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Accelerated cognitive decline in a rodent model for temporal lobe epilepsy

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ABSTRACT

Objective: Cognitive impairment is frequently observed in patients with temporal lobe epilepsy. It is hypothesized that cumulative seizure exposure causes accelerated cognitive decline in patients with epilepsy. We investigated the influence of seizure frequency on cognitive decline in a rodent model for temporal lobe epilepsy.
Methods: Neurobehavioral assessment was performed before and after surgery, after the induction of self-sustaining limbic status epilepticus (SSLSE), and in the chronic phase in which rats experienced recurrent seizures. Furthermore, we assessed potential confounders of memory performance.
Results: Rats showed a deficit in spatial working memory after the induction of the SSLSE, which endured in the chronic phase. A progressive decline in recognition memory developed in SSLSE rats. Confounding factors were absent. Seizure frequency and also the severity of the status epilepticus were not correlated with the severity of cognitive deficits.
Significance: The effect of the seizure frequency on cognitive comorbidity in epilepsy has long been debated, possibly because of confounders such as antiepileptic medication and the heterogeneity of epileptic etiologies. In an animal model of temporal lobe epilepsy, we showed that a decrease in spatial working memory does not relate to the seizure frequency. This suggests for other mechanisms are responsible for memory decline and potentially a common pathophysiology of cognitive deterioration and the occurrence and development of epileptic seizures. Identifying this common denominator will allow development of more targeted interventions treating cognitive decline in patients with epilepsy. The treatment of interictal symptoms will increase the quality of life of many patients with epilepsy.

1. Introduction

Patients with temporal lobe epilepsy (TLE) often experience neurobehavioral comorbidities such as cognitive dysfunction [1]; patients with epilepsy show long-term problems in cognitive areas such as attention, memory, mental speed, and language, as well as executive and social functions [2] that may be present in up to 75% of newly diagnosed patients with epilepsy. Contrary to sporadic seizure and their associated postictal consequences, cognitive comorbidities persist during the majority of the patients' lives. Cognitive functioning is one of the major factors determining the quality of life of patients with epilepsy [3].

Until now, there are different theories regarding the question why patients experience cognitive symptoms. One theory is that epilepsy is a neurodegenerative disease characterized by progressive cognitive decline due to seizures [4]. Clinical studies on the effect of repetitive seizures are inconclusive. Some show a deteriorating effect on cognitive functioning [5–7], yet others were unable to replicate these observations [8–11].

Specific characteristics in the electroencephalogram (EEG), such as increased slow wave activity and the presence of interictal epileptiform discharges, may predict memory decline [12–14]. Furthermore, the use of antiepileptic drugs and particularly polytherapy may contribute to cognitive deficits in patients with epilepsy (for a review, see: Eddy,

Abbreviations: D2, discrimination index; DNMTP, delayed nonmatching to position; EEG, electroencephalogram; EZM, elevated zero maze; OF, open field; ORT, object recognition task; SI, sensitivity index; SSLSE, Self-sustaining limbic status epilepticus; TLE, temporal lobe epilepsy.

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Rickards [15]). Medication could influence cognitive deficits either directly or indirectly by causing i.e., for example, sleepiness, which in turn, influences concentration.

The neuropathology of TLE is located in an area that is functionally involved in memory processing. Cognitive decline in epilepsy may therefore originate from the same anatomical structures and even from the same pathology. In line with this theory is the hypothesis that TLE is a dementing disease, i.e., seizures accelerate brain aging and age-related memory loss [16].

It is difficult to assess the contribution of single determinants of cognitive decline in clinical epilepsy studies because of the heterogeneity of patient characteristics and the multitude of potential contributing factors. At this point, we lack well defined, clinical studies controlling for differences in seizure frequency and severity. We therefore aimed at investigating cognitive decline in a rodent model for TLE, namely the self-sustaining limbic status epilepticus (SSLSE) model, and hypothesized that cognitive deterioration is accelerated in epileptic animals compared with that in controls without epilepsy. We tested animals longitudinally (Fig. 1) before and during epileptogenesis and in the chronic, recurrent seizure phase and correlated outcomes with seizure frequency. In addition, we examined the occurrence of anxiety, depression, and motor anomalies because these are known comorbidities of epilepsy and could act as potential confounders for memory outcomes.

2. Materials and methods

2.1. Subjects

Three-week-old, male Sprague Dawley rats (Charles River, Saint-Germain-Nuelles, France) were housed individually with a reversed 12-hour light–dark cycle (7 a.m.–7 p.m. lights off, radio on) in Makrolon™ (Eurostandard type III, Tecniplast) cages in a temperature-controlled room (20 ± 2 °C). All experimental procedures took place during the active phase of the day. Except for training and testing in the operant chamber, animals had *ad libitum* access to food and water. Experiments were approved by the local animal ethics committee and were in compliance with governmental and international guidelines and laws. Animals were habituated to the experimenter by daily handling before the start of the experiment.

2.2. Induction of self-sustaining limbic status epilepticus

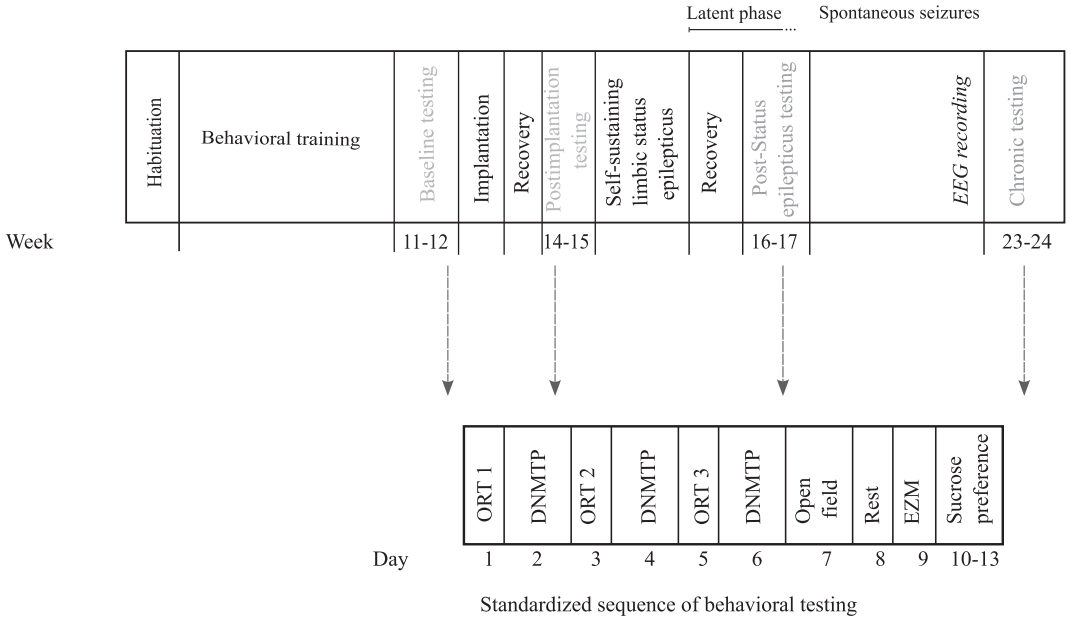
2.2.1. Implantation

At the age of 13 weeks (350–400 g), a custom-made, bipolar, recording and stimulation electrode (Department of Instrument Development, Engineering and Evaluation of Maastricht University and Prof. Y. Temel, Maastricht, The Netherlands, [17]) was stereotactically implanted in the left, ventral CA3 region of the hippocampus (coordinates relative to Bregma: 4.7 mm posteriorly, 5.0 mm laterally, and 5.0 mm ventrally, [18] using a rat stereotact (Dual Manipulator Lab Standard Sterotact, Stoelting Inc., Wood Dale, Ill, USA)). In addition, a reference electrode was fixed on top of the skull in front of Bregma. The construct was anchored with four stainless-steel screws attached to the skull with dental acrylic (Paladur, Heraeus Kulzer GmbH, Hanau, Germany).

The surgical procedure was performed under isoflurane anesthesia (5% for induction and 2.5% for maintenance; IsoFlo®, Abbott Laboratories Ltd, Berkshire, Great Britain). In addition, rats received 0.1 mg/kg buprenorphine hydrochloride s.c. (Temgesic, Schering-Plough Inc., Amstelveen, The Netherlands) 30 min before implantation to reduce perioperative pain. A total of 34 rats were implanted.

2.2.2. Continuous hippocampal stimulation

For the induction of SSLSE 18 rats were randomly assigned to undergo continuous hippocampal stimulation (see Lothman, Bertram [19]). During 1 h, animals were stimulated at 50 Hz (400 μA peak-to-peak, 1-ms biphasic square waves) in 10-s trains that were delivered



Abbreviations:
ORT: Object Recognition task
DNMTP: Delayed non-matching to position task in the operant chamber
EZM: Elevated zero maze

Fig. 1. Experimental timeline of neurobehavioral testing.