



Influence of anxiety on memory performance in temporal lobe epilepsy

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ARTICLE INFO

Article history:

Received 11 September 2013

Revised 4 October 2013

Accepted 8 October 2013

Available online 26 November 2013

Keywords:

Anxiety

Temporal lobe epilepsy

Visual memory

Verbal memory

ABSTRACT

This study examined the degree to which anxiety contributed to inconsistent material-specific memory difficulties among 243 patients with temporal lobe epilepsy from the Multisite Epilepsy Study. Visual memory performance on the Rey Complex Figure Test (RCFT) was poorer for those with high versus low levels of anxiety but was not found to be related to the TLE side. The verbal memory score on the California Verbal Learning Test (CVLT) was significantly lower for patients with left-sided TLE than for patients with right-sided TLE with low anxiety levels but equally impaired for those with high anxiety levels. These results suggest that we can place more confidence in the ability of verbal memory tests like the CVLT to lateralize to left-sided TLE for those with low anxiety levels, but that verbal memory will be less likely to produce lateralizing information for those with high anxiety levels. This suggests that more caution is needed when interpreting verbal memory tests for those with high anxiety levels. These results indicated that RCFT performance was significantly affected by anxiety and did not lateralize to either side, regardless of anxiety levels. This study adds to the existing literature which suggests that drawing-based visual memory tests do not lateralize among patients with TLE, regardless of anxiety levels.

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1. Introduction

For more than 40 years [1–5], neuropsychologists have administered memory tests to patients with epilepsy with the belief that right-sided temporal mesial lobe epilepsy (RTLE) was associated with nonverbal memory impairments and that left-sided temporal mesial lobe epilepsy (LTLE) was associated with verbal memory deficits. Numerous studies have supported the association between LTLE and verbal memory [6–12]. However, the association between RTLE and visual memory performance has been less consistent, with larger studies typically failing to find this relation [8,13–15].

These inconsistent findings might be due, in part, to the use of visual stimuli which can be verbally encoded. This is supported by studies

suggesting that tests using material that is more difficult to verbalize (e.g., dot locations or random patterns) typically revealed stronger associations between visual memory performance and RTLE or right hippocampus resections [16–19] compared with tests using abstract designs [20–22]. Functional neuroimaging studies also support this by indicating that the type of stimuli (e.g., line drawings) often used in visual memory tests is affected by verbal interference paradigms and reflects fMRI activation in verbal areas of the brain [23]. In addition, functional reorganization in chronic epilepsy may contribute to the unaffected temporal lobe taking over both verbal and visual memory functions [24].

However, psychological variables may also contribute to the inconsistent association of visual memory with the affected temporal lobe. In reviewing the literature, it appears that anxiety, in particular, has had a disproportionate impact on visual memory but not on verbal memory [25–27]. Specifically, obsessive-compulsive disorder [25–27] and more generalized agoraphobia [26] were associated with poorer visual memory performance on the Rey Complex Figure Test (RCFT) but not with verbal memory. Indeed, out of multiple articles reviewed, we only located one where verbal list learning performance was poorer among individuals with anxiety disorders [28]. Depression, on the

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¹ Susan Spencer was an integral part of this study but passed away prior to this article being submitted for publication.

other hand, has appeared to have more general effects on cognition [29,30], rather than specifically impacting visual memory. Thus, it is possible that anxiety could have contributed to inconsistent findings among drawing-based visual memory tests, whereas prior research does not suggest the same relationship between depression and visual memory.

The reason that anxiety results in disproportionately poorer visual than verbal performances may be related to different task demands among these memory tests. Specifically, drawing-based visual memory tests require more fine motor control, organization and planning, and processing speed demands than verbal measures [31,32], and these same functions appear to be problematic among individuals with anxiety disorders [33,34]. Furthermore, most visual memory tests have one exposure to test stimuli, whereas verbal list learning tests include repeat exposures. This makes such tests susceptible to fluctuations in attention and working memory which tend to be affected by anxiety [35,36].

The importance of properly assessing verbal memory or visual memory goes beyond providing information about whether test results are consistent with right-sided TLE or left-sided TLE. Properly assessing verbal memory or visual memory is an important part of predicting surgical outcomes. Several studies have found that verbal list learning memory was as good as and, in some cases, a better predictor of postoperative verbal memory than intracarotid amobarbital testing, whereas this has not been found among visual measures. Those with problematic presurgical verbal memory were less likely to experience postsurgical declines, whereas those with higher presurgical verbal memory were more likely to experience a significant decline in verbal memory [15,37,38]. The problems with consistent visual memory assessment in TLE have not yet made such a prediction possible [8,13–15]. Thus, it would certainly be important to identify whether nonneurological variables, such as anxiety, might affect presurgical visual memory results. Furthermore, it would be helpful to determine whether taking into account the level of anxiety may result in drawing-based visual memory tests being more useful for such predictions.

1.1. Current study

Poor performance on verbal list learning tests such as the CVLT appears to be fairly consistent among patients with LTLE. Anxiety has not been consistently associated with list learning performance; however, this has not been studied in TLE. Drawing-based visual memory performance, such as the RCFT, has not been consistently associated with RTLE but does seem to be affected by anxiety. However, the role of anxiety and how it may affect lateralizing information on visual memory tests have not been studied among patients with epilepsy.

In the current retrospective study, we examined the relations between anxiety and performance on verbal (CVLT) memory and visual (RCFT) memory in patients with left-sided TLE and in those with right-sided TLE. We expected that high levels of anxiety would be associated with poorer performance on the RCFT, whereas anxiety would not mediate verbal memory. We also anticipated that verbal memory would be sensitive to LTLE but did not expect the RCFT to be sensitive to RTLE. However, since anxiety levels did not appear to be taken into account in prior research, we tentatively hypothesized that there may be a potential relationship between RCFT and RTLE when limited to patients with low levels of anxiety.

2. Methods

2.1. Participants

This was a retrospective analysis of 243 patients who had undergone neuropsychological testing as part of a presurgical evaluation for patients with TLE who were taking part in the Multisite Study of Epilepsy Surgery (MSES). The MSES is a longitudinal study examining the outcomes of surgery at seven epilepsy centers in the United States of

America. In-depth discussion of patient recruitment, inclusion and exclusion criteria, and other characteristics are discussed elsewhere [39,40]. In brief, however, patients had to show evidence of medically refractory epilepsy with seizures that impaired consciousness on at least a monthly basis. All patients underwent a presurgical evaluation that was consistently performed across sites [41] and included EEG, PET, MRI, neuropsychological testing, and intracarotid amobarbital testing.

To be included in the analysis, patients had to have (1) been clearly identified with either right-sided or left-sided mesial TLE, (2) undergone either right or left anterior temporal lobectomy following their presurgical evaluation, (3) been identified as left-hemisphere language dominant according to intracarotid amobarbital testing, and (4) remained seizure-free for two years in order to improve the likelihood that the presurgical evaluation correctly lateralized the epileptogenic focus. Exclusion criteria included additional neurological disorders which would make the etiology for their cognitive difficulties unclear (e.g., history of moderate to severe TBI, substantial stroke outside of the surgical area, and similar neurological disorders). All study procedures were approved from each institution's human subject committee review board. The current analyses were limited to demographics, mesial TLE side, presurgical intellectual functioning, memory, and self-report anxiety functioning.

2.2. Measures

The estimation of overall intellectual functioning was based on the Full Scale IQ score provided by the Wechsler Adult Intelligence Scale, Revised Edition, WAIS-R [42]. We also examined the Verbal and Performance IQ scores since these may be differentially affected by the epilepsy side. We assessed visual memory using the Rey Complex Figure Test, RCFT [43,44], in which the examinee copies a complex design and then draws it from memory after short and long delays. We used the age-adjusted T-scores ($M = 50$, $SD = 10$) for the Immediate Free Recall and Delayed Free Recall which are in the published manual [44].

We assessed verbal list learning memory with the California Verbal Learning Test, CVLT [45]. The CVLT has demonstrated efficacy in identifying LTLE in previous studies [6,46]. Though one large study [12] recently found that the Rey Auditory Verbal Learning Test may be more sensitive to left-sided TLE than the CVLT, this was based only on the raw scores from the learning trials, not from the delayed trials. Moreover, the Rey Auditory Verbal Learning Test also has some problems with its normative data in some age ranges. For example, individuals who are 60 can get only one word correct on the long delay but still get a scaled score of 5 [47]. Also, the AVLT normative data were not available at the time this study began toward the end of the 1990s. Thus, the CVLT has received ample support for use in this study and had more useful normative data at the time we started this study. In this particular study, we used the age-adjusted Z-scores ($M = 0$, $SD = \pm 1$) for the short and long delays that are provided in the published manual [45].

We assessed anxiety with the Beck Anxiety Inventory, BAI [48]. The BAI asks the patient to indicate the prevalence and severity of general anxiety symptoms over the past week on a 0 to 3 scale. Thus, this is a not a state anxiety scale, but rather measures more longstanding anxiety symptoms. The BAI manual [48] indicates the following levels: scores of 8–15 indicate mild anxiety, scores of 16–25 indicate moderate anxiety, and scores of 26–63 suggest severe anxiety. In deciding how to use these scores, we noted that the literature suggested that the relationship between anxiety and memory performance has often been overstated because of a non-normal distribution where a small set of individuals with severe problems skews the results [49]. Indeed, we examined the BAI score distribution and found that it was not normally distributed. Specifically, a large group of patients performed within the range of 0–15 which was the modal range; however, there was a slightly lower secondary mode among the scores in the 20s with scores extending to the highest range of the test. This distribution and prior

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