NÖRO PSİKİYATRİ ARŞİVİ

Research Article / Araştırma Makalesi

Arch Neuropsychiatry 2016; 53: 199-204 • DOI: 10.5152/npa.2016.14862

Comparison of Cognitive Parameters between Bilateral and Unilateral Hippocampal Sclerosis

Bilateral ve Unilateral Hipokampal Sklerozda Kognitif Parametrelerin Karşılaştırılması

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ABSTRACT

Introduction: Recent studies showed that hippocampal sclerosis (HS) patients with unilateral involvement had more diffuse cognitive impairment than expected. Therefore, we aimed to compare the cognitive profiles of bilateral HS (BHS) patients with unilateral HS (UHS) patients.

Methods: Consecutive patients, diagnosed with epilepsy, who fulfilled two major magnetic resonance imaging (MRI) criteria (T1 atrophy and T2-FLAIR hyperintensity) for HS were included. Standard neuro-psychological test (NPT) battery consisted of the Turkish version of 15-word verbal memory processes test, Wechsler memory scale visual reproduction subtest, forward and backward digit span, phonemic and semantic fluency, and Stroop test were applied; and the groups with right HS, left HS, and bilateral HS were compared statistically.

Results: Ninety-one patients, completing the NPT (34 males, 57 females)-16 with BHS, 36 with right HS, and 39 with left HS-were included. Six out of 43 operated patients had BHS. There were no significant differences in education and handedness of the groups. Even though NPT performances of the BHS group were found to be poor compared to UHS subgroups, this was beyond statistical significance. Comparison of BHS with the right HS group showed a significant difference in the learning score of the Verbal Memory Processes Test, but recognition scores were found to be similar in all groups. Compared to the BHS group, both right and left HS groups revealed a significant difference in delayed recall score of the Verbal Memory Processes Test. Although there were no significant differences in the postoperative parameters of the BHS group, UHS subgroups had deficits in many postoperative parameters.

Conclusion: Our study revealed that bilateral involvement of the hippocampi was correlated with a poor cognitive performance. Retrieval failure, rather than a total recall problem, in the memory of the patients resembles a more diffuse involvement not only limited to limbic structures.

Keywords: Epilepsy, hippocampal sclerosis, bilateral hippocampal sclerosis, cognition

ÖZ

Amaç: Son yıllardaki çalışmalar unilateral hipokampal sklerozlu (HS) hastalarda kognitif tutulumun bilindiğinden daha yaygın olduğunu göstermektedir. Amacımız bilateral hipokampal sklerozlu hastalarla unilateral hipokampal sklerozlu hastaların kognitif tutulumlarını karşılaştırmaktır.

Yöntem: Klinik olarak epilepsi tanısı almış, MRG kriterlerine (T1'de atrofi ve T2-FLAIR'de hiperintensite) uygun şekilde HS saptanmış ardışık hastalar çalışmaya dahil edildi. Sözel bellek süreçleri testi, Weschsler bellek testinin alt testi olan görsel bellek testi, ileri ve geri sayı menzili, fonemik ve semantik akıcılık ve Stroop testlerini içeren standart nöropsikolojik test (NPT) bataryası uygulanmış olan sağ HS, sol HS ve bilateral HS gruplarında sonuçlar istatistiksel olarak karşılaştırıldı.

Bulgular: NPT'leri tamamlayabilen 16 bilateral HS, 36 sağ HS ve 39 sol HS olmak üzere toplam 91 hasta (34 erkek, 57 kadın) dahil edildi. Ameliyat olmuş 43 hastanın 6 'sı bilateral HS'ydi. Gruplararası el tercihleri ve eğitim durumlarında istatistiksel farklılık yoktu. Bilateral grubun NPT performansları unilateral gruplara göre daha düşük olmasına rağmen istatistiksel olarak anlamlı değildi. Bilateral HS'li hastaların sağ HS ile kıyaslanmasında sözel bellek süreçleri öğrenme skorunda istatistiksel olarak anlamlı fark olmasına rağmen tanımada fark yoktu. Sağ ve sol HS grubunda bilateral HS ile kıyaslandığında sözel bellek süreçleri testlerinde gecikmeli geri çağırma skorları anlamlı olarak düşüktü. Preoperatif ile postoperatif bulgular kıyaslandığında bilateral grupta istatistiksel anlamlı fark yokken, unilateral grupta birçok alanda bozulma dikkati çekti.

Sonuç: Çalışmamız bilateral hipokampal etkilenmenin düşük kognitif performansla ilişkili olduğunu göstermiştir. Hatırlama probleminden çok geri getirme eksikliği şeklindeki kognitif tutulum limbik yapılarla sınırlı kalmayan daha yaygın bir etkilenmeyi düşündürmüştür.

Anahtar kelimeler: Epilepsi, hipokampal skleroz, bilateral hipokampal skleroz, kognitif

INTRODUCTION

One of the most common syndromes causing of drug-resistant epilepsy is mesial temporal lobe epilepsy (MTLE) associated with memory problems (1,2). MTLE is mostly characterized by typical pathological changes such as hippocampal sclerosis (HS), which has its well-known MRI correlates and is mostly unilateral. However, there are some patients with bilateral involvement of hippocampi both neuroradiologically and pathologically (3,4). The reasons for reluctant use of surgical therapy options in patients with bilateral HS (BHS) have not been fully

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Received / Geliş tarihi: 27.01.2016 **Accepted / Kabul tarihi:** 03.02.2016 **Available Online Date / Çevrimiçi Yayın Tarihi:** 28.03.2016

explained. Mainly, one of the causes can be suggested as the fear of severe postoperative memory deficits, besides poor seizure control (5). Moreover, recent studies investigating cognitive involvement patterns of patients with unilateral HS (UHS) indicated that the involvement was more diffuse than previously thought and is not limited to the dominant versus non-dominant hemispheric patterns (6). Furthermore, research suggested that postoperative cognitive deficits of BHS were not that worse in comparison to unilateral cases (7). However, their already poor baseline performances, shown on neuropsychological tests (NPT), are still at risk for severe postoperative memory decline even though they may show significantly improved quality of life after epilepsy surgery (7,8).

There are no consecutive series investigating these interesting neuropsychological associations in BHS versus UHS patients in the same study design. We, therefore, aimed to investigate the differences of BHS patients in comparison to the UHS patients in terms of neuropsychological profiles and to compare their postoperative neuropsychological outcomes.

METHODS

Patients' Selection

We investigated our database for epileptic patients with MTLE during 2000–2014 who fulfilled the MRI criteria (mentioned later) for BHS and having at least one NPT in our epilepsy center. We included consecutive UHS patients who had undergone the same NPT battery and seen in our epilepsy center during 2013–2014 to ascertain their prognosis as a control group. The Ethical Committee of İstanbul University, İstanbul School of Medicine, approved the study, and the patients were included after their informed consent.

All MRI studies were performed with a 1.5-T scanner (Magnetom Siemens Symphony; Erlangen, Germany) with thin coronal in addition to sagittal and axial planes including T1- and T2-weighted images and fluid-attenuated inversion recovery (FLAIR) images to visualize mesial temporal regions optimally.

MRIs were re-investigated for the verification of HS diagnosis; presence of atrophy and high signal changes on T2 and FLAIR series in any one or more parts of the hippocampus were considered as the major criteria necessary to establish the neuroradiological diagnosis of HS (9,10). Patients with clear-cut UHS with suspicious findings of the other side had undergone 3-T MRI, and were included into the BHS group after confirmation of BHS (Figure 1). All patients were grouped as right HS, left HS, or BHS. Seizures and syndromes were diagnosed according to the revised terminology, and concepts for organization of seizures and epilepsies of the ILAE Commission on Classification and Terminology (11).

Neuropsychological Testing Battery

In the routine examination of the HS patients in our unit, the NPT is a standard approach to evaluate the mental status of the patients. Therefore, we obtained the neuropsychological evaluation results of each HS patients from their patient files. Preoperative and first-year postoperative neuropsychological evaluations were all reviewed and scores of the tests were transferred to an Excel sheet. These tests were used several times in our studies (12,13,14). Included tests functions, names, and parameters are as follows:

- Verbal memory: A 15-word Turkish verbal learning memory test (immediate recall, learning score, maximum learning score in 10 drills, 40-min delayed recall test, followed by total recall) (15).

- Visual memory: Wechsler Memory Scale (WMS) visual reproduction subtest (immediate recall, 40-min delayed recall test, followed by total recall) (16).

- Simple and complex attention: Digit span (forwards and backwards) (17).

- Complex attention: Phonemic and semantic fluency tests (animal naming; words with letters of K, A, and S; and perseverations).

- Executive functions: Stroop test (spontaneous corrections of commission errors, commission errors, and difference between time spent for reading and for color naming) (18).

The patients who could not learn the 15-word drilled list with appropriate motivation were excluded from further neuropsychological analysis. To exclude the possible negative impact of a recent seizure on cognition, we did not test patients who reported having had a seizure within the previous 24 h. Patients with active major depression and other serious medical and psychiatric diseases were not enrolled for the NPT.

Statistical Analyses

Descriptive statistics were applied, and right HS and left HS patients were compared with BHS separately; chi-square test, Fisher's exact test, and t test were used where appropriate. After applying Kruskal–Wallis test for triple group comparisons (right HS, left HS, and BHS), two groups' comparisons were also accomplished with the Mann–Whitney U test. Preoperative and postoperative tests' performances were also compared with Wilcoxon signed rank test in operated patients. Statistical Package for the Social Sciences Version 21 (IBM SPSS Statistics; New York, USA) was used, and the significance level was set at $p<0.05$.

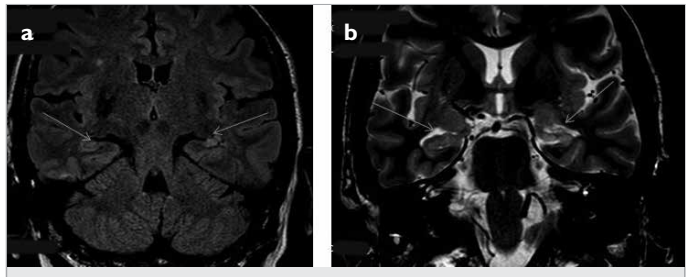

Figure 1. Bilateral hippocampal sclerosis with 3-T coronal MR imaging as demonstrated by our criteria; bilateral atrophy in T1-weight and high-signal FLAIR images bilaterally.

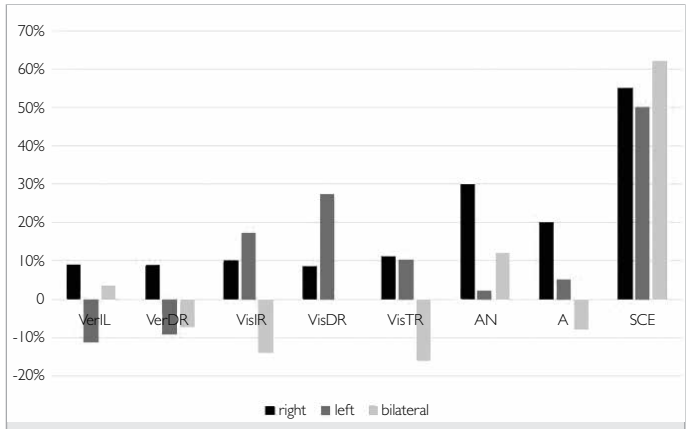

Figure 2. Postoperative versus preoperative neuropsychological test comparisons (values derived by subtraction of postoperative mean ranks from preoperative mean ranks, based on preoperative mean ranks for each statistically significant value; positive values indicate better performance in percentages, and negative values indicate worse performance after the operation in percentages).

VerIL: verbal immediate learning; VerDR: verbal 40-min delayed recall; VisIR: visual immediate recall; VisDR: visual 40-min delayed recall; VisTR: visual total recall; AN: animal naming; A: words beginning with the letter A; SCE: Stroop commission errors

Table 1. Preoperative neuropsychological test results

	Parameters, mean±SD, (min-max), n	Right HS (n:36)	Left HS (n:39)	BHS (n:16)	Level of significancy (right versus BHS; left versus BHS)
Turkish version of 15-word verbal memory process test	Immediate learning	6.00±1.64 (3-8), 33	5.63±1.61 (2-9), 38	5.31±1.92 (2-9), 16	Ns; Ns
	Learning score	105.91±23.14 (42-137), 33	104.03±21.21 (64-141), 38	93.44±20.45 (50-128), 16	0.038*; Ns
	Maximum learning score in 10 drills	13.06±2.27 (7-15), 33	12.76±2.06 (8-15), 38	12.06±2.21 (7-15), 16	Ns; Ns
	40-min delayed recall	9.88±3.90 (0-15), 33	9.87±3.08 (3-14), 38	7.81±2.76 (3-13), 16	0.041*; 0.024*
	Total recall	14.30±1.88 (8-15), 33	14.58±0.98 (1-15), 38	14.69±0.60 (13-15), 16	Ns; Ns
Wechsler Memory Scale visual reproduction subtest	Immediate recall	10.42±3.73 (3-14), 31	9.49±3.76 (2-14), 37	8.93±3.54 (3-14), 15	Ns; Ns
	40-min delayed recall test	8.58±4.62 (0-14), 31	8.32±3.63 (1-14), 37	5.67±4.62 (0-14), 15	0.050*; 0.053*
	Total recall	10.88±3.48 (3-14), 25	11.39±2.58 (5-14), 31	9.18±4.33 (3-14), 11	Ns; Ns
Simple attention	Digit span forward	4.44±1.82 (3-8), 36	4.74±1.72 (4-8), 39	5.31±1.58 (3-8), 16	Ns; Ns
Complex attention	Digit span backward	3.78±1.41 (0-7), 33	4.22±1.27 (2-7), 36	3.69±1.14 (2-6), 16	Ns; Ns
	Animal naming	15.33±7.21 (5-27), 36	15.79±6.05 (6-27), 39	14.88±4.32 (6-25), 16	Ns; Ns
	Animal naming perseverations	0.78±1.43 (0-6), 33	0.92±1.51 (0-6), 38	0.94±1.18 (0-4), 16	Ns; Ns
	Words beginning with the letter K	11.38±5.11 (3-25), 26	9.09±6.16 (0-22), 33	8.46±3.07 (4-16), 13	Ns; Ns
	Words beginning with the letter K perseverations	0.33±0.62 (0-2), 26	0.34±0.70 (0-3), 33	0.08±0.28 (0-1), 13	Ns; Ns
	Words beginning with the letter A	8.20±4.99 (1-18), 25	6.97±5.38 (0-20), 31	6.92±3.82 (2-12), 12	Ns; Ns
	Words beginning with the letter A perseverations	0.20±0.50 (0-2), 25	0.40±0.80 (0-3), 31	0.50±0.80 (0-2), 12	Ns; Ns
	Words beginning with the letter S	9.52±5.29 (0-22), 25	7.77±5.64 (1-22), 31	7.50±4.78 (2-16), 12	Ns; Ns
	Words beginning with the letter S perseverations	0.08±0.28 (0-1), 25	0.06±0.25 (0-1), 31	0.25±0.62 (0-2), 12	Ns; Ns
Stroop Test	Spontaneous corrections of commission errors	1.83±3.72 (0-19), 30	1.22±2.82 (0-13), 37	1.38±2.76 (0-10), 13	Ns; Ns
	Commission errors	3.77±4.45 (0-22), 30	3.76±3.75 (0-16), 37	3.69±2.56 (0-8), 13	Ns; Ns
	Difference between time spent for reading and time spent for color naming	56.07±45.34 (13-244), 30	49.50±29.40 (7-126), 36	55.31±25.65 (14-101), 13	Ns; Ns

Higher values indicate better test performance (except perseveration and Stroop test); SD: standard deviation; HS: hippocampal sclerosis; BHS: bilateral hippocampal sclerosis; Ns: not significant *with Mann–Whitney U test

Table 2. Postoperative neuropsychological test results

	Parameters, mean±SD, (min-max), n	Right HS (n=17)	Left HS (n=20)	BHS (n=6)
Turkish version of 15-word verbal memory process test	Immediate learning	6.59±1.50 (4-9), 17	5.00±2.05[4] (0-8), 19	5.50±2.42 (3-10), 6
	Learning score	110.11±21.15 (69-138), 17	86.47±26.60 (37-129), 19	81.66±35.38 (41-135), 6
	Maximum learning score in 10 drills	13.58±1.80 (10-15), 17	11.21±3.06 (6-15), 19	10.66±3.38 (7-15), 6
	40-min delayed recall	10.64±3.58 (5-15), 17	7.15±3.58[5] (1-13), 19	6.50±6.56 (0-15), 6
	Total recall	14.23±2.10 (7-15), 17	14.58±0.98 (1-15), 38	12.16±3.60 (6-15), 6
Wechsler Memory Scale visual reproduction subtest	Immediate recall	11.53±2.77 (6-14), 15	11.16±3.84[6] (1-14), 19	7.67±3.93 (2-14), 6
	40-min delayed recall test	9.47±3.74 (4-14), 15	10.61±3.64[7] (0-14), 19	5.67±4.93 (0-14), 6
	Total recall	12.13±2.61[1] (6-14), 15	13.00±1.50[8] (10-14), 15	7.67±5.20 (0-14), 6
Simple attention	Digit span forward	4.53±2.01 (0-7), 19	4.32±2.08 (0-7), 19	4.00±2.37 (0-7), 6
Complex attention	Digit span backward	3.71±1.40 (0-6), 17	3.89±1.33 (2-7), 19	2.80±1.79 (0-4), 5
	Animal naming	19.94±5.03[2] (12-30), 17	16.16±5.53[9] (9-27), 19	16.67±6.43 (6-26), 6
	Animal naming perseverations	0.65±1.05 (0-4), 17	1.26±1.36 (0-4), 19	1.17±0.41 (1-2), 6
	Words beginning with the letter K	13.62±5.20 (4-22), 13	10.47±7.76 (2-22), 17	7.33±4.04 (3-11), 3
	Words beginning with the letter K perseverations	0.38±0.51 (0-1), 13	0.53±0.87 (0-2), 17	1.00±0.00 (1-1), 3
	Words beginning with the letter A	10.17±4.88[3] (2-18), 12	7.29±4.92 (0-19), 17	6.33±5.86[11] (2-13), 3
	Words beginning with the letter A perseverations	0.33±0.65 (0-2), 12	0.18±0.73 (0-3), 17	0.00±0.00[12] (0-0), 3
	Words beginning with the letter S	12.33±5.08 (6-20), 12	8.71±5.63 (0-20), 17	7.33±7.09[13] (1-15), 3
	Words beginning with the letter S perseverations	0.58±1.24 (0-4), 12	0.18±0.39 (0-1), 17	0.00±0.00[14] (0-0), 3
Stroop test	Spontaneous corrections of commission errors	0.31±0.75 (0-3), 19	0.63±1.56 (0-7), 22	1.16±2.85 (0-7), 6
	Commission errors	1.66±1.54 (0-5), 15	1.88±1.8710 (0-6), 18	1.40±2.19 (0-5), 5
	Difference between time spent for reading and time spent for color naming	40.00±14.81 (22-73), 15	37.89±19.96 (10-85), 18	28.60±8.70 (15-36), 5

SD: standard deviation; HS: hippocampal sclerosis; BHS: bilateral hippocampal sclerosis; Ns: not significant

Higher values indicate better test performance (except perseveration and Stroop Test)

[1,4,5, 10]p=0.046, 0.032, 0.015, 0.004; compared to preoperative scores with Wilcoxon signed rank test based on negative ranks, respectively

[2,3,6,7,8,9]p=0.004, 0.041, 0.002, 0.001, 0.026, 0.006; compared to preoperative scores with Wilcoxon signed rank test based on positive ranks, respectively

[11,12,13,14]Not calculated

RESULTS

Only 91 patients (34 males, 57 females)-16 with BHS and 75 with UHS (right HS: 36, left HS: 39)-had complete results of the NPT required for this study. Among them, 28 of 36 right HS patients, 35 of 39 left HS patients, and 12 of 16 BHS patients were right-handed (not significant with Kruskal–Wallis test). The mean educations in years of right HS, left HS, and BHS groups were 8.68 [3.81], 7.64 [4.16], 6.93 [2.32] years, respectively. There was no significant difference between years of education between the three groups. Six patients from the BHS group, but only 1 from the UHS subgroups, had clinically overt mental retardation (p=0.007); these 7 patients could not complete the NPT and excluded from the study.

Preoperative NPT findings of the study groups are shown in Table 1. Comparison of BHS patients with unilateral HS patients (BHS vs right HS and BHS vs left HS) showed that there was a significant difference between the right HS group and BHS group in the learning score of the Verbal Memory Processes Test. Compared to BHS patients, both right and left HS patients revealed a significant difference in delayed recall score of the Verbal Memory Processes Test. Furthermore, the right HS and left HS patients showed difference in delayed recall score of WMS, but these were beyond the statistical significance (p=0.050 and 0.053, respectively).

Of the 49 patients, only 43 who underwent an operation had complete the NPT (right HS: 17, left HS: 20, and BHS: 6). Details of postoperative NPT results of the groups are shown in Table 2. Although there were no significant differences in the preoperative versus postoperative findings of the BHS group, UHS subgroups had decline in many postoperative parameters. Preoperative versus postoperative group comparison revealed significant differences in WMS and semantic and phonemic fluency tests in the right HS group. In the left HS group, the Verbal Memory Processes Test, WMS, semantic fluency, and Stroop tests were found to be impaired after the operation.

The performances in the NPT of the operated groups were visualized in Figure 2, based on subtraction percentages of preoperative minus postoperative means of each group. Positive values indicate better, negative values indicate worse postoperative test performances.

DISCUSSION

Neuropsychological profiles of bilateral HS patients are usually ignored in epileptology despite their utmost significance in epilepsy practice. Therefore, we aimed to investigate differentiating cognitive variables of BHS in comparison to UHS and showed that the BHS group had markedly decreased performance in verbal learning memory but not in visual memory.

The association of BHS with worsening of the cognitive abilities was noted only in a few small-sized studies (19,20). It was formerly believed that left HS patients have verbal memory deficits and right HS patients have visual memory problems and this modality-specific memory dysfunction has been used as a lateralizing tool in the evaluation temporal lobe epilepsy patients. However, in recent years, some studies disclosed that patients may have both verbal and visual memory deficits and cognitive impairment may be more diffuse than expected in the UHS patients (6). Our results indicated that HS is also associated with cognitive impairments mainly involving executive functions with episodic memory deficits.

On the other hand, it can be propound that WMS visual reproduction subtest is a less sensitive means than the verbal memory test, as suggested by Jeyaraj et al. (2). Subtypes of HS may be related with the severity of the damage caused by initial precipitating injury and personal background of the patients. It is important to distinguish and specify these subtypes to uncover the relevant mechanisms and provide appropriate treatment. One may postulate that if the involvement of the mesial temporal structure is less severe, cognitive impairment may be less devastating, such as minor to moderate memory problems seen in UHS. The clinical pictures may worsen when the insulting episodes recur, such as status epilepticus. Accordingly, the development of hippocampal damage does not seem to be restricted to those who have had febrile status epilepticus, but can occur following any cause of convulsive status epilepticus (21). Recently, older systems of grading the severity of cell loss in HS have been superseded by a recent classification. This new classification recognizes that it is not only the severity of cell loss that is important but also the pattern of this cell loss (22). We believe that integrating the degree of bilateral involvement on imaging and a grading system of cognitive involvement patterns may aid to further develop a more reasonable clinico-pathological system to be used in future studies.

Vogt et al. (8) emphasized that despite further deficits in verbal memory, surgically treated BHS patients reported a slightly better subjective outcome than pharmacologically treated BHS patients did. Furthermore, this recent retrospective study carefully assessed neuropsychological outcome after epilepsy surgery in 11 patients with BHS, and reported that verbal memory further declined in 73% of the BHS patients, despite severe impairments already evident at baseline whereas nonverbal memory performance did not change significantly in any patient after surgery (8). We intriguingly showed that UHS and BHS groups did not show any significant difference even before surgery in almost all domains investigating nonverbal memory. This finding may indicate that nonverbal memory is not a strictly lateralized function or that our NPT batteries are not that sensitive to measure nonverbal memory appropriately as has been debated (2,6).

Other reports also consistently showed significant memory worsening after surgery in patients with BHS especially when left hippocampus is resected (5,23). Despite significant postoperative changes of right HS and left HS patients, our BHS group did not show any significant difference postoperatively except in the domain of words beginning with the letter A, indicative of more global involvement. BHS patients provided an interesting research group for assessing memory function, given the complex functional interactions of the hippocampi with each other and other structures of the limbic system and there is the possibility of compensatory mechanisms.

We acknowledge the following limitations of our study. Our group comprised mostly drug-refractory patients admitted to a tertiary center with a small size of operated BHS, and the study design is retrospective; thus, different effects of variable antiepileptic drug treatments on cognition could not be assessed. However, our series is unique to compare the NPT profiles of BHS versus UHS and provided important results.

In conclusion, we showed that bilateral involvement of the hippocampi was correlated with a poor cognitive performance at the baseline, but did not show significant loss after surgery in many cognitive domains in comparison to unilateral patients. Retrieval failure, rather than a total recall problem, in the memory of these patients resembles a more diffuse involvement not only limited to limbic structures.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University İstanbul School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.N.V.Y., B.Baykan; Design – E.N.V.Y., B.Baykan; Supervision – E.N.V.Y., B.Baykan; Resources – E.N.V.Y., B.Baykan; Materials – E.N.V.Y., Ö.Ö, N.B., C.G., A.G., B.Baykan; Data Collection and/or Processing – E.N.V.Y., Z.M.; Analysis and/or Interpretation – E.N.V.Y., B.B., B.Baykan; Literature Search – E.N.V.Y.; Writing Manuscript – E.N.V.Y., B.B., B.Baykan; Critical Review – B.B., B.Baykan; Other – E.N.V.Y., B.Baykan.

Acknowledgements: The authors thank Prof. Serra Sencer for neuroradiological consultations and Prof. Dr. Altay Sencer and his team for neurosurgical interventions.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma için etik komite onayı İstanbul Üniversitesi İstanbul Tıp Fakültesi'nden alınmıştır.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir – E.N.V.Y., B.Baykan; Tasarım – E.N.V.Y., B.Baykan; Denetleme – E.N.V.Y., B.Baykan; Kaynaklar – E.N.V.Y., B.Baykan; Malzemeler – E.N.V.Y., Ö.Ö, N.B., C.G., A.G., B.Baykan; Veri Toplanması ve/veya İşlemesi – E.N.V.Y., Z.M.; Analiz ve/veya Yorum – E.N.V.Y., B.B., B.Baykan; Literatür Taraması – E.N.V.Y.; Yazıyı Yazan – E.N.V.Y., B.B., B.Baykan; Eleştirel İnceleme – B.B., B.Baykan; Diğer – E.N.V.Y., B.Baykan.

Teşekkür: Yazarlar radyolojik değerlendirmeler için Prof. Dr. Serra Sencer'e, nöroşirürji girişimleri için Prof. Dr. Altay Sencer ve ekibine teşekkür ederler.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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