A new method to model electroconvulsive therapy in rats with increased construct validity and enhanced translational value

Wiebke Theilmann a, c, Wolfgang Löschera, c, Katarzyna Socala,1, Helge Frielingb, c, Stefan Bleichb, c, Claudia Brandta, c, *

a Department of Pharmacology, Toxicology, and Pharmacy, University of Veterinary Medicine, Hannover, Germany
b Department of Psychiatry, Social Psychiatry and Psychotherapy, Medical School Hannover, Germany
c Center for Systems Neuroscience, Hannover, Germany

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ABSTRACT

Electroconvulsive therapy is the most effective therapy for major depressive disorder (MDD). The remission rate is above 50% in previously pharmacoresistant patients but the mechanisms of action are not fully understood. Electroconvulsive stimulation (ECS) in rodents mimics antidepressant electroconvulsive therapy (ECT) in humans and is widely used to investigate the underlying mechanisms of ECT. For the translational value of findings in animal models it is essential to establish models with the highest construct, face and predictive validity possible. The commonly used model for ECT in rodents does not meet the demand for high construct validity. For ECT, cortical surface electrodes are used to induce therapeutic seizures whereas ECS in rodents is exclusively performed by auricular or corneal electrodes. However, the stimulation site has a major impact on the type and spread of the induced seizure activity and its antidepressant effect. We propose a method in which ECS is performed by screw electrodes placed above the motor cortex of rats to closely simulate the clinical situation and thereby increase the construct validity of the model. Cortical ECS in rats induced reliably seizures comparable to human ECT. Cortical ECS was more effective than auricular ECS to reduce immobility in the forced swim test. Importantly, auricular stimulation had a negative influence on the general health condition of the rats with signs of fear during the stimulation sessions. These results suggest that auricular ECS in rats is not a suitable ECT model. Cortical ECS in rats promises to be a valid method to mimic ECT.

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1. Introduction

Electroconvulsive therapy (ECT) is the most effective therapy for pharmacoresistant major depressive disorder (MDD) (The UK ECT Review group, 2003; Heijnen et al., 2010). The use of ECT has constantly increased over the last decade but still the mechanisms of action are not fully understood. Clarification of the underlying mechanism leading to the therapeutic effect of ECT could significantly contribute to the understanding of the pathogenesis of MDD and the development of improved treatment strategies. Although new possibilities open up for non-invasive investigations in humans with improving imaging techniques many questions can only be addressed in animal models using invasive methods. A prerequisite to obtain data from animal research with high translational value is the validity of the model. Already in 1969, McKinney and Bunney proposed validating criteria to evaluate the translational value of models for mental diseases. Willner (1984) applied these criteria on animal models of depression which lead to an ongoing effort to improve such models for the highest validity possible. Electroconvulsive stimulations (ECS) in rats or mice are used to mimic ECT. Although ECS is a model for a treatment method and not a model for depression it is not less important to fulfill the validating criteria to obtain a high translational value. So far, experimental research is based almost exclusively on models in which rodents are treated with electroconvulsive stimulations (ECS) via auricular or, less often, corneal electrodes. In the clinical ECT setting the electrical stimulation is performed via cortical surface electrodes. It is well known that the electrode placement has a significant impact on the consequences of the induced seizure activity with respect to various parameters such as seizure type, pharmacological responsiveness and biochemical changes (e.g. Browning and Nelson, 1985; Isaak...
et al., 1985; Ferraro et al., 1990; Löscher et al., 1991). Therefore, it is
more than likely that the different placement of stimulation elec-

trodes in humans and rodents has a significant impact on the
translational value of the results because the construct validity of
ECS in rodents is not given. The aim of the present study is to pro-
appe an ECS method in rats using cortical screw electrodes placed
above the frontal cortex which simulates the bifrontal ECT in
humans. The cortical ECS was compared with the traditional
auricular ECS with respect to seizure parameters and acute and
chronic effects on well being and behaviour of the rats.

2. Material and methods

2.1. Animals

Male Wistar rats (9 weeks) were purchased from Janvier (Saint
Berthevin, France) and housed in groups under controlled envi-
ronmental conditions.

All rats were adapted to the laboratory and habituated to
handling for at least one week before starting the experiments.
Experiments were done in compliance with the European Com-
munities Council Directive of 24 November 1986 (86/609/EEC) and
were approved by the animal subjects review board of our insti-
tution. All efforts were made to minimize pain or discomfort of
the animals used.

2.2. Implantation of screw electrodes

Thirty three rats were anaesthetized with isoflurane (1.5–3.0%)
and local with tetracain and bupivacain. Buprenorphine was used
for postoperative analgesia (0.045 mg/kg i.m., Temgesic®, Essex
Pharma GmbH). Electrodes were placed bilaterally above the
frontal cortex (AP, +2.7 mm; L, ±4.0 mm) according to the atlas of
Paxinos and Watson (2007). A reference electrode was placed
above the right parietal cortex (AP, −2.0 mm; L, −2.0 mm) to allow
EEG recordings. Screw electrodes were fixed with one and a half
turn in the skull, so that the tip of the screw was right above the
cortex without touching it. Recovery time after surgery was 2
weeks.

2.3. Electroconvulsive stimulation

Implanted rats were randomly assigned to treatment groups,
i.e., auricular stimulation (n = 10), cortical stimulation (n = 12), or
sham stimulation (n = 11). Rats without surgery served as naive
controls (n = 9).

ECS was delivered once daily over five days. For auricular ECS
the stimulus was applied via ear-clip electrodes using the ECT Unit
57800 device (Ugo Basile, Comerio, Italy). One of the two electrodes
is attached to one ear and the other one to the other ear. Cortical
ECS was performed via the two frontal screw electrodes using the
A310 Accupulser (World Precision Instruments, Sarasota, USA). The
stimulus consisted of bidirectionally applied square wave pulses. In
pilot studies we determined stimulus parameters that induce
generalized seizures of at least 15 s duration in the EEG in all rats.
Parameters for auricular ECS stated in the literature vary between
studies. Frequency and pulse width were chosen according to
literature data (Biedermann et al., 2012; Newton et al., 2003).
Stimulus duration and current intensity were validated in pre-
liminary experiments. We started with stimulus duration of 0.2 s
and 50 mA current intensity corresponding to a charge of 1.8 mC.
With these parameters none of the rats developed a seizure.
We then stepwise increased current intensity to 70 mA without seizure
induction but the rats exhibited hyperlocomotion after the stim-
ulus. Next we increased stimulus duration to 0.5 s and stepwise
increased current intensity from 40 to 70 mA. All rats developed
generalized seizures when stimulated with 70 mA. Therefore
auricular ECS stimulation parameters used in this study were
0.9 ms pulse-width, 100 pulses/s, 0.5 s duration, 70–82 mA. This
corresponds to a charge of 6.3–7.4 mC. For cortical ECS, current
intensity was stepwise increased from 2.5 to 7.0 mA in preliminary
experiments. The other stimulus parameters were chosen on the
basis of clinical data (Department of Psychiatry, Medical School
Hannover, Germany). Parameters for cortical ECS were 1 ms pulse-
width, 100 pulses/s, 1 s duration, 7–10 mA which corresponds to a
charge of 1.4–2.0 mC. The charge was calculated using the formula:
charge = pulse width [s] × (frequency [Hz] × 2) × stimulus duration
[sec] × current intensity [mA] (Andrade et al., 2002).

For EEG recordings a one-channel amplifier (ADInstruments Ltd.,
Sydney, Australia) and an analogue-digital converter (Power-
Lab/800S, ADInstruments) were used. The duration of the seizure in
the EEG and the seizure type were determined. Control and sham
animals underwent the same handling procedure without electrical
stimulation.

2.4. Determination of the effects of ECS

Body weight was determined before and after ECS sessions as a
measure for the general condition. A reduction in body weight
points to a reduced well-being of the rats. Ultrasonic vocalisation
was recorded via Avisoft recorder (version 3.4.2, Avisoft Bio-
acoustic, Berlin, Germany) for 5 min during most of the ECS ses-

tions, starting 1 min before stimulation. Number and duration of
22 kHz-calls which are associated with distress and fear of rats
duration: >20 ms; frequency: 18–32 kHz (Portfors, 2007) were
analysed.

The forced swim test (FST) was performed according to Por-
solt et al. (1977) to evaluate the behavioural effect of ECS. Rodents
were individually placed in a transparent plexiglas cylinder (50 cm
depth, 25 cm diameter) containing 20 cm of water (25 ± 1 °C). Two
days before beginning of the ECS sessions a 15 min pre-test trial
was performed followed by a 5 min test trial 24 h later. The restet
trial (5 min) was performed 48 h after the last of a series of 5 daily
ECS. Behaviour was recorded with an HD-camcorder (Canon Legria
HFS21) and the immobility time (making only those movements
necessary to keep the head above the water) for each rat during
the first 5 min of the pre-test, the test and the restet trial was
quantified. The immobility time of each rat during the trials was
quantified.

To ensure that seizures did not have an effect on mobility of the
rats per se, locomotor activity was measured 24 h after the last
stimulation in a round open field made of black PVC (diameter
80 cm, height 80 cm). Distance moved and velocity was recorded
for 5 min and analysed with EthoVision®XT7 software (Noldus
Information Technology, Wagening, the Netherlands).

For the performance and analysis of the forced swim and open
field test and for determination of body weights the experimenter
was blinded to the treatment groups. The analysis of seizure
duration in the EEG and ultrasonic vocalization was also performed
blinded. For evaluating the seizure type the experimenter was
aware of the stimulation method used.

2.5. Statistical analyses

Depending on whether data were normally distributed or not,
either parametric or nonparametric tests were used for statistical
evaluation. In case of more than two groups, analysis of variance
(ANOVA) with post hoc testing was used. Fisher’s exact test was
used to compare the occurrence of 22 kHz-calls during ECS. All
statistical analyses were performed with the Prism 5 software from
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