Single Seizure and Cognition: Clinical and Translational Implications

Victor A. Aniol¹, Alla B. Guekht², Natalia V. Gulyaeva¹, ²

¹Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow, Russia
²Moscow Research and Clinical Center for Neuropsychiatry of the Healthcare Department, Moscow, Russia

nata_gul@pisem.net, nata_gul@yahoo.com

Abstract: Nowadays, there is no definite answer to the question whether a single seizure episode can influence cognitive functions. However, elucidating this issue has a great clinical significance, since adequate therapeutic interventions may be needed soon after the seizure occurrence if long-lasting cognitive impairments can be launched shortly after a seizure. The existing clinical observations in patients with new-onset epilepsy often imply the pre-existing brain pathology which may lead to both epileptogenesis and deterioration of mental functions. On the other hand, in some cases a positive correlation between seizure severity (frequency) and the degree of cognitive deterioration can be demonstrated suggesting that an effect of a single seizure episode may be negligible. In any case, objective difficulties of clinical investigations of seizure-induced cognitive impairments make the experimental studies on this issue highly actual, and some recent advance in this area suggests the existence of long-lasting cognitive effects of even a single seizure episode. Possible mechanisms and potential clinical significance of this phenomenon are discussed.

Keywords: seizure, single seizure episode, epilepsy, cognitive, hippocampus, neurogenesis

1. INTRODUCTION

Cognitive deficits are a well-known complication that often accompanies chronic epilepsy in humans [1, 2]. Neuropsychiatric problems are observed in 30-50% of patients with epilepsy [3]. Impairment of memory, primarily the short-term one, in association with epilepsy have been reported at least since the 1950-s when impairments in tactile learning and auditory perceptual tests have been documented [4]. Later, Loisseau et al. described impairments in verbal and nonverbal memory in a large group of patients with epilepsy [5]. In 1980-s a lot of data was collected, allowing to make some conclusions on the specificity of cognitive impairments depending on seizure type and localization of the focus [6]. Usually, generalized epilepsies are associated with attention deficits, while partial seizures, specifically those with a focus in the temporal lobe – with memory impairments. Moreover, according to the conventional point of view, localization of epileptic focus in the left hemisphere is associated with verbal memory impairment, whereas right-side localization is linked with nonverbal memory deterioration [7]. In addition, depending on the brain area involved in the propagation of epileptic activity, epilepsy may be accompanied by occurrence of auditory, olfactory, gustatory, somatic and visual hallucinatory phenomena [8].

Cognitive impairment is determined by factors directly associated with the epilepsy-related characteristics (age at onset, disease duration, duration and frequency of seizures, localization of epileptic focus and reasons for its formation, status epilepticus history), as well as antiepileptic therapy used [3,9-11]. Involvement of specific brain structures, severity and frequency of seizures, epileptic form EEG activity are associated with higher risk of cognitive impairment in patients with epilepsy. Aldenkamp et al. reported three specific types of cognitive disorders in epilepsy: the lack of memory, the lack of attention, and the violation of the "speed factor" - the slowness of information learning and skills acquisition [12]. Recently, other forms of cognitive impairments occurring in patients with epilepsy were described: transient epileptic amnesia, accelerated long-term forgetting, and remote memory impairment (See [13] for review).

Cognitive impairments were well documented in patients with temporal lobe epilepsy (TLE), however, epilepsies originating from other brain areas may also be accompanied by cognitive dysfunctions [14]. In contrast to TLE, the epilepsy arising from the frontal lobes demonstrates no
specific pattern of cognitive dysfunction. For example, patients with frontal lobe epilepsy demonstrate impaired motor coordination and response inhibition without any correlation with lesions visible on MRI [15]. As well, switching between tasks and social recognition (like humor appreciation and ability to detect emotional expression) was impaired in patients with frontal lobe epilepsy [16,17]. Sometimes, abnormalities of the long-term memory could also occur in frontal lobe epilepsy [18]. Possibly, there is no difference between TLE and frontal lobe epilepsy in associated memory impairments [19]. In contrast, occipital lobe epilepsy is characterized by decreased performance on visuospatial tasks, whereas patients with temporal epilepsy demonstrate impaired verbal long-term memory [20]. Patients with occipital lobe epilepsy often demonstrate visual hallucinations, however only in 1/3 of cases the underlying pathology may be visualized on MRI [21]. Patients with parietal lobe epilepsy exhibit a somatosensory aura with complex visual or auditory hallucinations and automatisms in case of temporolimbic propagation [22]. New-onset epilepsy accompanied by attention deficit is characterized by diffuse bilateral thinning of the cortex in the frontal, parietal and temporal lobes, with volume reductions in the brainstem and subcortical structures [23].

All this evidence, however, does not answer the question on the initial cause of epilepsy-related cognitive pathology. Indeed, memory or attention deficits and emotional changes may be the consequence of repeated seizure activity, as well as of the underlying brain pathology; additional complications may be induced by antiepileptic drugs, a number of them influencing the mental sphere [24]. In case if cognitive impairments develop independently of seizure occurrence and are determined by a pre-existing brain pathology, only etiotropic therapy could relieve both seizures and mental symptoms. On the other hand, if cognitive decline is caused by the epileptic activity itself, all measures should be taken for prevention of both seizure recurrence and forthcoming effect on cognition, using a specific therapy as early as possible. Thus, the main issue to be clarified is whether the seizure activity can lead to enduring cognitive impairments and which effect can be induced by just a single episode of seizures.

In this review we will focus on the existing data concerning long-lasting consequences of a single seizure. However, since such studies are quite rare, we have also included information about cognitive functions in patients with newly-diagnosed epilepsy before the start of antiepileptic treatment. We have taken into account only convulsive seizures, including partial, generalized seizures, or even status epilepticus. However, in most cases the generalized tonic clonic seizures are the most prominent and frequent feature of epilepsy syndromes. In fact, as demonstrated by CAROLE (“Coordination Active du Réseau Observatoire Longitudinal de l'Epilepsie”) study, the seizures most likely present as a first seizure are generalized (including secondarily generalized) tonic-clonic seizures [24,25]. In the first chapter of our study we have tried to give an overview of existing clinical observations of an influence of convulsive seizure per se on cognitive functions (Table). One group of data comprised several studies where non-epileptic patients who have presented a single episode of convulsive seizure due to pathologies of different origin were compared with those who didn't. Another group of studies assessed the cognitive functions in untreated patients with newly-diagnosed epilepsy. Validity of these studies for our objectives is compromised because in most of them no difference was made between patients with only one and several seizures; however, effects of rare seizure activity versus effects of long-lasting chronic epilepsy still could be elucidated. Finally, some information could be obtained from studies of cognitive effects of electrically-induced seizures in neuropsychiatric patients, but these data are less relevant for our purpose because of concomitant disease factor which can mask the effect of seizure per se. Though less valid for extrapolation to human pathology, animal studies can provide more detailed information and avoid the contaminating effect of chronic disease. Therefore, in the second part of our review we present the existing observations of deterioration of cognitive functions in widely applied animal models of epilepsy and single convulsive seizure. Finally, we briefly discuss the possible mechanisms which may underlie the enduring effect of a single seizure.

| Study                          | Pathology           | Groups and sample sizes | Tests          | Time of testing | Effect of seizure(s) |
|--------------------------------|---------------------|-------------------------|----------------|-----------------|----------------------|
| De Reuck et al., 2006 [12]     | ischemic stroke    | Seizure-free            | MMSE; mRS     | 2 years         | no effect            |
| Study | Diagnosis | Seizure-Free State | Assessment | Duration | Outcome |
|-------|-----------|--------------------|------------|----------|---------|
| Claassen et al., 2003 [13] | subarachnoid hemorrhage | 220; single convulsion 10 | telephone interview | 1 year | no effect |
| Strudwick et al., 2005 [14] | Type 1 diabetes, hypoglycemia | seizure-free 43; convulsion 41* | WISC III; CMS | 4 years | no effect |
| Witt, Helmstaedter, 2012 [20] | New-onset epilepsy | Healthy control 359; untreated new-onset epilepsy 247 | RAVLT | 1 year | decreased attention and/or verbal memory |
| Taylor et al., 2010 [22] | New-onset epilepsy | Healthy control 87; untreated new-onset epilepsy 155 | Neuropsychological test battery | 1 year | decreased psychomotor speed; decreased verbal and visual memory |
| Dunn et al., 1997 [26] | New-onset epilepsy | untreated new-onset epilepsy 40 | Child Behaviour Checklist | before the first seizure | behavior problems before the first seizure in 24% of children |
| Berg et al., 2005 [10] | New-onset epilepsy | Healthy control 613 | Interview | before the first seizure | educational problems before the first seizure in 15% of children |
| Hermann et al., 2006 [27] | New-onset epilepsy | Healthy control 50; untreated new-onset epilepsy 53 | Neuropsychological test battery | 1 year | Decreased intelligence, language, executive function and psychomotor speed |
| Velissaris et al., 2009 [28] | New-onset epilepsy | New-onset epilepsy 90 | AFSII; ABNAS; HADS | 1 month and 3 months | Increased depression and anxiety along with impaired cognitive functions |
| Aikia et al., 2001 [34] | New-onset epilepsy | Healthy control 46; untreated new-onset epilepsy 39 | WAIS | 0-19 years | impairments of verbal memory |
| Hermann et al., 2008 [29] | New-onset epilepsy | Healthy control 48; untreated new-onset epilepsy 52 | Neuropsychological test battery | 1 year | cognitive impairments only in the subgroup with concomitant neurological pathology |
| Sogawa et al., 2010 [32] | Epilepsy | epilepsy 258; sibling controls 78 | Neuropsychological test battery | 15 years | cognitive impairments depend on the number of seizures |

* An average of 2.5 seizure episodes. MMSE - Mini-Mental State Examination; mRS - Modified Rankin Scale; NEWQOL - Quality of Life in Newly Diagnosed Epilepsy Instrument; WAIS - Wechsler adult intelligence scale; HADS - Hospital Anxiety and Depression Scale; ABNAS - AB Neuropsychological Assessment Schedule; AFSII - Austin First Seizure Impact Interview; RAVLT - Rey Auditory Verbal Learning Test; CMS - Children Memory Scale; WISC-III - Wechsler Intelligence Scale for Children, third edition.

2. CLINICAL DATA

2.1. Non-Epileptic Seizures

In adults, effects of a single isolated unprovoked seizure have been evaluated in studies on focal symptomatic (or structural-metabolic) epilepsies in stroke, brain trauma, etc. De Reuck et al. compared 125 patients with late seizures after an ischemic stroke (66 patients with a single convulsion and 59 with recurrent seizures or epilepsy) with 125 patients without seizures after stroke (within 2
years) using MMSE (Mini-Mental State Examination) and mRS (modified Rankin Scale) protocols [26]. Recurrent seizures were associated with a higher mRS index as compared with patients without seizures, while the patients with only one seizure did not differ from the seizure-free group, indicating no influence of a single convolution on the mental state of stroke patients. Similar results were obtained by Claassen et al. who analyzed 247 cases of patients with subarachnoid hemorrhage survived for one year [27]. In 7% (17 patients) the hemorrhage was complicated by epilepsy (two or more seizures), in 4% (10 patients) only one episode of seizures occurred. The incidence of seizures was not accompanied by a decline in cognitive function for at least 12 months after the hemorrhage, although the method used for cognitive assessment (telephone interview) leaves the possibility for under-estimation of possible light impairments. However, these results were additionally supported by the data obtained in children by Strudwick et al., who compared children and adolescents with type I diabetes with reported seizures or coma induced by hypoglycemia with those without episodes of severe hypoglycemia [28]. A comprehensive battery of tests for learning and memory did not reveal any difference between the groups. Thus, a single convulsive episode in the context of pre-existing focal brain lesion does not seem to be associated with the development of cognitive impairments in patients. Similarly, in the rare cases of genetically determined diseases like Lafora disease and the syndrome of ring chromosome 20, the rapid development of cognitive impairment after seizure onset does not result from the first convulsion but rather is due to progression of the underlying disease inducing neuronal damage (like extensive neuronal accumulation of misfolded proteins caused by mutations in the genes encoding proteins laforin or malin in case of Lafora disease) [29,30].

A separate group of studies addresses the effects of electrically-induced seizures after electroconvulsive therapy (ECT) which is believed to be an effective approach to treat depression and some other psychiatric disorders. However, the main bulk of evidence concerning the effect of ECT seizures on cognition was obtained in patients suffering from depression, either comparing them to non-treated patients or with their own pre-treatment cognitive status. It was convincingly established (the results of numerous studies were reviewed by Calev et al.) that most prominent cognitive deterioration was observed in acute (up to several hours after the seizure) and early sub-acute period (up to several weeks after the seizure), whereas later (for several months after the ECT) no influence on cognition or even improved cognitive performance could be detected [31,32]. Strictly speaking, it is not easy to evaluate the effect of seizures on cognition in these examples since a relief of depression symptoms brought by ECT may mask effects of seizures per se.

2.2. New-Onset Epilepsy

One could expect to get evidence confirming or excluding possible effects of the first seizure on cognition from new-onset epilepsy studies. However, the information on possible cognitive impairments in these patients remains limited and clinical studies on this issue are methodologically difficult to perform [33]. In most studies, patients with new-onset epilepsy have experienced more than two seizures in a year preceding the cognitive assessment and are not suitable for the accurate assessment of the first seizure effects. It has been shown on a large group of patients that already after one-year history of epilepsy (with 4 or more seizures) patients demonstrate decreased attention (1/4), decreased memory (1/4), or both (1/4); while only half a of affected patients realized their impairments [34]. From a recent study in elderly patients with new-onset focal epilepsy before initiation of anti-epileptic treatment it was concluded that risk factors for cognitive impairment were neurological status and body mass index, rather than seizure frequency or severity and suggested that routine screening before treatment initiation is highly recommended in these patients [35].

Impaired verbal memory, visual memory, and increased reaction time were reported in patients with newly diagnosed epilepsy [36]. Hermann et al. have studied a group of 75 children (8-18 years) with newly diagnosed idiopathic epilepsy and compared it with a group of healthy children [37]. Questionnaire for Affective Disorders and Schizophrenia for children (K-SADS), as well as interviewing parents and school performance analysis were used to assess the preceding disorders. It has been found that attention deficit hyperactivity disorder (ADHD) is more common in children with epilepsy than in the group of healthy children (31% compared to 6%). In addition, the majority of children with newly diagnosed epilepsy debuted with ADHD even before the first convolution. Possibly it could be determined by pre-existing structural brain pathology appearing in altered volumes of the corpus callosum and whole brain white and/or gray matter tissue [38,39]. Similar results were obtained when evaluating behavioral problems before the first seizure and four months
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after it in a group of children aged 4 to 15 years, who demonstrated behavioral abnormalities before the seizures in 24% of cases [40]. The application of special educational programs in 613 children with newly diagnosed epilepsy was explored as a part of a large prospective study [24]. In 15% of children with idiopathic and cryptogenic epilepsy, a need for special education was noted even before the first convolution (in 7.3% of children with the first seizure in the first 5 years of life, 20% of children with a first seizure between 5 and 9 years old, and 25% of children with a first seizure over the age of 10 years). The academic performance and the results of neurophysiological examinations were compared in children (8-18 years) with newly diagnosed idiopathic epilepsy and healthy children. Despite the children with epilepsy demonstrated the signs of mild diffuse cognitive decline and deterioration of learning achievements in comparison with the control group, a portion of children with newly diagnosed epilepsy demonstrated learning problems even before the occurrence of the first seizure [41].

Velissaris et al. examined the presence of cognitive impairment and mood disorders in 90 patients with the first convolution at the age of 18 to 65 years one and three months after the seizure [42]. For subjective assessment of cognitive function by the patients a qualitative questionnaire Austin First Seizure Impact Interview (AFSII) and a semi-quantitative scale AB Neuropsychological Assessment Schedule (ABNAS) was used, while to assess the scale of emotional changes Hospital Anxiety and Depression Scale (HADS) was applied. The level of attention was examined objectively by a battery of computerized tasks. Both 1 month and 3 months after seizure, from 1/4 to 1/3 of patients complained for reduction of their cognitive functions, noting slow thinking, difficulty in remembering, forgetfulness, impaired concentration, and speech difficulties. These impairments were associated with increased depressive and anxiety indices, however, did not correlate with the level of attention. Patients with subsequent recurrent seizures showed more severe mood disorders and noted a greater cognitive decline not associated with the level of attention even before the appearance of repeated seizures. The authors suggested a leading role of emotional disorders in the development of cognitive decline in patients after first convulsions. Thus, cognitive impairments observed after the first seizures in the newly diagnosed epilepsy are closely related to emotional changes, and are not necessarily directly caused by the seizures since in some cases they precede the seizures onset. Emotional changes also often precede the clinical onset of epilepsy indicating the occurrence of independent parallel processes of motor manifestations of seizures and emotional disorders. Summarizing these observations, Rösche et al. focused on currently available data on the development of cognitive decline at an early stage of epileptogenesis both in genetically-induced and idiopathic epilepsy [33]. They suggested that increased depression and frequency of suicide attempts in adults often precede the onset of epilepsy, and in children behavioral disorders may occur before the first recognized seizure [33].

The occurrence of cognitive decline soon after the onset of epilepsy is often associated with organic brain pathology. Thus, Hermann et al. observed the dynamics of intellectual development in healthy children aged 8-18 years (n = 48) compared with matched age group of children with newly diagnosed epilepsy (n = 52) within two years after the epilepsy onset [43]. Mental development was assessed depending on the presence/absence of ADHD, educational achievements, as well as in different neuropsychological tests. The first two years of epilepsy were not accompanied by a significant decline in cognitive function in children without concomitant neurological pathology. If the epilepsy started on the background of concomitant neurological disorders, children showed significantly lower levels of cognitive development both at the beginning of the study and during the two-year observation period. Similarly, basing on the comparison of the data of Dutch epilepsy study with data received in other studies, Arts and Geerts concluded that the development of cognitive impairments in children immediately after the onset of epilepsy is rare and usually occurs only in clinical syndromes like Landau - Kleffner syndrome with continuous spikes and waves during sleep, West syndrome, Lennox - Gastaut syndrome, or Dravet syndrome, requiring an early start of an aggressive antiepileptic therapy [44]. This opinion is shared by Shinnar and Hauser who suggest that cognitive impairment after single seizures develops only in certain clinical syndromes and is associated with the development of the disease within this syndrome but not with observed convulsions per se [45]. Patients with TLE were most systematically investigated for brain pathology on MRI, and it is known that volumetric abnormalities, predominantly in form of atrophy, are evident both within and outside the primary epileptogenic region [46]. It has been found that subjects with TLE demonstrate diminished volumes of total gray and white matter on MRI and
increased volume of cerebrospinal fluid (CSF). Moreover, the CSF volume positively correlates with the impairments assessed by neuropsychological test battery [47]. Interestingly, not only total CSF volume, but also its contents correlate with neuronal damage in patients with epilepsy; such association was found for ubiquitin carboxy-terminal hydrolase, the enzyme elevated in patients with more frequent and prolonged seizures [48]. On the other hand, somatostatin level was decreased in the CSF of patients with epilepsy and did not correlate with psychological memory scores [49].

Cognitive impairments in patients with newly diagnosed epilepsy often correlate with seizure strength and frequency. Sagowa et al. presented the results of a long study of children with epilepsy and single seizure [50]. The data of neuropsychological testing, analysis of school performance and structured questionnaires showed that severity of cognitive impairment correlated positively with the number of seizures. In the group of children with single seizure, 28 % repeated year in the school, the group with 2 - 9 seizures represented 34 % of such children, and in the group with more than 10 seizures - 64 %. Indices of mental development in children with one seizure were higher than in children with epilepsy and did not differ significantly from the performance of their siblings controls. Similar results were obtained earlier by Abetz et al. in a group of 108 adult patients with newly diagnosed epilepsy, using a structured questionnaire NEWQOL: the severity of impairments of memory, reading skills, motor disturbances, poor concentration, and fatigue expression positively correlated with the frequency and severity of seizures [51].

Since the severity of seizure-related cognitive impairment in clinical studies depends on the frequency of seizures and their strength, it is difficult to reliably reveal an effect of a single seizure episode. However, longer duration of epilepsy does not necessarily mean a greater cognitive impairment. For example, verbal memory was already impaired in newly-diagnosed patients with epileptic focus in left temporal lobe even before the start of AED treatment, and these patients showed no deterioration at 5-year follow-up [52].

The controversy between the studies claiming the influence of seizure duration and strength on cognitive status and those which negate such influence could be explained by different study designs, methods applied, and heterogeneity of patient cohorts. The difficulties of clinical investigations of cognitive impairments related to seizures onset make the experimental studies on this issue highly actual.

3. Experimental Data

Impaired functions of learning and memory were reported in different animal models of acute and chronic seizures [53]. Two most widespread chemoconvulsants which are used to induce seizures in experiment, glutamate receptor agonist kainic acid and muscarinic acetylcholine receptor agonist pilocarpine, utilize a paradigm of a chronically altered epileptic brain. Indeed, both kainate and pilocarpine seizure models begin from a profound epileptic status which is later followed by spontaneous recurrent seizures. In these models, serious neuronal loss is observed in susceptible structures, namely in the CA3 area of the hippocampus, amygdala, and adjacent piriform and entorhinal cortex, a pattern very similar to that observed in human TLE. All these similarities to human epilepsy (pattern of neuronal loss and spontaneous seizures) made kainate and pilocarpine very suitable for experimental modeling of epilepsy; however, exactly the same features of these models are undesirable for investigation of effects of a single seizure.

The seizures elicited in rodents by kainic acid and NMDA resulted in long-term dysfunctions of memory and learning, demonstrated mainly in the spatial hippocampus-dependent tasks like Morris water maze test and radial arm maze [54-58]. Emotional memory was also affected according to impaired performance in the passive avoidance task, a test where an animal learns to avoid an environment in which an aversive stimulus was previously delivered [59]. Cognitive deterioration was evident several days after generalized seizures and lasted for up to 5 months [55,58,60]. Similar results indicating long-lasting impairment of learning and memory were received using pilocarpine-induced seizures [61-66]. These observations were additionally reinforced by the data obtained from such chronic epilepsy/epileptogenesis models like electric kindling or pentylenetetrazole (PTZ)-induced kindling (PTZK), models utilizing chronic administration of chemoconvulsant agent or repetitive electrical stimulation of epileptogenic structures like amygdala or hippocampus. Soon after the completion of PTZK rats demonstrated decreased shuttle-box performance and impaired learning in spatial tasks: radial-arm and water maze [67-76].
The most simple and widely utilized explanation of memory and learning impairments in these studies seems to be the development of neuronal damage to limbic structures, mainly the hippocampus [58]. Indeed, histological findings after kainic acid- and pilocarpine-induced seizures include profound neuronal damage in the hippocampus, amygdala, piriform and entorhinal cortex [58,77-80]. Similar to the above mentioned acute seizure models, cognitive dysfunction after PTZK was accompanied by neuronal degeneration in CA1, CA3 subfields and dentate gyrus (DG) of the hippocampus [72,81-83]. Moreover, protection against seizure-induced neuronal damage attenuated the subsequent cognitive deficits [72]. Since the severity of neuronal damage was strongly associated with number of seizures and their strength, the observations of neurodegeneration satisfactorily explained the development of cognitive decline in these seizure models on one hand, and related its development to the number and severity of seizures on the other [84,85]. It should be also noted that spontaneous recurrent seizures could be observed in pilocarpine, kainate, or kindling models, thus making these models irrelevant for analysis of the long-term effects of a single seizure.

Unlike other models of acute and chronic seizures, single episodes of PTZ-induced generalized clonic-tonic convulsion were shown not to induce neuronal loss in the hippocampus, and, therefore, for a long time this model was not regarded in a context of potential subsequent cognitive impairments [84-88]. However, Erdoğan et al. have demonstrated impaired fear-related memory in rats one and two weeks after PTZ-induced seizures [89]. Later, Assaf et al. further supported these findings by the demonstration of spatial and object memory deficits in mice that experienced episodes of PTZ-induced convulsions 3-5 weeks earlier [90]. Recently, we have performed a detailed long lasting behavioral study and demonstrated slowly developing impairments of short-term memory in rats after single PTZ-evoked seizure, appearing approximately 2 months after the seizure episode [91]. Thus, there is reliable experimental evidence indicating that cognitive impairments after PTZ-induced seizures may develop independently of major tissue damage.

4. POTENTIAL MECHANISMS OF FIRST SEIZURE EFFECTS ON COGNITIVE FUNCTION

If not neuronal cell loss, which cellular and molecular mechanisms can be responsible for cognitive function decline induced by a single seizure episode? Along with neuronal damage, seizures induce a number of other long-lasting microstructural changes in the neuronal circuitry; one of them is the altered hippocampal neurogenesis. The data on the influence of seizure activity on neurogenesis in the mature brain are rapidly growing. Increases in hippocampal cell proliferation have been reported after kainate- or pilocarpine-induced seizures [92-95]. Jiang et al. showed that increased proliferation was maintained for up to 14 days after seizures, gradually declining to the control level [96]. Parent et al. have demonstrated that increased neurogenesis after seizures might contribute to aberrant reorganization of hippocampal network; later this point of view was supported and further developed by other authors [97-99]. The time period from cell birth to incorporation of newly generated cells into the functional hippocampal circuits in the temporal profile of adult neurogenesis roughly corresponds to a delayed appearance of memory dysfunction in rodents [100,101]. Thus, altered hippocampal neurogenesis is one of the first candidate mechanisms for seizure induced slowly developing long-lasting cognitive impairments. This hypothesis was supported by the observations demonstrating that suppression of adult neurogenesis may improve cognitive function in seizure-experienced brain [57,102].

An important finding is that newly born neurons appearing shortly after status epilepticus and surviving during the time necessary for their functional integration into the neuronal circuit might demonstrate decreased excitability even in the absence of major morphological abnormalities [103]. In this case cognitive impairments could be explained by deteriorated passage of stimuli through the perforant pathway to the newly born dentate gyrus granule cells, which are currently regarded as key elements responsible for adaptation to novelty [104]. The main feature of animals experienced seizures may be not just the elevated number of neurons born after seizures but rather their qualitative abnormality: altered electrophysiological properties of survived newborn neurons. This concept corresponds with the data indicating that cognitive decline after seizures is accompanied by normal values of survived adult-born granule cells in the dentate gyrus of rats after a seizure episode [91]. It has been shown that neurons born short after seizures exhibit atypical spiny basal dendrites extending into the hilus of the dentate gyrus [57]. In addition, an ectopic hilar migration of granule cells generated after seizures is accompanied by atypical synchronization of their electric activity with CA3 pyramidal neurons [105]. Furthermore, extensive mossy fiber sprouting is characteristic for granule

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cells appeared after seizures [106]. Taken together, these alterations illustrate that long-lasting consequence of a single seizure is likely an abnormal integration of newly-generated neurons but not just an increased number of new neurons. Later, altered local circuits in turn may provoke both further seizure progression and memory impairments.

The neuroinflammation should be considered in the first place among potential causes for altered maturation of new-born neurons. This important process including an activation of microglial cells at the cellular level and elevated release of interleukins as the main molecular trigger takes place in the brain after seizures [107-109]. Indeed, interaction between inflammatory reactions in the brain and seizure development is a well-known phenomenon (see [110] for review). In some cases, epilepsy progression seems to be determined by an autoimmune response following a single breakdown of the blood-brain barrier [111]. On the other hand, generalized convulsions including those provoked by PTZ induce transient blood-brain barrier opening thus providing a risk for activation of neuroinflammatory processes in the brain [112].

The fate of newly generated cells in a long-term perspective may be also influenced by altered by a seizure episode local concentrations of neurotransmitters and neuromodulators like aspartate, glutamate, and GABA [76,113]. A single PTZ-induced convulsion induces increased expression of neuronal NO-synthase, NO production, or NO metabolites levels [114-116]. This may be particularly important since NO is a well-known regulator of proliferation and neurogenesis in the hippocampus [117-119] (see also [120] for review). Single neonatal seizure induces modifications in the distribution of superficial ionic transporters on the cell membrane of hippocampal neurons [121]. This may result in the changes in neuronal response to neurotransmitters and, as a result, in impaired hippocampal functioning.

Other possible mechanisms of seizure-induced decrease of memory and learning abilities may include impaired function of synaptic machinery proteins, slowly developing neuronal damage that could not be found at shorter time spans after the seizures, or establishment of aberrant synaptic connections in the dentate gyrus [122-124].

5. CONCLUSION

The existing clinical data related to potential effects of a single seizure "per se" are rare and do not allow to make a definite conclusion due to differences in the design of the studies, various pathologies accompanied by seizures (from symptomatic seizures to the first seizures in the context of epileptogenesis), different severity of underlying organic brain pathology. However, a brief review of clinical studies in this field does not exclude the possibility of negative impact of isolated seizure episode on the mental state of patients. On the other hand, limitations typical for clinical studies can be simply avoided using specifically designed animal models, and the results obtained in these models suggest that a single seizure episode can induce a slowly developing process of cognitive decline. The retarded development of cognitive decline in rodents (the changes can be reliably demonstrated after several months after the seizure episode) may explain additional important difficulties of respective clinical studies: seizure induced supposed cognitive decline in humans may be evident after many months. In addition, animal models are useful for investigations of molecular and cellular mechanisms underlying seizure-induced cognitive deficits.

In conclusion, it is noteworthy that long time period between the seizure and the manifestation of cognitive decline provides a time window for possible therapeutic interventions. Approaches to such therapy should be based on data of a thorough research on animal models. Elaboration of such “post-conditioning” treatments would provide a promising opportunity to prevent potential mental impairments in patients who have experienced seizure episode(s).

Supported by RFBR grant #16-04-01513 (VA)

ACKNOWLEDGEMENTS

Supported by RFBR grant #16-04-01513 (VA)
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