SHORT REPORT

Clinical relevance of memory performance during Wada is stimulus type dependent

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Objectives: This study aimed to investigate whether different types of memory stimulus provide different information during the Wada or intracarotid amytal procedure (IAP) in patients with refractory medial temporal lobe epilepsy (MTLE).

Methods: Eighty nine surgical candidates with documented MTLE and selected for left hemispheric language dominance underwent memory assessment with verbal and dually encodable stimuli during a presurgical IAP.

Results: The overall IAP memory performance with the left hemisphere is significantly better than with the right hemisphere regardless of lesion side. This can be explained by the left hemispheric advantage of encoding all stimuli, whereas the right hemisphere has only limited resources to encode verbal stimuli. More importantly, it appeared that dually encodable items remain more readily recognised following injection ipsilateral to the lesion, whereas verbal items are always better recognised following right hemisphere injection regardless of lesion side.

Conclusions: Verbal IAP stimuli show left hemispheric sensitivity in left language dominant MTLE patients. The dually encodable items of the IAP appear lesion sensitive.

Preoperative tests capable of quantitatively predicting memory outcome for individual patients would be an important resource for physicians and surgeons treating patients with refractory medial temporal lobe epilepsy (MTLE). An even more ambitious goal would be to predict material specific memory loss following unilateral temporal lobe resection. Centres treating patients with epilepsy have used a variety of stimuli to determine memory performance during the Wada or intracarotid amytal procedure (IAP) including real objects, line drawings, unfamiliar figures, faces, words, and rhymes.¹ The few studies that have evaluated the issue of stimulus type reported that different types of stimulus contribute differently to the clinical preoperative questions that the IAP memory performance can address.^{2–4} We aim to investigate the effect of using verbal stimuli versus dually encodable line drawings depicting simple objects or scenes on lesion lateralisation and side of injection, and to evaluate whether different types of memory stimulus provide different information during IAP in patients with refractory MTLE.

METHODS

Patients

Following institutional approval and informed consent, 89 patients with refractory medial temporal lobe epilepsy (50 right MTLE; 39 left MTLE) were included in the study. The location of the suspected seizure focus was determined according to the standard presurgical evaluation protocol on

the basis of all available data (including video-EEG, neurological examination, structural MRI, neuropsychological testing, PET, and SPECT) by members of the Reference Center for Refractory Epilepsy at Ghent University Hospital.⁵ MTLE patients were included only if they had undergone bilateral IAP showing left hemispheric language dominance and had a total IQ of 60 or higher. Average age was 31.9 years (standard deviation (SD) 9.9), average duration of formal education was 12.2 years (SD 3.1), WAIS Total IQ averaged 102.5 (SD 19.0), and the group consisted of 46 men and 43 women. The left and right lesion groups showed no significant differences in demographics using independent *t* tests and χ^2 tests where appropriate. Although there appeared to be a trend towards lower IQs in patients with left MTLE lesions, this difference was not statistically significant.

Intracarotid amytal procedure

Prior to each IAP, a carotid angiogram was performed in order to ascertain whether there were any anomalous circulation patterns that may influence distribution of the amobarbital. Sodium amytal (2 mg/kg at 15 mg per cc saline) was manually injected using a 5-F Headhunter catheter (Cook, Bloomington, IN) in the internal carotid artery 1 cm distal to the bifurcation using a transfemoral approach. The side ipsilateral to the side of the suspected seizure focus was injected first. Hemispheric language dominance was then assessed by the presence or absence of paraphasia, speech arrest, naming, and comprehension of simple aural commands. Thereafter, hemispheric memory performance was assessed by presenting the patient with 10 items (three written one syllable words, two line drawings of simple objects, three line drawings of action scenes, and two written two syllable words). Stimuli were presented at an average rate of 5 s per card. Patients were encouraged to name the stimuli. When aphasic, appropriate perception of and focusing on the stimulus was controlled for by gently moving the card in the patient's central visual field and the visual field ipsilateral to injection and observing the corresponding saccadic eye movements. Drug efficacy was determined by contralateral grip strength as determined by a neurologist using the 0–5 scoring system of the Medical Research Council. The patient was given a recognition task 12 min after injection. The previously presented items were shown again each with three distracters. Guessing was not encouraged. A total IAP memory score was calculated (maximum score = 10). In addition, an IAP memory score for verbal items (the one and two syllable words, maximum score = 5) and dually encodable items (the line drawings of objects and scenes, maximum score = 5) was determined. After the recognition test, the catheter was repositioned and the procedure was repeated with an alternative set of similar

Abbreviations: IAP, intracarotid amytal procedure; MTLE, medial temporal lobe epilepsy

Figure 1 Interaction effect between stimulus type, side of injection, and lesion side. Top panel: Verbal items are always better recognised following right hemisphere injection (straight line) than following left hemisphere injection (dotted line) regardless of lesion side. Bottom panel: Dually encodable stimuli remain more readily recognised following injection of the lesioned hemisphere than after injection of the healthy hemisphere.

stimuli following injection of the contralateral internal carotid artery.

RESULTS

If memory items are administered after the drug has washed out of the mesial temporal circulation, the probability that these items are recognised increases, giving rise to an increased recognition probability with increasing serial position. Curve estimation was calculated for the probability curves of the right and left MTLE groups using a linear model. Curve estimation did not reveal a significant trend of increased recognition probability over time.

Material specific IAP memory performance of the right- and left-sided MTLE patients is listed in table 1. A repeated measures multivariate analysis of variance with side of injection and stimulus type (verbal ($n = 5$) v dually encodable ($n = 5$)) as within subjects factor and lesion lateralisation as between subjects factor revealed a significant effect of injection side on IAP memory performance. Memory performance with the right hemisphere (that is, following injection of the left carotid) was significantly worse than with the left hemisphere (that is, following injection of the right carotid) (Hotelling's $T [1,76] = 46.9$, $p < 0.001$). Although lesion lateralisation showed no significant difference as regards overall IAP memory performance, there was a significant side of injection by lesion lateralisation interaction effect (Hotelling's $T [1,76] = 36.4$, $p < 0.001$). As can be seen from table 1, patients with right-sided MTLE show a larger discrepancy between right and left hemispheric IAP memory performance than do patients with left MTLE lesions. A main effect for stimulus type was also found (Hotelling's $T [1,76] = 10.1$, $p = 0.002$). In general, dually encodable items are more frequently recognised than are verbal items. A significant stimulus type by injection side interaction effect (Hotelling's $T [1,76] = 57.3$, $p < 0.001$) revealed that verbal items are more frequently recognised following right hemisphere injection, whereas dually encodable items do not

reveal an effect of injection side. A significant three way interaction effect (injection side by stimulus type by lesion lateralisation) illustrated in fig 1, revealed that dually encodable items remain more readily recognised following ipsilateral injection (that is, following injection of the lesioned hemisphere) than after contralateral injection (that is, following injection of the healthy hemisphere), whereas verbal items were always better recognised following right hemisphere injection regardless of the lesion side (Hotelling's $T [1,76] = 16.7$, $p < 0.001$).

DISCUSSION

The validity of the IAP results depends on adequate drug efficacy throughout the procedure and on the ability of each hemisphere to process the stimuli presented. Since the return of grip strength may be an overestimation of the actual period of drug efficacy,¹ we need to validate the behavioural data of our group. Analysis of the behavioural IAP data demonstrates that drug efficacy throughout the stimulus presentation phase of the amygdala procedure is maintained.

Injection side has a robust effect on general IAP memory performance. Regardless of their lesion side, patients perform better following amygdala injection of the right hemisphere. This may be due to the left hemispheric advantage that most pictorial IAP stimuli are very easy to encode verbally, whereas the right hemisphere has only limited resources to encode the presented verbal material (five written words). A second explanation concerns the effect of aphasia and touches on the more fundamental question of whether a left hemispheric IAP is a fair test to predict the postoperative memory capabilities of the right hemisphere. After all, it can be argued that the left hemispheric IAP does not mimic the outcome following a left temporal resection where language function remains largely preserved. If one eliminates the function necessary to perceive and process the information presented (that is, produce an aphasia that inhibits production and comprehension of verbal and verbalisable stimuli), one should not be surprised that the system is subsequently unable to encode and retain that information. Perhaps IAP induced aphasia, and not material specific memory dysfunction, may prove the more robust determinant of the poorer right hemispheric memory performance, although the lack of specific right hemispheric material may render this hypothesis premature. In a recent study, Lee *et al*⁶ compared the efficacy of two IAP memory methods using dually encodable stimuli to predict seizure onset laterality in children. One method used real objects and required no verbal response, whereas the alternative method used more mixed stimuli and required a verbal response. The method using real objects appeared superior in detecting the side of seizure onset in both left and right epilepsy patients, whereas the mixed

Table 1 Material specific memory performance during IAP

	Memory performance during IAP*			
	With the left hemisphere (right injection)		With the right hemisphere (left injection)	
	Verbal stimuli	Dually encodable stimuli	Verbal stimuli	Dually encodable stimuli
Right MTLE ($n = 50$)	4.23 (1.26)	4.24 (1.30)	1.48 (1.31)	2.19 (1.76)
Left MTLE ($n = 39$)	3.41 (1.50)	2.73 (1.98)	2.14 (1.29)	3.76 (1.34)

*Average performance (mean (SD)) for verbal ($n = 5$) and dually encodable ($n = 5$) stimuli following left or right hemispheric injection in patients with right- and left-sided MTLE. Performance with the lesioned (ipsilateral) hemisphere is given in *italics*.

stimuli method only differentiated in children with right seizure onset. The authors concluded that the use of mixed stimuli is less sensitive to the effects of unilateral seizure onset. As was also pointed out by the authors, both methods not only differed in the kind of stimuli used, but also in the degree of reliance on verbal mediation. We feel that this effect can also be interpreted in terms of aphasia bias. Requiring a verbal response stimulates verbal encoding and implies left hemispheric integrity. In children with left seizure onset, the mixed stimuli/verbal response condition reveals no performance difference following ipsilateral or contralateral injections. This may be due to the fact that during contralateral (right) injection the children have to use their diseased left hemisphere, and during ipsilateral (left) injection they are forced into a verbal strategy that is incapacitated by the induced aphasia. Either way they lose. In the real objects/no response condition, the left seizure onset group is not forced into a verbal encoding mode, and is, in addition to the natural appearance of the stimuli, perhaps inclined to use a more multimodal encoding strategy. This alternative strategy reduces the disturbing effect of the temporary aphasia on encoding during the ipsilateral (left) injection and does not lead to a verbally boosted performance following contralateral (right) injection, thus offering more sensitive detection of the lateralised pathology. Although further research is needed, not forcing the patient into a verbal strategy during IAP testing may be an interesting option that could potentially increase its sensitivity.

In an earlier study, Christianson *et al* evaluated material specific memory performance during IAP in 27 epileptic patients.² Regardless of lesion side, more words were recognised following right hemispheric injection than left hemispheric injection. Other stimuli (pictures of common objects, unfamiliar figures, and faces) did not show a lateralised effect of injection side, although a significant interaction with side of lesion was found. In patients with left MTLE, the left hemisphere showed the traditional advantage for words, whereas the right hemisphere performed better on pictures (common objects, figures, and faces). In a more recent study of 18 epilepsy patients, Kelley *et al* found that unfamiliar faces were remembered better than words following left hemispheric anaesthesia, whereas words were remembered better than faces following right hemispheric IAP.³ Loring *et al* evaluated IAP memory performance by using real objects and line drawings.⁴ They found that objects were superior to line drawings in discriminating between left and right MTLE groups.

Our results regarding differences between verbal and dually encodable stimuli confirm and extend these findings. Verbal stimuli are better recognised with the left hemisphere regardless of whether the patient's lesion is on the left or on the right. The use of verbal stimuli during IAP may validly contribute to the prediction of postoperative verbal memory deficits following resection of the language dominant MTL by assessing the verbal encoding abilities of the contralateral hemisphere and probing the residual verbal memory abilities of the ipsilateral hemisphere.⁷ Although it would be clinically relevant to assess the patient with material sensitive to either hemisphere, it has proven difficult to construct stimuli that are sensitive to the right hemisphere. Whereas the relation between left hemispheric dysfunction and verbal memory deficits is firmly established, most tests of visual memory, even when an effort is made to make the test as

non-verbalisable as possible, fail to discriminate between patients with left or right hemispheric lesions.⁸ Functional imaging reported right lateralised MTL activity with unfamiliar faces or kaleidoscopic pictures, but these were all group studies, and validity at the individual level is uncertain.⁹⁻¹⁰ More research is needed to achieve a valid stimulus set sensitive to right hemispheric integrity. Meanwhile, most epilepsy centres use dually encodable visual stimuli. Our results show that dually encodable stimuli that can be processed by both hemispheres reveal an effect of lesion: the diseased hemisphere always performs worse. Taken together, these results suggest that IAP performance with verbal items shows hemispheric sensitivity, whereas IAP performance with dually encodable items is lesion sensitive.

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