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Spatial memory for asymmetrical dot locations predicts lateralization among patients with presurgical mesial temporal lobe epilepsy

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ABSTRACT

This study examined the ability of an asymmetrical dot location memory test (Brown Location Test, BLT) and two verbal memory tests (Verbal Selective Reminding Test (VSRT) and California Verbal Learning Test, Second Edition (CVLT-II)) to correctly lateralize left (LTLE) or right (RTLE) mesial temporal lobe epilepsy that was confirmed with video-EEG. Subjects consisted of 16 patients with medically refractory RTLE and 13 patients with medically refractory LTLE who were left hemisphere language dominant. Positive predictive values for lateralizing TLE correctly were 87.5% for the BLT, 72.7% for the VSRT, and 80% for the CVLT-II. Binary logistic regression indicated that the BLT alone correctly classified 76.9% of patients with left temporal lobe epilepsy and 87.5% of patients with right temporal lobe epilepsy. Inclusion of the verbal memory tests improved this to 92.3% of patients with left temporal lobe epilepsy and 100% correct classification of patients with right temporal lobe epilepsy. Though of a limited sample size, this study suggests that the BLT alone provides strong laterality information which improves with the addition of verbal memory tests.

1. Introduction

Neuropsychological testing is used to provide information about the areas of brain dysfunction to assist with lateralization and localization of seizure onset, predict postsurgical cognitive performance, and provide information to the patient regarding their areas of difficulties. This is especially helpful for patients with medically refractory mesial temporal lobe epilepsy (TLE) where surgery may be a highly effective treatment but can result in significant memory impairment [1–3].

Verbal list learning test scores have been associated with dominant (usually left) mesial temporal lobe epilepsy (LTLE), although there appear to be differing levels of sensitivity and specificity according to some studies. For example, one study [4] found that the Rey Auditory Verbal Learning Test (RAVLT) [5], which requires learning a list of unrelated words over five learning trials, appeared to be better at lateralizing LTLE than the California Verbal Learning Test (CVLT) [6], which requires learning a list of 16 words from four different categories. It is possible that the differential sensitivity could be related to semantic clustering strategies available for the CVLT but not the RAVLT. Despite this, both tests have been generally helpful at lateralizing LTLE [7,8] and predicting postsurgical memory decline [1,9,10]. The Verbal Selective Reminding Test (Verbal SRT) has also been found to be sensitive to LTLE and related hippocampal cell count [11,12]. However, these findings were not always consistent, perhaps because the VSRT may be affected by executive functioning difficulties [13]. In summary, while verbal memory has generally been diminished in LTLE, it remains unclear which test provides the strongest laterality information.

Dysfunction associated with nondominant (usually right) mesial temporal lobe epilepsy (RTLE) has historically been thought to contribute to difficulties in visual-based memory tasks. This perception appears to be due to some early, relatively small studies that reported lower scores on visual-based memory tests for patients who had had right anterior temporal lobectomies [14–18]. However, the association between RTLE and visual memory performance has often not been replicated in more recent studies that used standardized clinical measures of memory among patients with presurgical or postsurgical temporal lobe epilepsy [19–22]. For instance, several large studies did not find significant associations between RTLE and popular figural memory tests such as the visual reproduction from the various Wechsler Memory Scales [23], Rey Complex Figure Test [24,25], or Brief Visual Memory Test-Revised [19].

There have been several commonly cited reasons for the lack of a consistent association between right mesial temporal lobe dysfunction and visual memory tests. These have included, but were not limited to, their reliance on nonmemory skills such as drawing abilities [26] and verbal encoding of visual stimuli; in addition, "nonverbal" memory tests typically have shared variance with verbal measures [26–28]. Some of the nondrawing based stimuli rely on recognition format which can lead to a restricted range of scores [29], and/or some tests might be too easy (e.g., they have a low ceiling effect) [30].

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Advances in our understanding of visual memory paradigms, however, have suggested some novel approaches to better assessing right mesial temporal lobe dysfunction. Effects on memory of identical stimuli (e.g., dots) at different locations have sometimes been associated with RTLE [31,32], with some meta-analytic support for this and similar stimuli [33,34]. However, this association was not always demonstrated [35], perhaps due to the low ceiling effects and/or the use of a grid pattern which may result in using verbal encoding strategies. An fMRI paradigm demonstrated that memory testing with asymmetrical random stimuli was more strongly associated with right temporal lobe activations than memory of faces which tended to be bilateral, or of line drawings which produced stronger left hemisphere activations [36,37]. Based on these and similar studies, the use of dot locations with an asymmetrical pattern that did not use line drawings or grids was previously integrated into a test of visual learning and memory called the Brown Location Test (BLT) [38].

In the BLT, examinees memorize 12 different dot locations that are presented on an unchanging asymmetrical random array of circles (See Fig. 1). The test is formatted in a similar way to verbal learning tests where there are five learning trials, an interference trial, short delay and long delay trials, and recognition subtests. It demonstrated good internal consistency and reliability of alternative forms, and all the subtests contributed to a single factor that was distinct from verbal memory performance on the CVLT-II [38]. It has normative data on 298 healthy controls, and was significantly associated with postsurgical visual memory impairments among patients who had undergone right temporal lobectomies [39]. However, the utility of the BLT for lateralizing RTLE within presurgical epilepsy evaluations was not examined.

1.1. Current study

The primary purpose of the current study was to determine whether the BLT was able to lateralize RTLE during presurgical evaluations. Specifically, we predicted that those patients with video-EEG confirmed RTLE would have significantly lower scores on the BLT Learning and Long Delay Recall Trials than those with LTLE. During this time, we also routinely administered two verbal memory tests (CVLT-II and VSRT), and we set out to determine which verbal memory test would provide the strongest lateralizing information. Finally, we wanted to determine to what extent the inclusion of the BLT, VSRT, and CVLT-II would improve our ability to lateralize TLE.

2. Methods

2.1. Participants

This was a retrospective analysis of 29 patients who had undergone neuropsychological testing as part of a presurgical evaluation for medically refractory epilepsy. In order to be included in the analyses, all patients had to have had video-EEG monitoring with clearly defined RTLE or LTLE, English had to be their first language, there had to be evidence that they were clearly left hemisphere dominant for language on fMRI, and when the results were questionable, left sided language dominance needed to be confirmed with intracarotid sodium amobarbital (Wada) testing. Patients had to demonstrate adequate effort on testing, and those with questionable effort based on embedded or stand-alone validity testing were not included in the analysis. Exclusion criteria included the presence of additional neurological disorders which would/might substantially affect the test results (e.g., history of moderate to severe TBI, cerebral infarction or hemorrhage, and similar conditions). Subjects were also excluded if they drank alcohol or used marijuana within 12 h of the evaluation. We found 108 patients in our database who had been administered the BLT, CVLT-II, and VSRT between April 2007 and May 2015. We excluded 49 patients who did not have mesial temporal epilepsy, 8 were poorly lateralized, and 19 had significant neurological complications (e.g., traumatic brain injuries, prior surgical resections, etc.). Out of this group, 32 had clearly lateralized right or left temporal lobe epilepsy and met full research criteria. We then excluded one patient with LTLE who smoked marijuana the day of the evaluation. We excluded two patients (1 RTLE, 1 LTLE) who provided insufficient effort based on multiple aspects of noncredible performance (e.g., atypically low scores on the CVLT-II Forced Choice Subtest, abnormally low true positive scores on the CVLT-II, and invalid performance on the Green Word Memory Test [40]). This resulted in 29 patients who met criteria and whose testing had taken place from July 2008 through May 2015. This project was reviewed by the institution's human subjects committee and considered exempt for full review due to the retrospective nature.

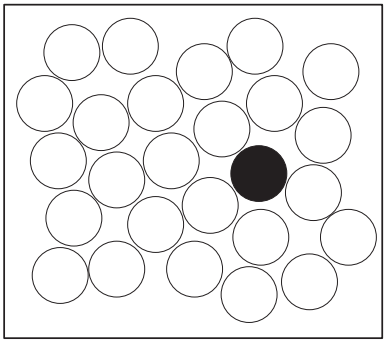

Fig. 1. Simplified example of the circle array with a dot location.

2.2. Measures

Estimation of overall intellectual functioning was based on the Full Scale IQ score provided by the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) [41]. We also used the Verbal Comprehension and Perceptual Reasoning Indices from the WAIS-IV to provide information about intellectual functioning within the verbal and visual domains.

We assessed verbal memory with two different tasks. The Verbal Selective Reminding Test (VSRT) requires the examinee to memorize a list of 12 words. After the list is read in its entirety the first time, the patient repeats the words he/she is able to recall. The examiner then only tells the patient the words they missed, rather than the entire list. This is repeated for 12 learning trials, or until the patient demonstrates that the list has been learned. The patient is tested 30 min later to determine which words they recall. It is worth noting that in this sample, patients were not administered the Multiple Choice Subtest of the VSRT, which makes the standardization slightly atypical. However, all of the patients were administered the test in the same manner. For the present study, we converted the raw scores to age- and gender-adjusted Z-scores [11]. Though several different scores can be derived, we used the Z-scores that reflected the total words recalled during the Learning Trials and the Long Delay Free Recall score. We chose these scores in order to provide comparable scores between the CVLT-II and BLT which also have the total Learning Trial and Long Delay scores. We decided to use Z-scores for the VSRT, CVLT-II, and BLT in order to provide information that may be readily interpreted for clinical use.

We also measured verbal memory with the California Verbal Learning Test, Second Edition [42]. This test requires the patient to learn 16 words over 5 Learning Trials. There are 4 semantic categories of words which allow the examinee to use learning strategies not present in the VSRT. There is also an Interference Learning Trial where an alternative list is presented one time after the five Learning Trials and prior to the Short Delay. There are both non-Cued Short and Long Delay and Cued Short and Long Delay categories. We used age- and gender-adjusted Z-scores derived from the published normative data [42] for the total Learning Trials and the Long Delay Free Recall Trial. Both verbal memory tests were administered the same day. The CVLT-II was administered very early in the evaluation, and the VSRT was administered approximately 4 h later near the end of the evaluation. In addition, there were