### THE ROLE OF NEUROPSYCHOLOGY IN DIAGNOSTICS AND TREATMENT OF PATIENTS WITH EPILEPSY

### Marina Malobabić

Epilepsy represents a neurological disease with a prevalence of approximately 1% of the world population. Besides unprovoked seizures which are the main characteristic of this disease, there can be a decline in cognitive functioning, including memory and concentration dysfunctions, executive dysfunction, and visuoconstructional and visuospatial dysfunctions. However, behavioral changes can also be seen throughout the disease duration and/or during postoperative treatment of drug-resistant epilepsy. This article aims to emphasize that neuropsychological diagnostics and neuropsychology as a science are making a valuable contribution to the diagnostic process and can be used as a tool for examining the localization and/or lateralization of brain damage, determining the severity of cognitive deficits, monitoring disease and treatment, which improves quality and safety of treatment, as well as further detection of neuropsychological comorbidities and their rehabilitation.

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University Clinical Center Niš, Neurology Clinic, Niš, Serbia

Contact: Marina Malobabić 48 Dr. Zorana Djindjića Blvd., 18000 Niš, Serbia E-mail: marinasudimac@gmail.com

#### Epilepsy and cognitive functioning

Epilepsy is a common disease characterized by two types of conditions: 1. At least two unprovoked (or reflex) seizures occurring greater than 24 hours apart; 2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; 3. Diagnosis of epilepsy syndrome (1) occurs with neuropsychological and psychiatric comorbidity (2).

Cognitive functions represent the brain's ability to analyze and use information from the environment (3) through functional systems (combination of mental abilities) in the brain, specifically attention, memory, language, praxis, and executive functions (4).

The issue of mental impairment and cognitive decline in epilepsy dates back to the late 19th century (5–7) when Gowers named it "epileptic dementia" and described it as a slow

cognitive decline resulting from chronicity and the accumulation of negative effects of seizures, treatment and other factors associated with epilepsy. Cognitive impairment in epilepsy can have different etiologies (8): 1. It may be the repercussion of epilepsy (9, 10), 2. Impaired cognitive domains can be comorbidity resulting from the same underlying pathology (11), 3. Seizures themselves can lead to cognitive impairment (12, 13), 4. Antiepileptic drug therapy may cause cognitive decline (14).

Over time, neuropsychology has clinical demonstrated its great role in characterizing the impact of epilepsy on the degree of cognitive impairment. The number of factors is reduced to the following ones: age of onset (15), as children with the early-onset disease are at higher risk of losing scores on intelligence tests; disease duration, a factor often identified with the age of onset (16-18); seizure type and frequency (19) (status epilepticus on already vulnerable brain changes cognitive status by reducing cognitive reserve capacity); epileptic encephalopathy, several studies in adult patients with encephalopathy have shown an important role of inflammation related to coanitive impairment as an essential feature (20, 21); comorbidities-patients with seizures after stroke or traumatic head injury show a more pronounced cognitive decline compared to the patients without seizures, hence seizures can be understood as exacerbating factor on an already vulnerable brain (22); and antiepileptic medications which can induce cognitive decline as a reaction to treatment (20, 23).

Causes of epilepsy can be congenital or acquired. Young people are more often affected by genetic form, congenital or developmental factors, while acquired factors, such as brain tumors or stroke, are more common among older people (24). With a prevalence from 0.8% to 1.2%, epilepsy is one of the most common chronic neurological disorders (25, 26); 30% to 40% of patients in this group suffer from a drug-resistant form of epilepsy (epilepsy that cannot be adequately controlled by antiepileptic drugs) (27, 28).

## The place where Neuropsychological assessment meets epilepsy

One of the first cognition studies in epilepsy was conducted in England when a "healthy group" was compared with two groups of patients with epilepsy. The results showed that there were differences between groups in recognition, registration, and reactions. However, in areas such as sensory discrimination, voluntary movement rapidity, rhythmic movement, and maximal voluntary contractions—relatively simple processes—the differences between groups were insignificant (29).

In the US in 1912, Wallin (30) used the first Binet-Simon IQ scale in two groups: "brightest epileptic school children" and "bright, average and backward pupils in public school" where he found that there was less overall intellectual damage in patients with epilepsy compared to "feebleminded" and at the same time he pointed out the importance of a clinical psychologist in research and practical work. As early as the 1980s, tests used to examine the cognitive decline in epilepsy were mainly WAIS and Halstead neuropsychological test battery (31-33).

In the 20th century, psychological and neuropsychological tests were primarily used as diagnostic and prognostic measures. Modern practices in the field of epilepsy evaluation and management include neuropsychology as an important component of research and patient treatment, hence epilepsy and neuropsychology enjoy a special and synergistic relationship (34, 35).

Neuropsychological assessment of epilepsy can provide information on the prediction of cognitive and psychiatric outcomes, the degree of cognitive and behavioral functioning after surgery, lateralization and/or localization of present brain damage (36), it can provide a baseline evaluation of cognitive functions, antiepileptic effects and identification and formulation of a treatment plan patients with psychogenic non-epileptic for seizures as well (2), which is why certain patterns can be identified in certain epileptic syndromes (4). Additionally, neuropsychological assessment aims to define the impact of epileptogenic foci in the interictal period (3), the relationship between localization and lateralization of epileptogenic foci,

and the dysfunction of certain cortical and subcortical regions in the interictal period.

Partial or focal seizures may be the product of focal temporal, frontal, or occipital lobes, with or without secondary generalization (37, 38). Focal epilepsy or localization-related epilepsy is usually characterized in terms of their lobar site of origin, and neuropsychology has historically focused on the relationship between structure and function such as executive function in frontal lobe epilepsy (FLE) and memory in temporal lobe epilepsy (TLE) (34).

Cognitive characteristics have been mostly studied in temporal lobe epilepsy, as it is the largest group of epilepsies eligible for surgical treatment and has the most favorable surgical outcomes (39), especially in patients with those undergoing hippocampal sclerosis or anterior temporal lobe resection (40). Studies have shown an association between right temporal lobe epilepsy and visual learning (41, 42) or decreased visual memory (43), although recent neuropsychological and neuroimaging studies have progressively challenged this model (44), while left temporal lobe epilepsy has been associated with language impairment (45) and verbal memory (46). One of the goals of а neuropsychological evaluation is to determine the risk of memory and speech impairment postoperatively, after temporal lobe resection. The first step in this direction is to determine whether the epileptogenic zone is in the dominant or nondominant hemisphere with several methods and techniques: Edinburgh handedness inventory (47, 48) seizure semiology analysis (49), postictal neuropsychological test (50), neuropsychological assessment (51), functional magnetic resonance imaging (52), Wada test (53, 54).

Other cognitive functions are expected to remain relatively intact because both seizure onset and focal epileptiform abnormalities are limited to temporal lobe structures encoding new contents (34). However, it is concluded that greater attention needs to be directed to the domains of executive functions and speed (55). Neuropsychological impairments, for this reason, are more prevalent than expected in temporal lobe epilepsy and more associated with distributed brain anomalies (56). It can be seen that the difference between focal epileptic syndromes (e.g. temporal versus frontal) is less pronounced in children with epilepsy due to the impact of epilepsy on the neurodevelopmental process (57).

It has been anticipated that epilepsy will continue to be a major clinical area that reflects the importance and benefits of neuropsychological testing which will continue to play an important role in establishing phenotypes (and perhaps endophenotypes) of epilepsy (35). Neuropsychological evaluation remains, in addition to MRI and EEG, the most important method for indicating cognitive deficits in epilepsy and determining the epileptic focus (41).

We cannot continue without mentioning the impact of the psychological share in the neuropsychological testing, important for detecting the psychological comorbidities of epilepsy (most often anxiety and depression), which should certainly be included in the comprehensive treatment of patients with epilepsy (58). Neuropsychologists in epilepsy centers are generally preoccupied with conducting а comprehensive evaluation of patients with epilepsy (59) and for this reason probably do not treat depression or anxiety more often, despite the ideal position for that kind of treatment (34). While the importance of mental health work is recognized by the epileptologist community, more work should be invested and mental health care should be implemented to provide adequate care to patients with epilepsy (60).

## The role of neuropsychology in epilepsy surgery

Historically, epilepsy surgery provided one of the most important pieces of evidence for the relevance of certain brain structures in cognitive functions through one of the most significant cases in the history of neuropsychology, the surgery of Henry Gustav Molaison, better known as HM, in 1953, who developed profound anterograde after surgical removal of mesial amnesia structures of both temporal lobes 8 cm long from the temporal pole (61) including hippocampus bilaterally (4, 62, 63). More studies are analyzing the long-term outcomes of epilepsy surgery and have found stable or even improved cognitive status (28, 64), which is why epilepsy surgery has become an evidence-based treatment for patients with drug-resistant epilepsy (65). Successful epilepsy surgery leads to seizure freedom and stabilization of cognitive functioning in two-thirds of patients (66).

It should be noted that there are always risks for the bad outcome of postoperative recovery of cognitive functions. Risk factors for postoperative verbal memory deficits may be the following (67): 1. Left temporal resection (dominant hemisphere surgery) (64); 2. Adequate function of the ipsilateral hippocampus (68); 3. Insufficient functional capacity of the contralateral hippocampus (69); 4. Size of the resection (70); 5. Surgery in older age (71); 6. Later epilepsy onset (72) and 7. Absence of postoperative remission (73).

Surgery also has potential neuropsychological risks within visual memory after right temporal lobe surgery (74). Spatial memory impairment is 6 times more pronounced in patients who underwent right anterior temporal lobe resection than left anterior temporal lobe resection (75). Some studies have shown improvement in executive functions after surgery (64, 76).

Another progress in this domain is the evaluation of the super-selective surgical

procedure for mesial temporal lobe epilepsy (12). neuroimaging, With improvements in neuropathology, and genetics, the number of epilepsies with unknown etiology has significantly changes decreased, encouraging in the classification of seizures and epilepsies, and also putting cognitive dysfunction in better perspective (77). The neuropsychological literature in this field has accumulated a lot of knowledge, which raises the question of why neuropsychology is still not fully integrated into the routine treatment of patients with epilepsy (12). A little over 30 years after Michael Trimble's work (78) and more than 80 years after the beginning of epilepsy surgery, neuropsychological knowledge is still not included in the required treatments of patients. Although early neuropsychological evaluation is often implied in children with early-onset epilepsy, it has not yet, although it should become a routine in the treatment of adult patients with epilepsy (12).

# Cognitive rehabilitation among epilepsy patients

Cognitive rehabilitation has a positive effect on the outcomes of memory therapy before and after surgery, but its use is still being considered among groups of patients at risk (79). Modalities and outcomes of rehabilitation are important issues for clinical treatment and research. A holistic approach to rehabilitation seems to be more useful than selective interventions (80). Predicting postoperative cognitive changes enables the desian and implementation of prerehabilitation programs as a part of preoperative treatment, to prepare the patient for postoperative changes (81).

A study conducted by Geraldi et al. (82) supports the role of memory rehabilitation after left temporal lobe surgery, and fMRI results suggest concomitant changes in the brain networks that underlie the results achieved after rehabilitation. Such findings are encouraging and suggest that rehabilitation should be considered as part of mandatory surgical evaluation and preparation. Also, research shows the importance of the application of cognitive rehabilitation in attention-deficit (80).

A period of intensive pre-surgical training can be useful for cognitive functions that have previously been shown to be impaired after surgery, especially for high-risk patients (e.g. verbal memory in left temporal lobe resections) by giving them some "reserve skills" to use after surgery. The post-surgical rehabilitation period (after a 6-month recovery period) should be adjusted individually to target the specifically identified weaknesses in each patient (83).

#### Conclusion

Epilepsy is a common neurological disease that can lead to cognitive impairment worsened by antiepileptic therapy. Successful epilepsy surgery can lead to seizure freedom and stabilization or improvement of cognitive even status Neuropsychological diagnostics play an important role in predicting postoperative cognitive and behavioral functioning, formulating treatment strategies, and examining the effect of antiepileptic drugs and the impact of the epileptogenic focus. Neuropsychological deficits are a leading comorbidity of epilepsy and can be exacerbated by treatment, making regular neuropsychological evaluation crucial. Cognitive rehabilitation tailored to individual patient needs is proposed as part of neuropsychological treatment and has shown significant results, with studies encouraging its use before surgical treatment in certain patient groups. Overall, neuropsychology in epilepsy has been trusted for decades and has contributed positively to the diagnosis and treatment of epilepsy.

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### ULOGA NEUROPSIHOLOGIJE U DIJAGNOSTICI I LEČENJU OSOBA SA EPILEPSIJOM

Marina Malobabić

Univerzitetski klinički centar Niš, Klinika za neurologiju, Niš, Srbija

Kontakt: Marina Malobabić Bulevar dr Zorana Đinđića 48, 18000 Niš, Srbija E-mail: marinasudimac@gmail.com

Epilepsija predstavlja neurološko oboljenje koje se javlja kod otprilike 1% svetske populacije. Osim neprovociranih epileptičnih napada, koji su glavna odlika, kod obolelih se javljaju smetnje u kognitivnom funkcionisanju; one koje se tiču pamćenja, koncentracije, egzekutivnih funkcija, vizuokonstruktivne i vizuospacijalne smetnje. Takođe, mogu se pojaviti bihevioralne promene u toku trajanja bolesti i/ili nakon operativnog tretmana tipova epilepsije rezistentnih na farmakoterapiju. Cilj ovog rada bio je da ukaže na to da neuropsihološka dijagnostika i neuropsihologija kao nauka daju veoma vredan doprinos dijagnostičkom procesu i da mogu poslužiti kao alat za ispitivanje lokalizacije i/ili lateralizacije oštećenja mozga, za određivanje težine kognitivnog deficita, kao i za praćenje bolesti i lečenja. Na taj način poboljšava se kvalitet i bezbednost tretmana obolelih od epilepsije, a doprinosi se i daljem otkrivanju neuropsiholoških komorbiditeta i njihovoj rehabilitaciji.

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*Ključne reči*: neuropsihološka procena, hirurgija epilepsije, kognitivna disfunkcija

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