelis et al., 2005) and whether and what antiepileptic drugs are used (Bulteau et al., 2000) are some of the epilepsy related variables that have been identified as potential causes for academic problems.

In addition, neuropsychological functioning has been related to academic achievement. Fastenau et al. (2004) has identified three underlying neuropsychological constructs that were strongly associated with academic achievement: "Verbal/Memory/Executive Functioning", "Rapid Naming/

Working Memory" and "Psychomotor". Aldenkamp et al. (2005) found that the dominant neuropsychological factor responsible for academic difficulties was lower intelligence. In addition attention deficits (Williams et al., 2001) have been reported in children with unsatisfactory academic progress.

Psychosocial variables and family functioning are likely to moderate the relationship between neuropsychological impairment and academic difficulties (Austin & Dunn, 2008). There is a high risk of psychosocial problems in children with epilepsy (Berg et al., 2007; Hoie et al., 2006), but most studies on academic achievement do not include the assessment of psychosocial functioning. The presence of Attention Deficit Hiperactivity Disorder (Fastenau et al., 2008), lower self-esteem (Adewuya et al., 2006), social skill deficits and depressive symptomatology (Sturniolo & Galletti, 1994) as well as negative attitudes toward epilepsy (Austin & Dunn, 2008) have been associated with school difficulties. The presence of parental mental health problems (Dunn et al., 2010) and disorganized or unsupportive home environments (Adewuya et al., 2006; Fastenau et al., 2004) are both identified as risk factors for worse academic results.

The goal of the present study was to describe the school achievements of children and adolescents with common childhood epilepsy syndromes. In more detail, we investigated the influence of the following epilepsy related variables on school achievements, assessed as the results described by teachers in Portuguese and Maths, including: (i) type of epilepsy (Frontal Lobe Epilepsy, Childhood Absence Epilepsy, Benign Epilepsy with Centro-Temporal Spikes), (ii) age at epilepsy onset, (iii) duration of active epilepsy, (iv) frequency of seizures and (v) treatment (no medication, monotherapy, duotheraphy).

2. Methods

2.1 *Participants*

Participants were 90 children with epilepsy, who were recruited from neuropaediatric units of Hospital Garcia de Orta and Coimbra's Paediatric Hospital. This study was approved by the institutional review boards of both institutions. Children with epilepsy were selected based on the following inclusionary criteria: They were (i) between 6 and 15 years of age; (ii) diagnosed with Frontal Lobe Epilepsy (FLE), Childhood Absence Epilepsy (CAE) or Benign Epilepsy with Centro-Temporal Spikes (BECTS); (iii) administered the Wechsler Intelligence Scale for Children – Third Edition and obtained a Full Scale IQ ≥ 70; and (iv) receiving no more than two antiepileptic medications.

2.2 *Measures*

As part of the Achenbach Teacher's Report Form (Fonseca et al., 1995), teachers informed us: (i) whether the child benefited from special education services; (ii) whether he or she had repeated years at school; and (iii) about the classification of their performance in Portuguese and Maths (1 *Very Inferior,* 2 *Inferior,* 3 *Normal,* 4 *Superior,* 5 *Very Superior*).

2.3 *Statistical Analysis*

Statistical analysis was carried out with the assistance of the program *Statistical Package for the Social Sciences* (SPSS, Chicago, IL, USA – Version 17.0). Associations between categorical variables were analyzed using Chi-Square Tests. Analysis of variance (ANOVA) was used to test mean differences in demographic and clinical variables, and in school results across the three types of epilepsy (FLE, CAE, BECTS), with post-hoc analysis using *Tukey HSD*. Also, independent samples t-tests were conducted to compare patients with and without special teaching and patients with and without retentions at

school. To analyze the effects of epilepsy related clinical variables (type of epilepsy, age at onset, active duration, frequency of seizures and treatment) on school results (Portuguese and Maths) simple regression analyses were carried out. Results were judged statistically significant if the *p*-value was identical to or smaller than .05.

3. Results and Discussion

There were no significant differences between groups for age at testing and parental education (see Table 1). For the variable gender the Frontal Lobe Epilepsy group differed from the CAE and BECTS groups, which can be explained by the fact that FLE seems to me more frequent in males (Braakman et al., 2012). Gender differences for the school results were tested, and no differences were reported between boys and girls. For the neurological features no significant differences were observed between the groups (FLE, CAE and BECTS) for any of the epilepsy-related variables (age at onset of epilepsy, active duration of epilepsy, seizure frequency and treatment).

All the children included in the study attended mainstream schools, without separate classrooms for children with special needs. 30% (N=27) of the 90 children were receiving support from special education services, and 18% (N= 16) had at least repeated one year at school. Inclusion in special education programs in mainstream schools among the general population in Portugal is 2,6% (Direcção Geral de Inovação e Desenvolvimento Curricular – Curriculum Development and Innovation General Service, 2009). Our study confirms results from several studies (Berg et al., 2005; Braakman et al., 2012) that report a higher percentage of children included in special education programs compared to normal children.

We compared children with and without special education services for differences on epilepsy-related variables. Children with a longer duration of active epilepsy were more likely to be receiving support from special education services [$t(88) = 2.341$, $p=.025$] or to have at least repeated one

Table 1: Demographic and neurological features

	FLE (N=30)	CAE (N=30)	BECTS (N=30)	*p*-Value
Age	M=10.13 (SD=2.73)	M=9.93 (SD=2.54)	M=9.77 (SD=2.43)	.858
Gender				
Boys	77% (N=23)	30% (N=9)	33% (N=10)	
Girls	23% (N=7)*	70% (N=21)	67% (N=20)	.001
Years of education (mother)				
Up to 9th grade	17% (N=5)	23% (N=7)	20% (N=6)	
9th grade	30% (N=9)	30% (N=9)	47% (N=14)	
12th grade	30% (N=9)	20% (N=6)	20% (N=6)	
Superior	23% (N=7)	27%(N=8)	13% (N=4)	.660
Age at onset (years)	M= 6.40 (SD=3.10)	M=6.83 (SD=2.32)	M=6.77 (SD=2.43)	.792
Seizure frequency				
No seizures (last 6 months)	57% (N=17)	70 % (N=21)	60% (N=18)	
< 1 a month	30% (N=9)	13% (N=4)	37% (N=11)	.177
≥ 1 a month	13% (N=4)	17% (N=5)	3% (N=1)	
Active duration (months)	M=27.57 (SD=36.24)	M=22.63 (SD=17.95)	M=20.90 (SD=26.44)	.632
Treatment				
No medication	7% (N=2)	13% (N=4)	27% (N=8)	.087
Monotherapy	80% (N=24)	73% (N=22)	73% (N=22)	
Duotherapy	13% (N=4)	13% (N=4)	_	

* Differs from CAE (*p*=.001) and from BECTS (*p*=.001).

year at school [*t*(88) = 2.540, *p*=.020]. Groups did not differ for type of epilepsy, age at onset, frequency of seizures and treatment.

According to their teachers, 36% (N=32) in Portuguese and 40% (N=36) in Maths were performing bellow expected. The results of the comparison between the 3 groups of children with epilepsy (FLE, CAE and BECTS) revealed no significant differences (see Table 2). Our results, together with other studies that report teachers assessment of the child's academic abilities (Katzenstein et al., 2007; McNelis et al., 2005), also excluding children with a diagnosis of mental retardation, shows that teachers ratings of school performance of children with epilepsy are lower. Academic achievement problems are also

Table 2: School status

	FLE (N=30)	CAE (N=30)	BECTS (N=30)	*p*-Value
School attendance				
Normal	60% (N=18)	70% (N=21)	80% (N=24)	.240
Special education	40% (N=12)	30% (N=9)	20% (N=6)	
Retentions at school	20% (N=6)	27% (N=8)	7% (N=2)	.119
Portuguese classifications				
Very inferior	27% (N=8)	10% (N=3)	–	
Inferior	13% (N=4)	33% (N=10)	23% (N=7)	
Normal	50% (N=15)	50% (N=15)	70% (N=21)	
Superior	10% (N=3)	7% (N=2)	3% (N=1)	.145
Very superior	–	–	3% (N=1)	
Math classifications				
Very inferior	20% (N=6)	20% (N=6)	3% (N=1)	
Inferior	27% (N=8)	23% (N=7)	27% (N=8)	
Normal	40% (N=12)	50% (N=15)	60% (N=18)	
Superior	13% (N=4)	7% (N=2)	10% (N=3)	.438
Very superior	–	–	–	

reported in studies that use standardized achievement tests, such as the Wide Range Achievement Test that provides an assessment of reading, writing and computational abilities (Aldenkamp et al., 2005; Piccinelli et al., 2008; Schoenfeld et al., 1999).

In the linear regression analysis (see Table 3), school results in Portuguese were correlated to type of epilepsy and active duration of epilepsy. There was no significant effect for age at epilepsy onset, frequency of seizures and treatment (*p*-values > .073). School results in Portuguese were higher for children with BECTS when compared with FLE (*p*= .029). Also, a lower result in Portuguese (*p*= .013) was associated with a longer duration of active epilepsy. For school results on Maths there was no significant effect for the epilepsy-related variables, although there was a tendency towards a significant result for lower results on Maths and a longer duration of epilepsy (*p*= .059). Future research, that also includes standardized academic achievement tests, needs to analyse carefully the influence of epilepsy-related variables for each specific academic area, such as Maths and Maternal Language.

Table 3: Linear regression analysis

	Dependent variables			
Independent variables	Portuguese		Maths	
included in the model	β	*p*	β	*p*
FLE vs CAE	.096	.646	.025	.910
FLE vs BECTS	.484	.029	.358	.126
CAE vs BECTS	.388	.073	.383	.096
Age at onset	-.040	.264	-.052	.170
Active duration	-.009	.013	-.007	.059
Frequency of seizures	.067	.602	.058	.671
Treatment	.265	.172	.239	.247
r2	.122		.080	
F	1.931		1.210	

The present study found that longer duration of epilepsy was associated with lower results in Portuguese. Also these children with a longer duration of epilepsy benefited more frequently from special education services and were more likely to have repeated years at school. This finding is supported by previous studies (Adewuya et al., 2006; Seidenberg et al., 1988).

The limitations of the present study include the fact that school results were rated by students' teachers that were aware that their pupils suffered from epilepsy. Similar studies that have also used teachers' ratings have reported that the diagnosis of epilepsy may lower teachers' expectations of academic performance of children with epilepsy (Katzenstein et al., 2007; William, 2003). Therefore future studies, that intend to study risk factors for academic achievement, should include standardized measures of school achievement (not available for Portuguese) on the neuropsychology assessment protocols, besides tests of intelligence, memory, attention, executive functions, language, visuoperceptive functions, socio-emotional functioning and family functioning.

In conclusion, we have shown that academic achievement problems are frequent in children with epilepsy. In our study, type of epilepsy (FLE) and a longer duration of active epilepsy were the main risk factors for

school performance. These children should be targeted, as soon as possible, for neuropsychological assessment in order to establish effective remedial education plans.

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DISCUSSÃO GERAL E CONCLUSÕES FINAIS

Discussão Geral e Conclusões Finais

A discussão geral integra, analisa e resume os principais resultados dos estudos realizados, anteriormente apresentados sob a forma de artigos. Assim serão objecto de discussão os principais resultados relativos ao funcionamento intelectual, memória, atenção e funções executivas, linguagem e aos desempenhos escolares de acordo com as variáveis clínicas relativas à epilepsia: *Tipo de Epilepsia [Epilepsia do Lobo Temporal (ELT), Epilepsia do Lobo Frontal (ELF), Epilepsia de Ausências na Criança (EAC) e Epilepsia Benigna com Pontas Centro-Temporais (EBPCT)], Idade de Início da Epilepsia, Duração activa da Epilepsia, Frequência das Crises e Medicação Anti-Epiléptica.* Finalmente serão apresentadas implicações científicas e clínicas, as potencialidades e limites destas investigações, bem como delineadas áreas de investigações futuras.

Tipo de Epilepsia

As crianças com *Epilepsia do Lobo Temporal* (ELT), que recordamos, apenas foram estudadas no domínio da atenção e funções executivas (*Capítulo I*), apresentaram dificuldades na manutenção da atenção, atenção selectiva, atenção dividida e fluência verbal fonémica. Estes resultados são similares aos identificados noutros estudos (Hernandez et al., 2002, 2003; Igarashi et al., 2002). Os problemas identificados na prova fluência verbal fonémica poderão também ser explicados pelas dificuldades que os

sujeitos com ELT apresentam no domínio da linguagem (Cohen et al., 1990; Jambaqué, 2001; Jansky et al., 2005; Sauerwein et al., 2005). Por outro lado, os desempenhos dos sujeitos com ELT diferenciaram-se do grupo de controlo nas medidas relativas ao tempo utilizado para resolver as tarefas, e não no que diz respeito aos erros e lacunas cometidas. Este dado poderá traduzir défices na velocidade de processamento, eventualmente primários aos défices na área da atenção (Hernandez et al., 2003). Esta lentificação poderá, por sua vez, afectar os recursos atencionais destas crianças e adolescentes. Finalmente, as dificuldades na atenção e funções executivas na ELT poderão ter duas explicações complementares, de natureza neuroanatómica e funcional: (i) os défices no funcionamento executivo têm subjacente uma disfunção da ligação fronto-temporal (Laurent & Arzimanoglou, 2006); (ii) o hipocampo pode estar envolvido nalgumas áreas do funcionamento executivo (Corcoran & Upton, 1993). Este estudo vem demonstrar a importância da avaliação de crianças com ELT nos domínios da atenção, funções executivas e velocidade de processamento, alertando também para a necessidade dos protocolos de avaliação serem compreensivos, devendo para tal incluir o exame de outros domínios neurocognitivos, nomeadamente os da linguagem e memória, com o objectivo de distinguir áreas de dificuldades primárias e secundárias.

O grupo de crianças com *Epilepsia do Lobo Frontal* (ELF) apresentou um perfil de dificuldades mais generalizadas, em oposição aos grupos com EAC e EBPCT, tendo a ELF impacto em vários domínios neurocognitivos, mesmo quando excluídos da análise os sujeitos com ELF sintomática. Assim, em convergência com investigações prévias (Braakman et al., 2011; Nolan et al., 2003; Prévost et al., 2006), o nosso estudo evidencia que as crianças e adolescentes com ELF apresentam resultados inferiores no funcionamento intelectual (*Capítulo II*). As dificuldades avaliadas através da escala de inteligência utilizada (WISC-III) demonstraram sobretudo dificuldades na velocidade de processamento e nos subtestes que mais se correlacionam com o desempenho escolar (Informação, Aritmética, Memória de Dígitos e Código). As dificuldades na velocidade de processamento, também

reconhecidas noutros estudos (Auclair et al., 2005; Braakman et al., 2012; Bulteau et al., 2000; Hernandez et al., 2003) são de extrema importância, sobretudo quando se trata de identificá-las em crianças em idade escolar, atendendo ao facto de que a velocidade de processamento é fundamental para a implementação eficiente de outras funções cognitivas que suportam as aprendizagens. No que diz respeito à avaliação do funcionamento mnésico (*Capítulo III*), o grupo com ELF manifestou maior risco de apresentar dificuldades na memória verbal (Lista de Palavras) e visual (Tabuleiro de Corsi). As dificuldades mnésicas ocorrem fundamentalmente nas fases de aprendizagem, apresentando os sujeitos dificuldades na codificação inicial da informação. Outras investigações relatam que as crianças com ELF apresentam estratégias de codificação da informação menos eficazes do que as crianças dos grupos de controlo (Jambaqué et al., 1993; Verche et al., 2011). Por outro lado, no domínio da atenção e funções executivas (*Capítulo IV*) o grupo com ELF exibiu dificuldades na manutenção da atenção (Teste da Barragem de Sinais), na atenção dividida (*Trail Making Test* – Parte B) e na capacidade de planeamento e resolução de problemas (Torre de Londres). Tendo em conta que os lobos frontais desempenham um papel fundamental na mediação da atenção e funções executivas (Braakman et al., 2011), estes resultados eram esperados, e são suportados por estudos anteriores que relatam dificuldades na capacidade de resistir à interferência (Auclair et al., 2005; Culhane-Shelburne et al., 2002; Hernandez et al., 2003), na capacidade de prestar atenção e resistir a impulsos (Culhane-Shelburne et al., 2002; Hernandez et al., 2003; Prévost et al., 2006) e na capacidade de organização e planeamento (Luton et al., 2010). Os estudos que avaliam a linguagem nas crianças com ELF são escassos, sendo que a maioria dos protocolos apenas inclui medidas de avaliação da fluência verbal (Hernandez et al., 2002; Riva et al., 2005). Neste sentido, o nosso estudo constitui um importante contributo na caracterização das funções da linguagem neste tipo de epilepsia na idade pediátrica. A nossa investigação (*Capítulo V*) mostra que as crianças com ELF apresentam um elevado risco de desenvolver problemas linguísticos, na medida em que apresentaram os resultados mais baixos em todas

as tarefas administradas que envolvem mais directamente a linguagem (Fluência Verbal Semântica, Fluência Verbal Fonémica, Compreensão de Instruções, Nomeação Rápida de Cores e Formas, Nomeação Rápida de Números, Consciência Fonémica – Eliminação, Consciência Fonémica – Substituição). Estes resultados são congruentes com os apontados nos poucos estudos disponíveis, que recorrem a um menor número de testes e que também identificam défices na fluência verbal e na consciência fonológica (Hernandez et al., 2002; Riva et al., 2005; Vanasse et al., 2005). Considerando que estudos de neuroimagem implicam os lobos frontais no desempenho de tarefas de consciência fonológica (Price, 1998, 2010), e que, por outro lado, as dificuldades na consciência fonológica poderão ser preditoras de problemas na leitura e na escrita (Shaywitz, 2003; Snowling, 2000; Vellutino et al., 2004), julgamos que estudos futuros deverão também examinar, de modo sistemático e estandardizado, o desempenho escolar das crianças com ELF em idade escolar, nomeadamente nos domínios específicos da leitura e da escrita. No que concerne aos resultados escolares (*Capítulo VI*), a ELF foi o tipo de epilepsia a que se associou dificuldades mais acentuadas no domínio do Português, sendo que 40 % das crianças deste grupo se encontram abrangidas pelo ensino especial e que 20% já foram retidas. Na disciplina de Português 40% obtêm uma classificação inferior à média esperada e na Matemática 47%.

O grupo com *Epilepsia de Ausências da Criança* (EAC) apresentou dificuldades específicas que incidiram nos domínios da atenção e funções executivas (*Capítulo IV*), e na área da linguagem (*Capítulo V*). A nível escolar (*Capítulo VI*) destacamos o facto de 30% das crianças com EAC se encontrarem abrangidas pelo ensino especial e 27% já terem ficado retidas. Por outro lado, 43% apresentaram resultados inferiores ao esperado nas disciplinas de Português e Matemática. No que diz respeito ao estudo das funções da atenção e funcionamento executivo, o grupo com EAC apresentou dificuldades específicas na atenção dividida (*Trail Making Test* – Parte B) e na capacidade de planeamento (Torre de Londres). A atenção e as funções executivas são os domínios cognitivos mais frequentemente

estudados nas crianças e adolescentes com EAC, havendo vários estudos a documentarem dificuldades nestes domínios (Caplan et al., 2008; Chevalier et al., 2000; Henkin et al., 2005; Kernan et al., 2012; Pavone et al., 2001; Vega et al., 2010). Por outro lado, no domínio da linguagem apresentaram dificuldades nas provas de Fluência Verbal Fonémica, Compreensão de Instruções, Nomeação Rápida (Cores e Formas, e de Números) e na Consciência Fonémica (prova de Substituição). A sinalização destas dificuldades neste grupo parecem particularmente importantes, na medida em que problemas nestes domínios têm sido relacionadas com dificuldades académicas, sobretudo no domínio da leitura e escrita (Vanasse et al., 2005) e com a presença de psicopatologia (Caplan et al., 2005, 2009). Estudos realizados na última década apontaram que as crises de ausências poderão não ser verdadeiramente generalizadas, mas ter um início focal na área pré-frontal (Blumenfeld et al., 2003; Clemens et al., 2007; Hughes, 2009; Tucker et al., 2007), o que poderá justificar as dificuldades observadas nos domínios da atenção, funções executivas e linguagem.

O grupo com *Epilepsia Benigna com Pontas Centro-Temporais* (EBPCT) apresentou apenas dificuldades generalizadas no domínio da linguagem (*Capítulo V*). Embora o perfil de dificuldades apresentadas seja mais leve, em comparação com os outros dois grupos investigados (ELF e EAC), o estudo demonstra que estas crianças apresentam défices cognitivos específicos, sobretudo no processamento fonológico, que podem interferir no seu rendimento escolar. Outros estudos têm reportado de forma sistemática problemas na leitura e escrita (Miziara et al., 2012; Monjauze et al., 2005; Piccinelli et al., 2008; Pinton et al., 2006; Vinayan et al., 2005), que se relacionam nomeadamente com as dificuldades evidenciadas no processamento fonológico. As dificuldades nos domínios da linguagem, incluindo a leitura e a escrita têm sido relacionadas com a quantidade de actividade paroxística (Deonna et al., 2000; Riva et al., 2007; Tedrus et al., 2009), sobretudo durante a noite (Ebus et al., 2011; Overvliet et al., 2011; Piccinelli et al., 2008). Esta relação entre actividade interictal e os problemas linguísticos, levanta questões relativas à necessidade da

utilização dos fármacos anti-epilépticos, tendo em conta que as indicações para tratamento farmacológico são restritas à frequência das crises, não considerando a presença de actividade interictal (Pinton et al., 2006). Desta forma, estudos futuros deverão examinar esta questão, com o objectivo de confirmar se o tratamento da actividade interictal pode melhorar as funções da atenção e rendimento escolar. Por último, demonstramos neste estudo que a utilização do termo benigna para designar a EBPCT é desadequado, tendo em conta as dificuldades específicas na linguagem que se associam a este tipo de epilepsia, corroborando a ideia anteriormente defendida por Anne Berg (Berg et al., 2010).

Idade de Início da Epilepsia

A idade de início da epilepsia não se relacionou com o funcionamento intelectual, linguagem e resultados escolares (*Capítulos II, V e VI*) das crianças observadas nos nossos estudos, o que vem contrariar resultados de estudos anteriores (Arzimanoglou et al., 2004; Cormack et al., 2007; Jokeit & Ebner, 2002). Porém, devemos ter em conta que a idade média de início da epilepsia nas nossas investigações foi de 6 anos de idade, dado que poderá explicar a ausência de impacto desta variável clínica no funcionamento intelectual, na medida em que esta influência parece sobretudo incidir nas crianças cuja epilepsia tem início no primeiro ano de vida (Cormack et al., 2007). Pelo contrário, as crianças com uma idade de início da epilepsia mais precoce obtiveram resultados mais baixos no Tabuleiro de Corsi (*Capítulo III*), na Barragem de Sinais (*Capítulo I*) e na Torre de Londres (*Capítulo I, IV*), isto é, nas provas que avaliam a memória de trabalho, manutenção da atenção, capacidade de planeamento e resolução de problemas. Estes resultados são corroborados por outros autores que identificam dificuldades nas tarefas que avaliam a atenção e as funções executivas, que são mais acentuadas nas crianças que apresentam uma idade de início da epilepsia mais precoce (Luton et al., 2010; Kernan et al., 2012; Neri et al., 2012). É expectável

que o impacto da idade de início precoce da epilepsia seja mais crítico no domínio específico da atenção e funções executivas. Por um lado, estas funções cognitivas estão sediadas nos lobos frontais e esta região cerebral é a que atinge a maturidade mais tarde. Por outro lado, a maturação dos lobos frontais é progressiva e só se completa durante a adolescência (Anderson, 2002; Anderson et al., 2001; Hernandez et al., 2001).

Duração Activa da Epilepsia

A duração activa da epilepsia foi o preditor mais forte do funcionamento intelectual (*Capítulo II*). Uma maior duração activa da epilepsia associou-se a resultados mais baixos nos resultados compósitos da escala de inteligência (QI Escala Completa, QI Verbal, Índice de Compreensão Verbal e no Índice de Velocidade de Processamento). O efeito negativo desta variável clínica no funcionamento intelectual das crianças e adolescentes com epilepsia é confirmado por outros estudos (Bulteau et al., 2000; Caplan et al., 2008; Sherman et al., 2012; Singhi et al., 1992). Estes resultados merecem destaque, pois alertam-nos para o risco destas crianças virem a apresentar um declínio no seu funcionamento intelectual. Dodrill e colaboradores (2004) encontraram uma relação ligeira mas real, entre a duração activa da epilepsia e o declínio cognitivo. Investigações futuras deverão analisar, longitudinalmente, sobretudo os indivíduos com uma maior duração activa da epilepsia, com o objectivo de determinar a estabilidade dos seus quocientes intelectuais. Por outro lado, a duração activa da epilepsia também se associou a dificuldades no funcionamento mnésico (*Capítulo III*) e na linguagem (*Capítulo V*), problemas que são confirmados por outros estudos (Caplan et al., 2006, 2008, 2009; Nolan et al. 2004; Riva et al., 2005; Schoenfeld et al., 1999). Finalmente, as crianças com uma maior duração activa da epilepsia apresentaram uma maior probabilidade de estarem abrangidas pelo ensino especial ou de terem ficado retidas, assim como apresentaram resultados mais baixos na disciplina de Português

(*Capítulo VI*), resultados confirmados por estudos anteriores (Adewuya et al., 2006; Seidenberg et al., 1988). Os efeitos da epilepsia crónica têm sido comprovados em estudos que demonstram que uma história de epilepsia longa se associa a um desenvolvimento cerebral adverso, com impacto na estrutura e funções cerebrais (Hermann et al., 2002, 2007).

Frequência das Crises

A análise do impacto da frequência das crises no funcionamento neurocognitivo (*Capítulos II, III, IV e V*) e nos resultados escolares (*Capítulo VI*), não revelou qualquer efeito. No entanto, a maior parte dos sujeitos (62%) que integraram as amostras clínicas encontrava-se sem crises há 6 meses ou mais, 27 % tinham menos de uma crise por mês, e os restantes 11% uma ou mais crises por mês, facto que poderá ter contribuído para os resultados obtidos. Por outro lado, nas síndromes epilépticas estudadas o controlo das crises é mais facilmente alcançado com a introdução da medicação anti-epiléptica, pelo que estas crianças não apresentam habitualmente uma frequência elevada de crises. De qualquer modo, os resultados alcançados são corroborados por outros estudos, que não relatam um impacto significativo desta variável no funcionamento neurocognitivo (Adewuya et al., 2006; Chaix et al., 2006; Weglage et al., 1997).

Medicação Anti-Epiléptica

Estudos anteriores documentaram que a medicação anti-epiléptica pode ter um impacto negativo nas funções neurocognitivas, nomeadamente na capacidade de concentração, vigilância e memória de trabalho (Hoie et al., 2006; Meador, 2001). No nosso estudo não se observou um efeito desta variável, tanto nas dimensões neurocognitivas avaliadas (*Capítulos II, III, IV, V*), como nos resultados escolares (*Capítulo VI*). Porém, a maior parte dos

sujeitos (75%) estavam medicados com um único fármaco (monoterapia), apenas 9% com dois fármacos (duoterapia) e 16% sem medicação. De todo o modo, os resultados obtidos são corroborados por outros estudos que não identificam efeitos do tratamento farmacológico nas funções neurocognitivas (Berg et al., 2008; Hernandez et al., 2003). Por outro lado, estudos recentes demonstram que no passado as dificuldades nos domínios da atenção e funções executivas podem ter sido erradamente atribuídas aos efeitos negativos da medicação anti-epiléptica, uma vez que nos referidos estudos foram encontradas dificuldades nestes domínios no momento do diagnóstico da epilepsia, ou seja, mesmo antes das crianças iniciarem a medicação (Bhise et al., 2010; Hermann et al., 2006).

Com base nos resultados obtidos, lançamos a hipótese de que o impacto das diferentes variáveis clínicas relativas à epilepsia seja distinto consoante a área do funcionamento neurocognitivo examinada. No entanto, a literatura existente não abordou até hoje esta questão de forma sistemática, pelo que estudos futuros deverão explorar a associação destes factores e as diferentes áreas do funcionamento neuropsicológico destas crianças, não assumindo à partida que estas variáveis influenciem de forma idêntica os diferentes domínios neurocognitivos.

Implicações, potencialidades e limites das investigações realizadas

Em primeiro lugar apresentámos um estudo preliminar (*Capítulo I*), que comparou as funções da atenção e funções executivas num grupo de crianças e adolescentes com epilepsia do lobo temporal, com um grupo de crianças sem problemas de saúde emparelhado no que diz respeito às variáveis idade, género, área de residência e escolaridade dos pais. Porém, este estudo apresentou limitações importantes. Neste estudo, as crianças apenas foram avaliadas no domínio da atenção e das funções executivas. Se atendermos ao facto de que cada teste examina não só as

funções primárias mas também as secundárias, os protocolos de avaliação neurocognitiva deverão alargar-se a várias outras dimensões. Por outro lado, o impacto das variáveis clínicas nas funções avaliadas foi apenas parcialmente considerado, tendo em conta que a metodologia deste estudo apenas analisou o impacto da idade de início da epilepsia e a evolução das crises.

Os estudos posteriores (*Capítulos II, III, IV, V e VI*) seguiram um plano de investigação mais sistemático que comparou o funcionamento neurocognitivo de três tipos de epilepsia distintos, bem definidos, e que não diferem entre si no que diz respeito à idade de início, duração activa da epilepsia, frequência das crises e medicação anti-epiléptica. Esta comparação constitui uma das grandes potencialidades do conjunto das investigações apresentadas. Simultaneamente, as nossas investigações integraram um grupo de controlo saudável, emparelhado quanto às variáveis idade, género e escolaridade dos pais, facto que traduz uma mais valia metodológica no estudo das comorbilidades neurocognitivas das crianças e adolescentes com epilepsia. Contrariamente ao nosso estudo, a maioria das investigações comparam apenas um grupo de crianças com epilepsia com um grupo de controlo (Cerminara et al., 2013; D'Agati et al., 2012; Killory et al., 2011; Luton et al., 2010; Vega et al., 2010), ou comparam somente os desempenhos entre vários tipos de epilepsia (Auclair et al., 2005; Culhane-Shelburne et al., 2002; Hernandez et al., 2002, 2003), e não ambos os casos em simultâneo (isto é, comparação entre vários grupos clínicos, por um lado, e com um grupo de controlo, por outro) como nos nossos estudos. Realçamos, ainda, o esforço realizado para integrar um número de sujeitos significativo nas diferentes subamostras, de forma a permitir a sustentabilidade das conclusões alcançadas, cumprindo de forma rigorosa os critérios de inclusão, e procurando potenciar a capacidade de previsão dos resultados obtidos para o contexto clínico. Adicionalmente, na revisão da literatura realizada podemos constatar que importantes e numerosos estudos foram realizados com amostras iguais, ou inferiores às nossas (Auclair et al., 2005; Conant et al., 2010; Culhane-Shelburne et al., 2002; D'Agati et

al., 2012; Deltour et al., 2007; Ebus et al., 2011; Gottlieb et al., 2012; Henkin et al., 2005; Hernandez et al., 2002, 2003; Hommet et al., 2001; Kernan et al., 2012; Luton et al., 2010; Neri et al., 2012; Nolan et al., 2004; Piccinelli et al., 2008; Pinton et al., 2006; Prévost et al., 2006; Riva et al., 2005; Vanasse et al., 2005). Além disso, as crianças dos nossos estudos foram comparativamente avaliadas num grande número de aptidões cognitivas (funcionamento intelectual, memória, atenção, funções executivas, linguagem), incluindo o protocolo de avaliação várias provas em cada um dos diferentes domínios considerados. Do ponto de vista científico, os estudos realizados constituem uma evidência adicional da validade e utilidade dos resultados na Bateria de Avaliação Neuropsicológica de Coimbra (BANC) no contexto específico da epilepsia (Epilepsia do Lobo Temporal, Epilepsia do Lobo Frontal, Epilepsia de Ausências da Criança e Epilepsia Benigna com Pontas Centro-Temporais). Do ponto de vista clínico, demonstram a importância de melhorar a compreensão e caracterização das crianças e adolescentes com estes diagnósticos. Finalmente, parece-nos fundamental sublinhar o facto dos participantes das amostras clínicas neste estudo serem seguidos em dois centros de desenvolvimento de excelência nacionais (Centro de Desenvolvimento da Criança Torrado da Silva do Hospital Garcia de Orta e Centro de Desenvolvimento da Criança Luís Borges do Hospital Pediátrico de Coimbra), facto que assegura uma elevada acuidade dos diagnósticos das crianças incluídas.

Contudo, estes estudos apresentam limitações que importa sublinhar. Em primeiro lugar, não foi possível estudar o efeito dos fármacos anti-epilépticos nas dimensões neurocognitivas em estudo, tendo em consideração que a maioria dos sujeitos estava medicada com apenas um fármaco (76%), apenas 9% medicados com dois fármacos e 15% sem medicação. Por este motivo, os efeitos negativos da medicação nas funções neurocognitivas não poderão ser excluídos. Só uma metodologia longitudinal, em que o funcionamento neurocognitivo destas crianças seja avaliado antes do início da medicação anti-epiléptica, durante a medicação e após a retirada da mesma poderá contribuir para esclarecer

o impacto real do tratamento farmacológico nos diferentes domínios neurocognitivos. Em segundo lugar, embora o protocolo de avaliação das nossas investigações seja extenso, pensamos que a inclusão de outros testes de avaliação, nomeadamente no domínio da memória e da atenção, poderia completar de forma significativa as conclusões alcançadas. Assim, no domínio da memória verbal, apenas foi incluída uma prova, a Lista de Palavras, que é muito susceptível à atenção e funcionamento executivo. Por outro lado, os testes de memória tradicionais poderão não conseguir captar todo o impacto das dificuldades mnésicas no dia-a-dia das crianças. Deste modo, estudos futuros deverão integrar medidas de funcionamento mnésico com maior validade ecológica (Kadis et al., 2004; Smith & Vriezen, 1997), bem como incluir outras medidas de avaliação da memória verbal (por ex., memória de histórias, pares de palavras, frases memorizadas). Na área da atenção e das funções executivas, e tendo em conta que se tratam de domínios cognitivos multidimensionais (Alberto, 2003), a inclusão de medidas de avaliação adicionais (por ex., testes de realização contínua, manutenção da atenção auditiva, questionários de comportamento) poderia permitir uma avaliação mais compreensiva destas funções específicas. Por último, a avaliação do funcionamento escolar das crianças e adolescentes com epilepsia foi realizada apenas com base nas classificações realizadas pelos seus professores, tendo estes conhecimento do diagnóstico de epilepsia dos seus alunos. Na medida em que investigações anteriores demonstraram que o conhecimento acerca do diagnóstico de epilepsia, pode baixar as expectativas dos professores, no tocante ao desempenho dos seus alunos (Katzenstein et al., 2007; Williams, 2003), será fundamental que estudos futuros integrem também medidas estandardizadas de desempenho académico.

Estudos Futuros

Como referimos na *Introdução* deste trabalho, *Epilepsy is still a puzzle*, e como tal, não poderíamos deixar de delinear, de forma breve e

esquemática, a realização de novos estudos que poderão ajudar a articular melhor algumas peças deste puzzle…

i. A realização de um estudo de metodologia longitudinal, com o objectivo de monitorizar o curso das dificuldades apresentadas pelo grupo de crianças e adolescentes com epilepsia estudado neste trabalho, analisando simultaneamente a relação das diferentes variáveis clínicas relativas à epilepsia (etiologia, tipo de epilepsia, idade de início da epilepsia, duração activa da epilepsia, frequência das crises, medicação anti-epiléptica), com eventuais alterações no funcionamento neurocognitivo. A realização de estudos longitudinais poderá auxiliar o prognóstico para cada tipo específico de epilepsia. Finalmente, estudos longitudinais poderão ajudar a responder à questão que permanece em aberto, que diz respeito à melhoria nas funções neurocognitivas (Deonna et al., 2000; Northcott et al., 2006), ou, pelo contrário, a presença de consequências a longo-prazo (Ay et al., 2009; Monjauze et al., 2005; Papavasiliou et al., 2005). O estudo longitudinal do impacto das variáveis clínicas relativas à epilepsia, nas mudanças no funcionamento neurocognitivo ao longo do desenvolvimento, poderá identificar as crianças e adolescentes com epilepsia em risco.

ii. Tendo em conta os limites já reconhecidos relativamente à caracterização do desempenho escolar destas crianças, que inclui apenas a avaliação por parte dos seus professores, consideramos fundamental a adaptação e estandardização para a população portuguesa de medidas de desempenho escolar – cf. a título exemplificativo: *Wechsler Individual Achievement Test* – Third Edition (WIAT-III; Wechsler, 2009), *Wide Range Achievement Test* – Fourth Edition (WRAT-4; Wilkinson & Robertson, 2006). A inclusão deste tipo de instrumentos de avaliação do desempenho académico, no protocolo de avaliação neuropsicológica das crianças e adolescentes com epilepsia, conjugados com a avaliação do funcionamento neurocognitivo irá permitir um diagnóstico completo, rigoroso e útil das áreas fortes e de vulnerabilidade destas crianças, o

que poderá auxiliar no delineamento de planos de intervenção escolar eficazes.

iii. O estudo realizado no domínio da linguagem revelou dificuldades no processamento fonológico nos três tipos de epilepsia. Tendo em conta que as dificuldades no processamento fonológico são comuns nos sujeitos com dislexia (Albuquerque, 2003), será importante que estudos futuros se foquem na incidência desta dificuldade específica da leitura e da escrita, nas crianças e adolescentes com epilepsia. Os estudos disponíveis são escassos, abrangem amostras pouco representativas (Canavese et al., 2007; Papavasiliou et al., 2005) e protocolos de avaliação pouco compreensivos.

iv. Considerar as variáveis contextuais para além das variáveis estritamente médicas. Importa reconhecer que factores não relacionados com a epilepsia, que incluem as atitudes parentais (Austin et al., 2004; Fastenau et al., 2004; Rodenburg et al., 2005), o estigma (Reno et al., 2007; Gzirishvili et al., 2013), o nível sócio-económico (Mitchell et al., 1991; Piccinelli et al., 2010), a baixa auto-estima (Austin et al., 2010), a ansiedade e depressão (Caplan et al., 2005; Dunn & Austin, 2004; Stevanovic et al., 2011; Williams et al., 2003), também parecem contribuir para as comorbilidades neurocomportamentais que se observam nas crianças e adolescentes com epilepsia.

v. As dificuldades no relacionamento interpessoal e a tendência para o isolamento social foram frequentemente relatadas pelos pais das crianças e adolescentes que integraram a amostra clínica deste trabalho, como aliás é demonstrado por estudos que sinalizam dificuldades ao nível das competências sociais neste grupo de crianças (Davies et al., 2003; Jakovljevic & Martinovic, 2006; Tse et al., 2003). Por outro lado, estudos recentes documentaram dificuldades no reconhecimento e compreensão de estados mentais, em adultos com epilepsias do lobo frontal e do lobo temporal recorrendo a tarefas de avaliação da Teoria da Mente (Giovagnoli et al., 2011, 2013). Propomos a utilização futura de uma metodologia semelhante, com o objectivo de confirmar se

estas dificuldades estão presentes na idade pediátrica, possibilitando assim uma melhor compreensão das dificuldades sócio-emocionais das crianças e adolescentes com epilepsia, por forma a sustentar o planeamento de intervenções psicológicas eficazes.

vi. Finalmente, e atendendo a que o impacto da epilepsia se pode prolongar pela vida adulta (Sillanpää et al., 2004, Wakamoto et al., 2000), a avaliação neuropsicológica não deve ser artificialmente desligada das preocupações relativas à reabilitação, psicoterapia ou aconselhamento. Neste sentido, estudos futuros que se possam constituir como uma medida da eficácia de intervenções (reabilitação cognitiva, grupos de auto-ajuda, acções de formação para professores e pessoal auxiliar, psicoterapia individual ou em grupo) com estes grupos de crianças são imprescindíveis (Djordjevic & Jones-Gotman, 2011; Elafros et al., 2013; Shore et al., 2008). Um protocolo de avaliação constituído por testes da BANC utilizados nas nossas investigações será neste contexto de particular utilidade.

Conclusões Finais

As comorbilidades neurocognitivas são frequentes nas crianças e adolescentes com epilepsia, mesmo na ausência de um comprometimento do funcionamento intelectual global. Os estudos empíricos apresentados justificam a necessidade de crianças e adolescentes com epilepsia serem avaliadas precocemente, através de protocolos de avaliação neuropsicológica compreensivos, com o objectivo de estabelecer planos educativos adequados e de prevenir o efeito cumulativo dos défices neurocognitivos nos resultados escolares. Os estudos realizados, têm um impacto directo na prática clínica dos diferentes profissionais que lidam com as famílias e crianças com epilepsia, nos pontos que passamos a resumir:

- As crianças com *Epilepsia do Lobo Temporal* apresentaram dificuldades na área da atenção e funções executivas (únicos domínios avaliados

neste grupo), que parecem relacionar-se sobretudo com as dificuldades apresentadas na velocidade de processamento.

- As crianças e adolescentes com *Epilepsia do Lobo Frontal* apresentaram um perfil de problemas neurocognitivos generalizados, apresentando dificuldades no funcionamento intelectual, velocidade de processamento, memória verbal, memória de trabalho, manutenção da atenção, atenção dividida, capacidade de planeamento, resolução de problemas, fluência verbal, compreensão verbal, nomeação rápida e consciência fonémica. Apresentaram também resultados escolares inferiores na disciplina de Português.
- O grupo com *Epilepsia de Ausências na Criança* apresentou dificuldades específicas circunscritas às áreas da atenção e funções executivas e na linguagem, mais concretamente na atenção dividida, planeamento, fluência verbal, nomeação rápida e consciência fonémica.
- Os sujeitos com *Epilepsia Benigna da Infância com Pontas Centro-Temporais* evidenciaram um perfil de dificuldades neurocognitivas circunscrito à área da linguagem, tendo manifestado evidência de problemas na compreensão, nomeação rápida e consciência fonémica.
- A *Idade de Início da Epilepsia* precoce relacionou-se com dificuldades na atenção e funções executivas.
- As crianças que apresentaram uma *Duração Activa da Epilepsia* mais prolongada mostraram problemas no funcionamento intelectual (sobretudo na área verbal), na memória verbal e na compreensão. Estas crianças apresentaram igualmente resultados inferiores na disciplina de Português.
- A *Frequência das Crises* e a *Medicação Anti-Epiléptica* não tiveram efeito nos diferentes domínios neurocognitivos avaliados.

A avaliação neurocognitiva é de particular utilidade para os cuidadores das crianças com epilepsia, na medida em que o conhecimento do estilo de aprendizagem destas crianças, bem como do seu perfil de áreas fortes e de vulnerabilidade neurocognitiva poderá tornar pais e professores

mais empáticos e capazes de dar resposta às necessidades destas crianças e adolescentes.

Por último, esperamos que este trabalhado, centrado no funcionamento neurocognitivo de crianças e adolescentes com epilepsia, constitua um contributo importante para que no nosso país, os neuropsicólogos sejam integrados nas equipas que cuidam das crianças e adolescentes com epilepsia. Se considerarmos, que as consequências da epilepsia são muitas vezes mais sérias, do que a própria doença em si, apenas com o recurso a uma abordagem multidisciplinar, que integre neuropediatras, neuropsicólogos, enfermeiros, terapeutas, professores e assistentes sociais, será possível minimizar o impacto negativo da epilepsia na vida académica e sócio-emocional destas crianças e adolescentes.

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