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SHORT COMMUNICATION

Memory in paediatric temporal lobe epilepsy: Effects of lesion type and side

Francesca Cormack[a,*], **Faraneh Vargha-Khadem**[a], **Stephen J. Wood**[b,c], **J. Helen Cross**[d], **Torsten Baldeweg**[a]

[a] *Developmental Cognitive Neuroscience Unit, UCL Institute of Child Health, Guilford Street, London, UK*
[b] *School of Psychology, University of Birmingham, UK*
[c] *Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Australia*
[d] *Neurosciences Unit, UCL Institute of Child Health & Great Ormond Street Hospital for Children NHS Trust, Great Ormond Street, London, UK*

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Summary This study investigated the role of underlying pathology on memory function of children with temporal lobe epilepsy (TLE). Memory was assessed in 44 children with TLE resulting from hippocampal sclerosis (HS) or dysembryoplastic neuroepithelial tumours (DNT), and 22 control children. Delayed story and paired associate recall performance was significantly more impaired in children with HS compared to those with DNT, irrespective of the affected side. Semantic memory was impaired in both HS groups, and also in the left DNT group. These results suggest a role for type, and to a lesser extent, side of pathology in the memory profile of children with TLE.

Introduction

In adults, left temporal lobe epilepsy (TLE) is associated with deficits in remembering verbal material (Helmstaedter and Elger, 1998; Helmstaedter et al., 1997). There is some evidence of a similar, though less severe and consistent, deficit in children (Nolan et al., 2003; Jambaqué et al., 2007; Helmstaedter and Elger, 1998; Lee et al., 2002). However, comparisons between adult and child data are limited by differences between these populations in terms of the underlying pathology.

Although the most common epileptogenic lesion in adults with refractory TLE is hippocampal sclerosis (HS), tumours, particularly dysembryoplastic neuroepithelial tumours (DNT), are a more frequent cause of paediatric TLE (Harvey et al., 2008). There is some evidence that HS and lesional pathology have different effects on declarative memory in adults (Helmstaedter and Elger, 1998; Helmstaedter et al., 1997). However, such differential effects have not been consistently replicated in children (Gonzalez et al., 2007; Nolan et al., 2003), due perhaps to

* Corresponding author at: MRC Cognition and Brain Sciences Unit, Chaucer Road, Cambridge CB2 7EF, UK. Tel.: +44 01223 273604; fax: +44 01223 359062.
E-mail address: francesca.cormack@mrc-cbu.cam.ac.uk (F. Cormack).

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the presence of extra-temporal pathology (Gonzalez et al., 2007) or the mix of pre- and post-operative cases (Nolan et al., 2003) in these samples.

Here, we examine the effect of side of seizure onset on preoperative memory performance in a relatively homogenous cohort of children with either HS or DNT as their sole pathology. We predicted that verbal declarative memory function, i.e. episodic and semantic memory, would be affected differently by pathology type (Jambaqué et al., 2007; Helmstaedter and Elger, 1998).

Methods

Participants

Participants were 44 children with drug resistant TLE, who were assessed at Great Ormond Street Children's Hospital NHS Trust. All children subsequently underwent temporal lobe resection following a full presurgical evaluation. Children had radiological evidence of either unilateral HS, or temporal lobe DNT as their sole pathology with no extra-temporal abnormality seen on MRI. The spatial distribution of DNT lesions is shown in Fig. 1. Four groups were defined according to pathology and laterality (Left HS — LHS; Right HS — RHS; Left DNT — LDNT; Right DNT — RDNT). Clinical and demographic characteristics of the study groups are shown in Table 1. Performance scores from a group of healthy, age-matched control children ($n = 22$) were used to calculate *Z*-scores for each neuropsychological measure. Ethical permission was granted by the Great Ormond Street Hospital for Children Research and Ethics Committee.

Neuropsychology

Intelligence

The age appropriate Wechsler Intelligence Scale was used (6—16 years 11 months WISC-III ($n = 58$); ≥17 years WAIS-R ($n = 8$)). The mean of performance on the Information, Vocabulary and Comprehension subscales was calculated as an index of semantic memory as used in patients with developmental amnesia (Mishkin et al., 1998; Vargha-Khadem et al., 2001). Digit Span was used to assess verbal working memory.

Memory and learning

Three subtests from the Wechsler Memory Scale (WMS) (Wechsler and Stone, 1945; Gadian et al., 2000) are reported:

(1) *Story recall*: two stories recalled immediately after presentation (story recall immediate) and after a 90-min filled interval (story recall delayed). The child version of the stories was used for participants below the age of 12 ($n = 21$). There was no difference in mean performance of participants who completed the child or adult version.
(2) *Design recall*: geometric designs reproduced both immediately (design recall immediate) and after a 40-min delay (design recall delayed).
(3) *Verbal paired associate learning (VPA)*: 10 word pairs (six related and four unrelated) presented over three trials (VPA immediate), and after a 90-min filled delay (VPA delayed recall). Related and unrelated pairs were combined to overcome the restricted number of items.

Delayed recall in all subtests is expressed as a percentage of the immediate recall score. Mean scores were analysed using a two-way ANOVA with factors of pathology type (HS vs. DNT) and side (left vs. right). Relationships between continuous variables were analysed with Pearson's correlation coefficient.

Results and discussion

Demographic, clinical and intellectual characteristics

There were no significant group differences in age at testing, gender, or full scale IQ (Table 1). Age at onset of epilepsy was younger in HS compared to DNT ($F(1,39) = 8.0$, $p = 0.032$). There was no main effect of side or type of pathology on performance IQ (PIQ) or verbal IQ (VIQ). When patients were compared to controls, the LDNT and LHS groups had lower VIQ ($F(3,40) = 4.7$, $p = 0.002$; Post hoc tests: LDNT $p = 0.042$, LHS $p = 0.047$). The RHS group showed a similar reduction in VIQ (effect sizes: LHS $d = -1.0$; for LDNT $d = -1.2$; for RHS $d = -1.6$), although this did not reach statistical significance.

Memory

There was no significant difference between the groups on digit span, indicating that this aspect of verbal working memory was equally preserved in the four groups.

Children with HS performed worse on delayed story recall than those with DNT pathology ($F(1,39) = 4.8$, $p = 0.034$) regardless of side of pathology. Similarly, VPA delayed recall was more impaired in the HS cases than in those with DNT pathology ($F(1,39) = 7.7$, $p = 0.009$) irrespective of side of pathology.

The results for verbal story recall and VPA are consistent with previous studies in adults (Helmstaedter et al., 1997, 1998), which have shown that hippocampal pathology is associated with greater impairment in delayed recall. In contrast, studies of memory impairment in children have been mixed, with several studies reporting no impairment (Helmstaedter and Elger, 1998; Lee et al., 2002). However, the underlying pathology has frequently not been taken into account, potentially obscuring the impact of hippocampal damage. Furthermore, both VPA and word list learning tasks (Helmstaedter and Elger, 1998; Helmstaedter et al., 1997; Gonzalez et al., 2007) are assessed after repeated presentations of the test material. In contrast, stories are presented only once, potentially yielding a more direct measure of hippocampus-dependent episodic memory (Jambaqué et al., 2007; but see Saling, 2009 for an alternative view). This is consistent with the relatively modest impairment in VPA (within one SD of the control group mean) in contrast to the impairment in story recall which was of 2—3 SD. It is possible in principle that differences in VIQ or earlier age at onset of epilepsy may explain the poorer recall performance of the HS group reported here. However, including these covariates did not alter the results.

Table 1 Demographic characteristics of the patient groups and control participants. Results show means unless indicated. Numbers in brackets denote standard deviations.

	LDNT	LHS	RDNT	RHS	Control
N	11	17	9	7	22
Gender (f:m)	7:4	12:5	2:7	4:3	9:13
Age (years)	11.2 (2.8)	11.7 (3.2)	12.8 (3.2)	12.5 (2.7)	13.5 (3.3)
Epilepsy onset (years)	5.3 (3.5)	4.2 (2.9)*	5.6 (2.9)	3.3 (1.6)*	–
Age at surgery (years)	12.8 (3.7)	14.2 (4.5)	13.9 (2.9)	12.7 (3.4)	–
Full-scale IQ	81.2 (11.7)	87.8 (19.5)	91.6 (22.1)	79.4 (14.9)	96.3 (9.5)
Verbal IQ	80.6 (16.3)**	81.8 (17.6)**	98.0 (22.7)	79.6 (10.6)	95.4 (9.4)
Performance IQ	89.1 (15.2)	93.0 (24.8)	90.5 (17.7)	81.8 (16.8)	98.7 (15.9)

LDNT, left-sided DNT lesions; RDNT, right-sided DNT lesions; LHS, left-sided hippocampal sclerosis; RHS, right-sided hippocampal sclerosis.
* Significantly younger age at onset than DNT participants ($p < 0.05$).
** Significantly lower VIQ than controls ($p < 0.05$).

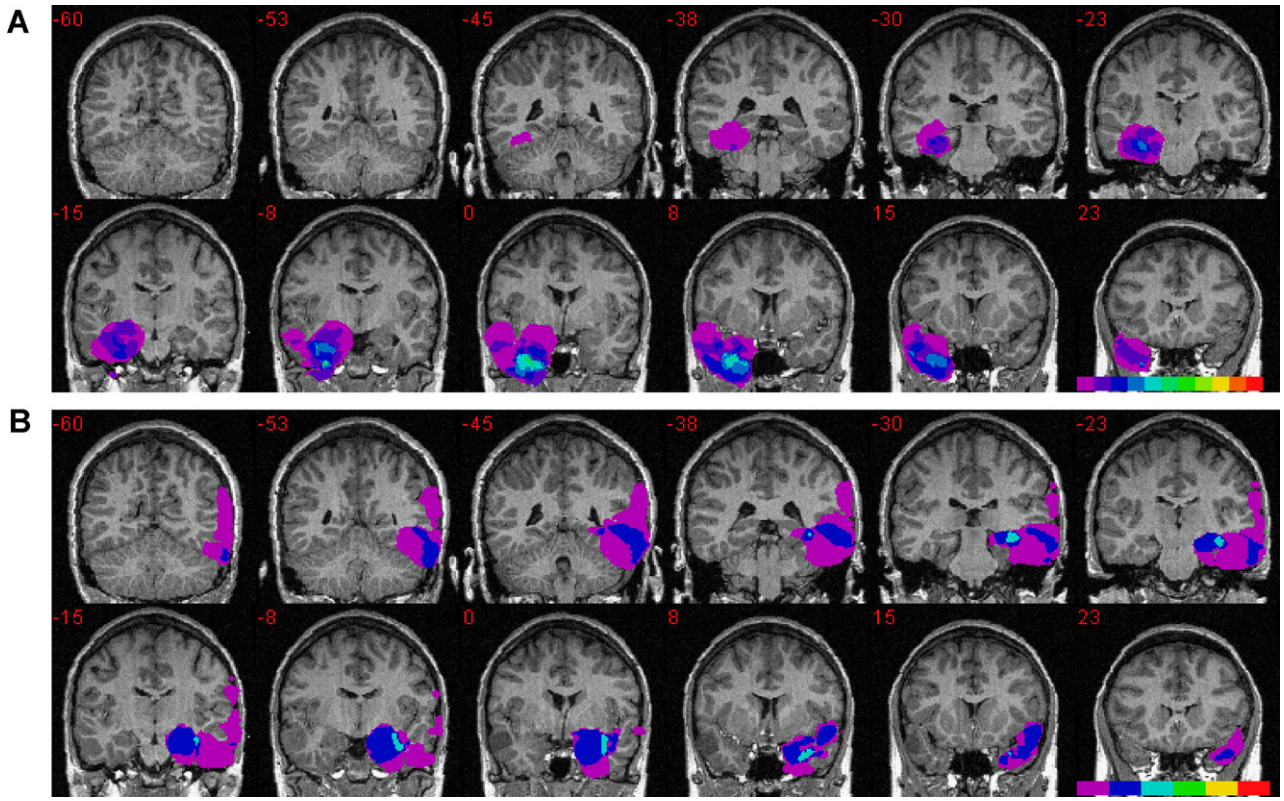

Figure 1 Lesion overlap maps for the left (A) and right (B) DNT groups. For each participant a T1-weighted 3D dataset was acquired using an MPRAGE sequence on a 1.5 T Siemens Vision system. Lesions were traced using MRIcro (http://www.cabiatl.com/mricro/mricro/index.html) and were then smoothed and normalised to the MNI template using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). Colour bars indicate the number of patients with lesions affecting a particular area. Lesion location is anterior temporal in the majority of cases, extending to the medial temporal lobe in 5 LDNT cases and 4 RDNT cases.

In the present study we observed that verbal semantic memory was impaired in children with HS and those with left sided DNT. Semantic memory was more impaired in those with left sided pathology ($F(1,39) = 6.0$, $p = 0.019$), and there was a significant interaction between type and side of pathology ($F(1,39) = 4.1$, $p = 0.05$), indicating that RDNT cases were the only group not to show a deficit (Fig. 2).The semantic memory deficit is consistent with previous data from adults (Giovagnoli et al., 2005) and children (Jambaqué et al., 2007; Rzezak et al., 2011), and the role of the anterior temporal lobe in semantic memory (Giovagnoli et al., 2005).

It is important to stress that the effect of pathology is most likely driven by lesion location, as DNT tumours were predominantly located in lateral and anterior temporal regions, especially on the left side. However, when

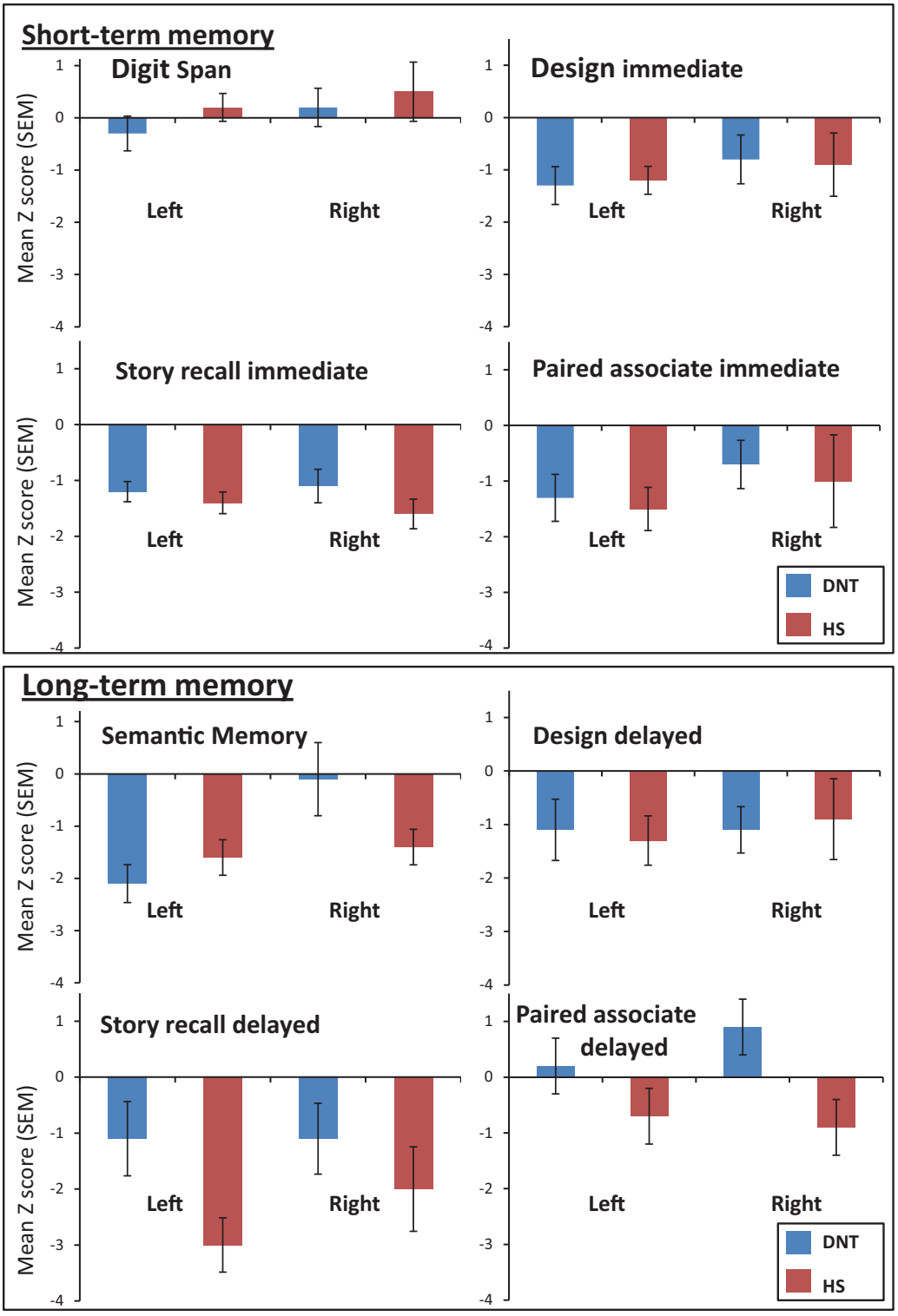

Figure 2 Mean *Z*-scores for the four patient groups on measures of short and long-term memory. LDNT, left-sided DNT lesions; RDNT, right-sided DNT lesions; LHS, left-sided hippocampal sclerosis; RHS, right-sided hippocampal sclerosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

we tested whether the extension of DNT lesions into medial temporal structures (Fig. 1) influenced semantic and episodic memory scores, we found no differences between those with and without medial temporal involvement (LDNT: $n = 5$, RDNT: $n = 4$), and no interaction with side of pathology. It is possible that this negative result is attributable to a lack of statistical power for this comparison.

The present study adds significantly to the data in children as it focuses only on preoperative cases with single pathology, and examined explicitly the interaction between

laterality and pathology type. Furthermore, the use of *Z*-scores allowed us to compare the severity of impairment across domains. Interpretation would, however, be strengthened by the development of clinical tests for the direct comparison of episodic and semantic memory, in analogy to the standardisation of recall and recognition memory performance (Baddeley et al., 1994). Furthermore, recruitment of a more extensive sample of children with temporal lobe epilepsy would allow for the creation of equal sized groups better matched for overall intellectual function. This would clarify the interpretation of differences in memory function and allow the exploration of the effect of anterior temporal lobe pathology on semantic memory in particular, as well as permitting the exploration of issues such as gender (Smith et al., 2009) and attention (Engle and Smith, 2010) in explaining the declarative memory performance of these children.

In conclusion, we have found that children with TLE show a distinct profile of memory impairment, dependent primarily on the type of underlying pathology but also to some degree on the laterality of seizure onset. The loss of semantic memory considerably constrains verbal intellectual abilities, and, given the severe impact of early onset TLE on intellectual development (Cormack et al., 2007; Guimarães et al., 2007), calls for early identification and treatment. It is of note that cessation of seizures after left anterior temporal lobe surgery in childhood is associated with improved VIQ scores at long-term follow-up (Skirrow et al., 2011). However, it remains to be determined if the extent of anterior temporal resection influences postoperative semantic memory development, given the present evidence for left DNT lesions impacting on this important declarative memory domain.

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