The effects of mesial temporal and cerebellar hypometabolism on learning and memory

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Abstract

The effects of mesial temporal (MT) and cerebellar hypometabolism were studied using measures of verbal, visual and motor skill learning. Twelve patients with refractory temporal lobe epilepsy who showed asymmetrical mesial temporal lobe hypometabolism on [^{18}F] fluoro-2-deoxy-glucose positron emission tomography (FDG-PET) were given tests involving 4 consecutive learning trials and a 30-min delayed recall trial. Delayed recognition was also assessed for the words and designs, and skill transfer was evaluated for mirror drawing. Compared to 9 normal control participants, patients with more marked MT hypometabolism on the left had impaired delayed recall of words and patients with more marked MT hypometabolism on the right showed impaired learning of novel designs, but normal retention over delay. Patients were not impaired in their mirror-drawing performance. The findings for MT hypometabolism correspond well to those obtained in other studies where patients have been classified on the basis of side of hippocampal atrophy or temporal lobe excision. (*JINS*, 2001, *7*, 353–362.)

Keywords: Temporal lobe, Memory, PET, Epilepsy, Cerebellum

INTRODUCTION

The ability to recall recently presented material is impaired in patients with structural lesions of the temporal lobe (e.g., Baxendale et al., 1998b; Helmstaedter et al., 1991; Meyer & Yates, 1955; Milner, 1968; Milner et al., 1968; Saykin et al., 1989). Depending on the type of stimuli, the nature and extent of the pathology (e.g., hippocampal sclerosis *vs.* anterior temporal lobectomy) and the side of the lesion, these deficits may manifest as an impaired ability to learn material presented repeatedly over trials (Barr et al., 1990; Gleissner et al., 1998; Hudson et al., 1993; Saling et al., 1993), loss of material over a delay interval (Martin et al., 1991; Sass et al., 1992), or both (Helmstaedter et al., 1993; Miller et al., 1993; Rausch & Babb, 1993). In a study of epileptic patients with marked, unilateral hippocampal atrophy, Jones-Gotman (1996) neatly demonstrated dissociations in side-of-lesion effects on recall using a pair of word and design list-learning tests. Unoperated patients with left hippocampal atrophy showed significantly poorer retention of words

over a 24-hr interval compared to patients with right hippocampal atrophy, but there was no difference in their ability to acquire the words initially over four learning trials. Conversely, patients with right hippocampal atrophy had more difficulty learning the abstract designs than did patients with left hippocampal atrophy, but they were able to retain both types of material over a delay. Other investigators have found similar results using alternative word and design list learning tasks in patients with unilateral temporal lobe epilepsy (Helmstaedter et al., 1993) and in patients who have undergone temporal lobectomy (Helmstaedter & Elger, 1996).

When recognition memory has been studied preoperatively in patients with temporal lobe epilepsy, results have been mixed. Some investigators have found recognition memory for words and faces to be intact (Helmstaedter & Elger, 1996; Miller et al., 1993, 1998). Others have noted that patients with left temporal lobe epilepsy made more errors than patients with right temporal lobe epilepsy on word recognition tasks (Bortz et al., 1995; Seidenberg et al., 1993), whereas patients with right temporal lobe epilepsy made more errors than patients with left temporal lobe epilepsy for recognition tasks involving complex scenes (Baxendale et al., 1998a). Importantly, it was noted by Baxendale (1997) that preoperative recognition memory (for words and faces)

was worse in patients with cortical dysgenesis as well as hippocampal sclerosis than in patients with hippocampal sclerosis alone. Because none of these studies included a matched normal control group, the question of whether the number of recognition errors made by patients with temporal lobe epilepsy falls within normal limits remains unanswered.

Hippocampal atrophy has been correlated with glucose hypometabolism on positron emission tomography (PET) studies (Engel et al., 1982; Gaillard et al., 1995; Semah et al., 1995). Therefore, one could expect to see similar patterns of cognitive impairment irrespective of whether patients show hypometabolism on functional imaging or atrophy on structural imaging. Consistent with lateralization results from lesion studies, two investigations of patients with temporal lobe epilepsy have revealed that reduced glucose metabolism in the left temporal lobe is associated with poor verbal memory (Rausch et al., 1994; Woodard et al., 1997). Further study in this area would provide a better understanding of the relationship between neuropsychological test performance and brain metabolism and, in turn, would facilitate decision making when patients with focal seizures are considered for surgery.

Given the extensive literature on other types of memory, it is somewhat surprising that there is a paucity of data regarding procedural or skill learning in patients with temporal lobe epilepsy. Because amnesic patients (many of whom have temporal lobe pathology) improve on procedural learning tasks over trials and can retain newly learned skills over a delay interval (Cohen & Squire, 1980; Gabrieli et al., 1993; Milner, 1962; Nichelli et al., 1988; Nissen et al., 1989), it has been assumed that patients with temporal lobe epilepsy have normal skill learning and retention abilities. However, patients with seizures often show cerebellar atrophy (e.g., Haberland, 1962; McLain et al., 1980; Salcman et al., 1978) and/or cerebellar hypometabolism (Seitz et al., 1996) and this structure is thought to play a role in motor skill learning (Gomez-Beldarrain et al., 1997; Inhoff et al., 1989; Jenkins et al., 1994; Jueptner & Weiller, 1998; Pascual-Leone et al., 1993; Sanes et al., 1990; Seitz et al, 1994). Hence, it is possible that some patients with temporal lobe epilepsy, specifically those with cerebellar abnormalities, would have difficulty learning and retaining new motor skills.

In the present study, we used [18F] fluoro-2-deoxyglucose (FDG) PET to investigate (1) the effects of asymmetrical mesial temporal hypometabolism on word and design list learning, delayed recall and delayed recognition; (2) the effects of mesial temporal and/or cerebellar hypometabolism on motor skill learning.

METHODS

Research Participants

The participants were selected from among patients with intractable temporal lobe epilepsy who underwent exten-

sive clinical work-up (including FDG-PET scanning) for possible temporal lobectomy over a 2-year period. Patients were excluded if they had a seizure during scanning, signs of widespread cerebral hypometabolism or evidence of atypical speech representation. In the final sample, there was only one left-handed patient and, in her case, speech was found to be lateralized to the left hemisphere using intracarotid sodium Amytal testing. All other participants were right-handed and presumed to have left-hemisphere speech representation.

Twenty-one patients were originally considered for inclusion. Of these, only 12 patients who showed asymmetric glucose hypometabolism in the mesial temporal region were included in the final sample. In order to establish the amount of normal variability in the asymmetry of this brain region, data from 13 participants with no known neurological history were taken from the FDG-PET database at Royal Prince Alfred Hospital. This normative sample comprised 8 men and 5 women, ranging in age from 23 to 44 years ($M = 30.2$ years). Patients were included in the final sample if their mesial temporal lobe asymmetry scores (see below) fell more than 1 standard deviation away from the mean of the normal control subjects. As can be seen in Table 1, 4 patients had relatively reduced metabolic rates in the left mesial temporal region (LMT group) and 8 patients showed more marked hypometabolism in the right mesial temporal region (RMT group). These 12 patients were also classified on the basis of whether or not cerebellar hypometabolism was evident on their PET scans. Nine participants (3 LMT, 6 RMT) had a mean level of cerebellar metabolism that fell more than 1 standard deviation below the normal mean (see Table 1). Visual inspection gave no indication that those with cerebellar hypometabolism had generally more widespread cerebral hypometabolism than those without cerebellar abnormalities.

The performance of the patient groups was compared to that of a group of 9 nonepileptic, age- and education-matched volunteers (5 M/4 F; M age = 31 years, range = 21–49 years, M education = 13 years, range = 11–15 years). These normal control (NC) participants were given the same neuropsychological tests but did not have PET scans.

None of the participants had a history of head injury, neurological disorders other than epilepsy (for the patient groups) or alcohol abuse, and all patients were receiving anticonvulsant medication at the time of testing. Written informed consent was obtained from all participants prior to testing and the study was approved by the institutional Human Research Ethics Committees.

PET Methodology

All PET scans were done on an ECAT 951R whole body tomograph (Siemens/CTI, Knoxville, TN) with a 60 cm transaxial field-of-view (FOV) and an axial FOV of 10.8 cm. Thirty-one image planes were produced, spaced 3.38 mm apart (16 direct, 15 cross planes). Transaxial spatial resolution was 5.9 mm full width at half-maximum at the center

Table 1. Patient demographics

Patient	MT group	MT asym score[1]	Cb score[2]	Sex	Age (years)	Education (years)	Age of onset (years)	Sz duration (years)
K.R.	LMT	.36	2.7	M	25	17	20	5
M.H.	LMT	.26	2.3	F	45	15	21	20
G.O.	LMT	.25	2.8	F	32	11	27	5
W.O.	LMT	.41	4.0	M	44	13	5	39
P.C.	RMT	−.30	2.6	F	23	11	3	20
Z.K.	RMT	−.75	3.1	M	23	12	12	11
C.L.[3]	RMT	−.42	2.5	M	23	10	21	2
B.G.	RMT	−.38	2.7	F	31	16	19	12
G.M.	RMT	−.61	2.1	M	24	16	15	9
F.T.	RMT	−.52	3.9	F	22	13	1	21
L.T.	RMT	−.58	3.0	F	43	17	28	15
S.P.	RMT	−.42	2.4	M	25	18	7	11

[1]For PET database normal controls, M asymmetry score (LMT-RMT) = 0.0, SD = .25.
[2]For PET database normal controls, M level of cerebellar metabolism = 4.14, SD = 1.07.
[3]Participant did not complete the mirror-drawing task.
Note. MT = mesial temporal; LMT = greater left mesial temporal hypometabolism; RMT = greater right mesial temporal hypometabolism; Cb = Cerebellar metabolism level; Sz = seizure.

of the FOV with a z-axis resolution of 4.6 mm. Participants fasted for at least 6 hr before the study. Cannulas were placed in the back of both hands for injection of isotope and for sampling of arterialized blood (Phelps et al., 1979). The participants' hands were heated prior to and throughout the study in heated water baths. Injected dose of FDG was 5.3 Mbq/Kg. For the patients, video EEG monitoring was carried out using scalp EEG electrodes for 30 min before the injection of isotope and throughout the uptake and scanning period to ensure that the PET scan was not carried out post- or intraictally. At the time of injection, participants' eyes and ears were patched in a quiet, dimly lit room. After injection of isotope, blood was sampled throughout the study at timed intervals to determine the input function for measurement of cerebral glucose metabolism (CMRGlu). The 30-min uptake period was carried out 'off camera.' The participant was then positioned on the scanning bed and the head immobilized by a thermoplastic mask that was molded to the contours of the face. Study duration was typically 70 min and emission data were acquired for the entire brain. Data were reconstructed after correction for scatter and random coincidences. Measured attenuation correction was done with a postinjection method validated at this institution (Hooper et al., 1996). There were 13 normal participants, 8 men and 5 women with an age range of 23 to 44 years and a mean of 30.2 years, who were also scanned to provide normative data.

A neurologist experienced in interpreting PET scans (M.J.F.), who had no knowledge of the neuropsychology results, performed quantitative analysis. Measurement of CMRGlu was done through the placement of multiple circular regions of interest (ROIs) with a 7.2 mm diameter on the PET scans. The PET and MR imaging study of 1 participant who had no detectable structural abnormalities served as a template for placement of the ROIs. The PET data were resliced along the long axis of the temporal lobe to visualize the mesial temporal structures. The MR scan was aligned to the PET data using a registration algorithm (Ardekani et al., 1995) developed and validated at our institution. ROIs were placed on the resliced PET scan slices and the coregistered MR study was used to verify the location of the ROIs. The other PET studies were then realigned to this reference study using another algorithm that was developed for this purpose (Eberl et al., 1996). In each temporal lobe, 21 cortical ROIs were placed to obtain values for CMRGlu in the anteromesial temporal cortex, amygdala, hippocampus, and parahippocampal gyrus. However, this orientation of the PET slices is not suitable for the accurate measurement of cerebellar glucose metabolism because of partial volume errors from the occipital cortex. Thus, before measuring cerebellar glucose metabolism, the reference study was resliced along the canthomeatal line and the other studies were then aligned to it. Metabolism was then assessed in each cerebellar hemisphere at the level of the dentate nuclei. The dentate nuclei are clearly visualized on transaxial PET image planes. Ten ROIs were placed in each cerebellar hemisphere adjacent to, but not overlapping, one another to sample the underlying regional cortex. To account for any systematic errors in the assessment of CMRGlu, the cortical ROIs were then normalized to the average value obtained from six ROIs that were placed in the white matter of the centrum semiovale of each hemisphere (three in each hemisphere). These white matter ROIs were the same dimensions as the cortical ROIs and they were positioned in the anterior, middle and posterior parts of the centrum semiovale approximately 6 mm above the bodies of the caudate nuclei. For the temporal lobes an asymmetry score was generated by subtracting the mean score for the left temporal lobe from the mean score for the right.

Fig. 1. The words (left panels) and designs (right panels) used in the learning and recognition tests. The stimuli were presented individually on cards. Half the participants learned List A and were given List B items as distractors on a subsequent recognition trial, while the reverse was true for the other half of the participants.

Materials

Word and design memory tests

The stimuli for these tests were copies of the ones used in the experiments by Jones-Gotman and colleagues (Jones-Gotman, 1996; Jones-Gotman et al., 1997). They consisted of 26 abstract words with low imageability ratings and 26 abstract designs that were simple enough to be copied rapidly but sufficiently complex to discourage verbal labeling (Figure 1). Each was printed individually on a 10 × 7 cm white card. Two word lists and two design lists (13 items each) were used. Half the participants learned List A and were given List B items as distractors during recognition memory testing and the reverse was true for the other half of the participants.

Mirror-drawing test

The mirror-drawing apparatus was similar to the one used by Milner (1962) to test H.M. It consisted of a horizontal metal shield (28 × 22 cm) mounted approximately 20 cm above the desk, and a vertical mirror (26 × 20 cm) mounted behind the shield. A sheet of paper bearing a figure was placed on the desk under the metal shield. The shield was positioned in such a way that the participants could only see the figure and their hand in the mirror. Two figures were used: a six-point star and a Maltese cross with the same number of sides and angles as the star. Care was taken to make all the sides of the two figures the same length, such that the figures had equal perimeters. The figures had a double outline, separated by 5 mm, and the participants were required to keep their pen between the outlines while tracing around the figure.

Procedure

Word and design memory tests

The word and design memory tests were administered separately, but the procedure for the two tests was identical. Each stimulus was presented for approximately 10 s and participants were asked to copy it on a small piece of paper, after which the paper and stimulus were removed. Following presentation of all 13 words or designs, participants were given a blank sheet of paper and were asked to reproduce as many words (or designs) as possible, in any order. Four such learning trials were administered. A delayed recall trial was carried out without prior warning after 30 min. Immediately after this, a recognition test was administered, in which the participants were shown the original 13 words or designs and 13 distractors in random order and were asked to respond "yes" or "no," depending on whether the stimulus had been in the original learning list or not.

On the learning and delayed recall trials, subjects received 1 point for each correct word and for each design that could be unambiguously recognized by a naive rater. On recognition trials, the number of hits and false positive errors was recorded.

Mirror-drawing test

In the mirror drawing apparatus, participants were required to trace around the figures as quickly as possible in an anticlockwise direction from a set starting point, using their preferred hand. They were first given the Maltese cross figure, followed by four learning trials tracing the star figure. Thirty min after the last learning trial, delay trials were administered in which participants were asked to trace the star and the Maltese cross again. The total time taken to trace

around the figure was recorded on each trial. Each time the pencil tracing went outside the double lines of the figure it was counted as an error. An error score was thus achieved for each trial.

Order of procedures

All but 1 patient were tested within 1 week of their PET imaging studies; the remaining patient was tested 6 months after she had her scan. Each was given the memory tests in a single session lasting approximately 1.5 hr. The tests were administered in the following order: (1) word learning trials; (2) design learning trials; (3) mirror-drawing learning trials; (4) word delayed recall and recognition; (5) design delayed recall and recognition; and (6) mirror-drawing delay trials. Where necessary, the time intervals between Steps 4, 5, and 6 were filled by obtaining demographic information from the participants, to ensure that the learning and delayed trials of each test were separated by 30 min.

Statistical Analyses

For the word and design memory tests, two-way Group (three levels) $\times$ Trial (five levels: four learning trials, one delay trial) ANOVAs with repeated measures on the trial factor were performed. Percent retention was calculated using this formula: ((Trial 4 $-$ Trial 5)/Trial 4) $\times$ 100, and one-way ANOVAs were used to compare the groups for retention of the words and designs. Recognition memory was evaluated by comparing groups on the number of correct hits and the number of false positive responses. Pearson product-moment

correlations between test scores and mesial temporal asymmetry scores were evaluated when the ANOVAs reached significance.

Performance on the mirror drawing test was analyzed using two-way Group $\times$ Trial (seven levels: Maltese Cross, four star learning trials, delayed star trial, repeat Maltese Cross) ANOVAs with repeated measures on trial. These were carried out for both the time and error scores.

Significant interactions were broken down by comparing the three groups on each trial. Scheffé pair-wise *post-hoc* tests were used to compare means when the ANOVA was significant. For mirror-drawing, data for 1 participant (C.L.) are missing because he refused to complete the test.

RESULTS

Demographic Comparisons

Comparing patient groups to the NC group yielded no significant differences in age or educational level. Similarly, no differences were found between the patient groups in age of onset or years of seizure disorder (see Table 1).

Effects of Mesial Temporal Hypometabolism on Memory for Words and Designs

On the word list-learning test, there was an interaction between Group $\times$ Trial [$F(8,72) = 2.11$, $p < .05$] as well as a main effect of trial [$F(4,72) = 36.2$, $p < .001$], but no significant overall group effect [$F(2,18) = 1.51$, $p = .25$]. As can be seen in Figure 2a, participants improved over the
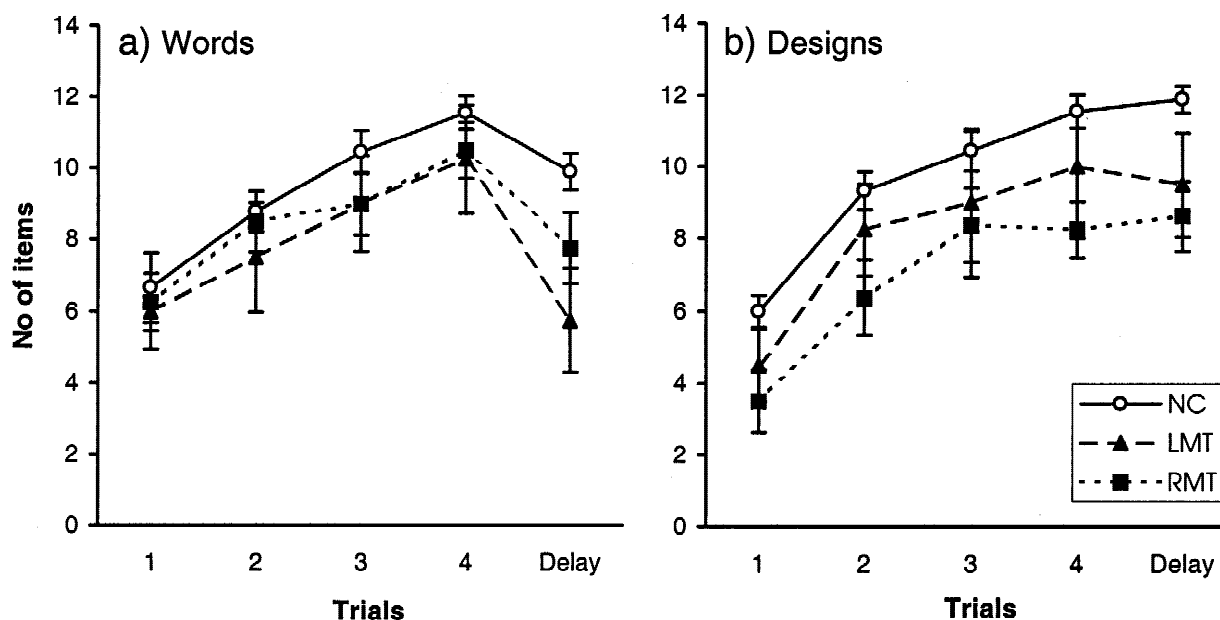
Fig. 2. Mean number of (a) words and (b) designs recalled on each of the four learning trials and after 30-min delay by patients with left mesial temporal (LMT) hypometabolism, patients with right mesial temporal (RMT) hypometabolism, and normal controls (NC). Vertical bars represent standard error of the mean.

four learning trials and then showed a drop between the last learning trial and the delayed recall trial. There were no significant group differences on any of the four learning trials, but there were on the delay trial [$F(2, 18) = 5.5$, $p < .05$] and for percent retention [$F(2, 18) = 7.2$, $p < .01$]. Scheffé *post-hoc* comparisons for the delay trial and percent retention showed that the LMT group was significantly impaired compared to the NC group. Pearson product-moment correlation tests indicated that the relationship between the PET asymmetry score and the word list percent retention score approached significance [$r(11) = -.56$, $p = .058$].

For word recognition, there were no significant between-group differences in the mean number of hits (LMT: 11.5; RMT: 11.6; NC: 12.9) or mean number of false positive responses (LMT: 0.5; RMT: 0.3; NC: 0.1). Recognition memory scores were not correlated with the PET measure of mesial temporal asymmetry [hits: $r(11) = -.03$, $p = .94$; false positives: $r(11) = .09$, $p = .78$]. For design learning, the Group × Trial interaction was not significant [$F(8, 72) = 1.1$, $p = .40$]. There was, however, a main effect of group [$F(2, 18) = 4.4$, $p < .05$]. Scheffé *post-hoc* comparisons indicated that the RMT group differed significantly from the NC group (see Fig. 2b). There was a also main effect of trial [$F(4, 72) = 106.1$, $p < .001$], with all groups showing gradual improvement over the learning trials and good retention after a delay. There were no differences between the NC, RMT, and LMT groups in their percent retention score for designs [$F(2, 18) = .20$, $p = .82$]. The total learning score for designs was not correlated with the mesial temporal lobe asymmetry score obtained from PET [$r(11) = .24$, $p = .46$]. Furthermore, groups did not differ in design recognition memory; only 2 patients (B.P. and P.C.) made a single error each.

Effects of Mesial Temporal and Cerebellar Hypometabolism on Mirror Drawing

For both the time and the error scores, patients were compared to the NC group across the seven mirror drawing trials (Figure 3). For both scores, there was a significant effect of trial [time: $F(6, 102) = 30.1$, $p < .001$; errors: $F(6, 102) = 8.0$, $p < .001$], but no group effects [time: $F(2, 17) = .01$, $p = .98$; errors: $F(2, 17)$, $p = .88$] or interactions [time: $F(12, 102) = .37$, $p = .97$; errors: $F(12, 102) = .37$, $p = .97$]. Figures 3a and 3b show that for all three groups, there was a reduction in tracing time and in error rate across the seven trials, indicating acquisition of the mirror-drawing skills and transfer of these skills to an alternative figure. Mesial temporal asymmetry was not correlated with the difference scores for time [$r(10) = .17$, $p = .62$] or errors [$r(10) = -.01$, $p = .98$] on the two Maltese cross trials (the largest difference observed).

Even when the NC group was compared to the more select group of patients who had significant cerebellar hypometabolism (i.e., a level more than 1 *SD* from the control mean) there was no main effect for group [time: $F(1, 15) =$
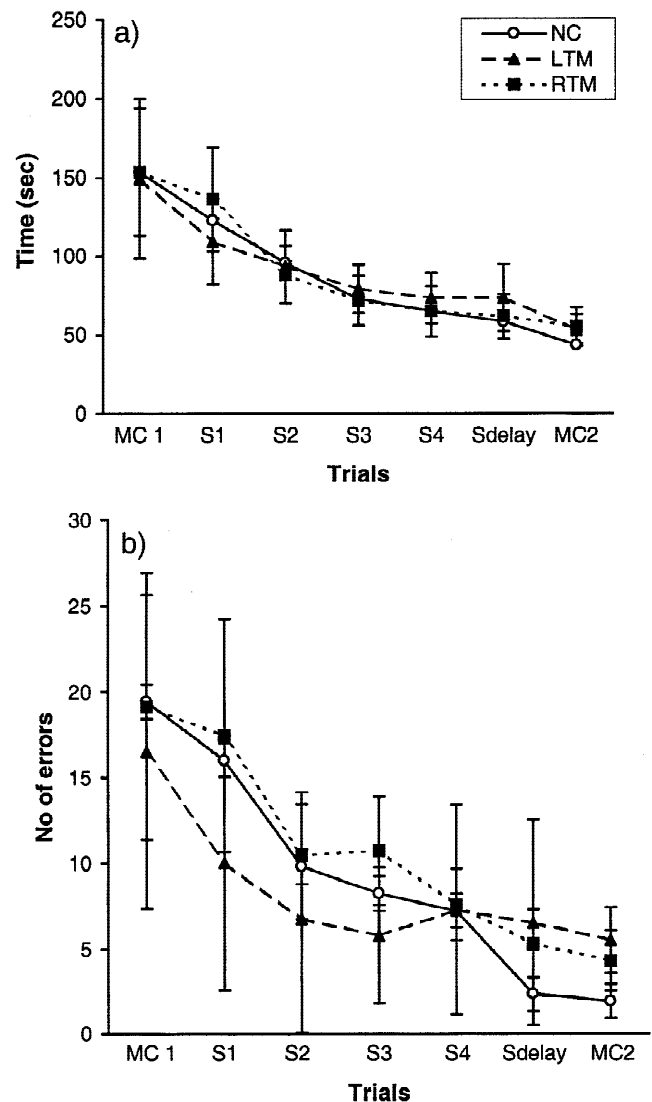
Fig. 3. Comparison of patients with left mesial temporal (LTM) hypometabolism, right mesial temporal (RMT) hypometabolism and normal controls (NC) on the mirror-drawing task. Top panel (a) shows mean time taken to trace the Maltese cross (MC) and star (S) figures on the learning and delayed (Sdelay and MC2) trials. The bottom panel (b) shows the mean number of errors. Vertical bars represent standard error of the mean.

.04, $p = .85$; errors: $F(1, 15) = .02$, $p = .89$] and no interaction [time: $F(6, 90) = .24$, $p = .96$; errors: $F(6, 90) = .26$, $p = .95$]. The main effect of trial again reached significance [time: $F(6, 90) = 31.2$, $p < .001$; errors: $F(6, 90) = 10.2$, $p < .001$]. Because we had hypothesized that cerebellar metabolism might be related to motor learning ability, Pearson product-moment tests were carried out. Cerebellar metabolism did not predict learning ability, in that the mean level of cerebellar metabolism was not correlated with either the change in time taken to trace [$r(10) = .07$, $p = .85$] or the change in the number of errors made [$r(10) = .06$, $p = .87$] across the two trials on the Maltese cross.

DISCUSSION

This study examined the effects of mesial temporal hypometabolism on tests of word-list, design-list and motor-skill learning and retention. Patients with relatively low metabolic rates in the left mesial temporal region had significant difficulty recalling a word list after a 30-min delay interval but demonstrated adequate word-list learning over the four presentation trials. In contrast, across the design list-learning trials, the RMT group showed an impairment compared to normal control participants. Both patient groups showed normal retention of the designs over a delay interval. No impairments in word or design recognition memory or in the ability to learn mirror drawing skills were found when patients with mesial temporal hypometabolism were compared to a normal control group. Moreover, cerebellar hypometabolism was not found to lead to impairments in mirror-drawing skills.

The pattern of impairments on the list-learning tests seen in association with left or right mesial temporal hypometabolism in this study is similar to that found preoperatively when patients with temporal lobe epilepsy are classified on the basis of MR evidence of hippocampal atrophy (Jones-Gotman, 1996). Thus, at least for this brain region, our results support the hypothesis that the patterns of cognitive impairment associated with glucose hypometabolism are consistent with those caused by structural lesions. However, a direct evaluation of this hypothesis by applying both functional and structural imaging along with neuropsychological testing remains to be done. For clinical purposes, it is important to note that, for word retention, we found similar group differences to those reported by Jones-Gotman et al. (1997) in spite of the fact that we shortened the delay interval from 24 hr to 30 min.

In our study, patients with reduced metabolism in the mesial temporal region did not have impaired recognition memory. Unfortunately, the excellent performance of all participants created a ceiling effect for both word and design recognition, and this limits the conclusions that can be drawn. Nevertheless, our findings are consistent with those of other studies. Helmstaedter and Elger (1996) tested a large number of patients with temporal lobe epilepsy on a German version of the Rey Auditory Verbal Learning Test (Helmstaedter & Durwen, 1990) prior to surgery. Many of the patients in their study were found to have hippocampal sclerosis and yet their delayed recognition memory was intact. In contrast, impaired recognition memory for words has been reported after temporal lobectomy (Helmstaedter & Elger, 1996; Majdan et al., 1996) and in patients with cortical dysgenesis in addition to hippocampal sclerosis (Baxendale, 1997). Together, these results indicate that extramesial temporal lobe structures are required for recognition, which offers some support for the hypothesis first put forward by Aggleton and Shaw (1996) and elaborated by Aggleton and Brown (1999) that the hippocampus is not important for certain kinds of recognition memory.

The present study did not find a relationship between mesial temporal hypometabolism or cerebellar hypometabolism and the ability to learn, retain or transfer the motor skills required for mirror drawing. Although mesial temporal hypometabolism was not expected to impair skill learning, the negative findings for the cerebellum may at first seem inconsistent with previous studies that ascribe a role for the cerebellum in motor skill learning. There are, however, a few possible explanations. For example, functional activation studies indicate that the cerebellum contributes to later, but not to very early stages of skill learning (Halsband & Freund, 1993; Shadmehr & Holcomb, 1997). Thus, if our participants had been tested over many more trials, perhaps those with cerebellar hypometabolism would have eventually shown impaired performance compared to those with normal cerebellar function. However, Sanes et al.'s (1990) results would argue against this, because they found that patients with cerebellar atrophy were not impaired over a series of 50 trials of mirror drawing. A more likely explanation is that the importance of the cerebellar component in motor skill learning rests on the nature of the task. Studies to date indicate that the cerebellum has a role in learning a series of finger movements (Doyon et al., 1996; Gomez-Beldarrain et al., 1997; Jenkins et al., 1994; Jueptner et al., 1997; Pascual-Leone et al., 1993) and motor adaptation (Deuschl et al., 1996; Weiner et al., 1983), but not in learning a pursuit motor task (Grafton et al., 1992) or in drawing practiced designs in rotated orientations (Timmann et al., 1996). As stated by Desmond and Fiez (1998), a unified explanation of the role of the cerebellum in motor skill learning has yet to be achieved, some 20 years after Eccles (1978) published his "comprehensive" theory on learning and the cerebellar cortex.

In summary, the present results clearly indicate that a number of factors help to determine whether left or right mesial temporal dysfunction causes a significant impairment on tests of learning and memory. These factors include type of stimulus material (e.g., words *vs.* novel designs), stage of memory processing (acquisition *vs.* retention) and means of assessment (recall *vs.* recognition), as noted, in part, by other researchers (e.g., Dobbins et al., 1998; Jones-Gotman, 1996; Jones-Gotman et al., 1997; Milner, 1958, 1973; Saling et al., 1993). The left mesial temporal region is particularly important when words must be recalled after a delay interval. In contrast, the right mesial temporal region plays a role in encoding novel designs. Neither the left nor the right mesial temporal region is important for the retention of learned designs, at least over a 30 min interval (but see Jones-Gotman, 1986, for evidence that the right hippocampus is important for the retention of designs over a 24-hr period). It is generally argued that left temporal and right temporal lesions have different effects on the mnemonic processing of word lists *versus* design lists, because a word list comprises verbal material and a design list consists of visuospatial material. However, the possibility that novelty of the stimulus is an important factor (designs being novel and words being nonnovel) has also been raised (Majdan et al.,

1996; Owen et al., 1996) and we are currently investigating this issue.

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