HHS Public Access

Author manuscript

Conf Proc IEEE Eng Med Biol Soc. Author manuscript; available in PMC 2019 February 18.

Published in final edited form as:

Conf Proc IEEE Eng Med Biol Soc. 2018 July ; 2018: 5422–5425. doi:10.1109/EMBC.2018.8513686.

A Novel Modular Headmount Design for non-invasive Scalp EEG Recordings in Awake Animal Models*

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Abstract

We have designed and developed a novel, non-invasive modular headmount to be used for awake animal scalp electroencephalography (EEG). The design is based on a developing rat that will accommodate rapid head growth. Desired characteristics include non-invasiveness, adjustable quantity and positioning, light weight, and tolerability by the animal. Axial Dependent Modular Electrode Mount (ADMEM), as designed here, addresses the aforementioned constraints by using light-weight and adjustable materials. The initial prototype of ADMEM has been tested in vivo with rat pups, using the open field test to assess for stress and anxiety at two post-installation time-points: one day after ADMEM installation (acute time-point) and four days after ADMEM

*Research supported by NIH grant R01NS27544, funding from UCLA's Capstone Initiative, and UCLA Brain Injury Research Center (BIRC).

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installation (sub-acute time-point). There was no significant difference in normal developmental weight gain between Control and ADMEM rat groups. Although no significant difference was found in the level of anxiety between groups at the acute time-point, the ADMEM group spent significantly less time in the center of the open Held test, suggesting higher anxiety. The test also showed no difference in the measured traveled distances between Control and ADMEM groups on either time-points.

I. Introduction

Scalp Electroencephalography (EEG) has shown to be a very effective technique for studying neurological processes underlying brain electrical activity. Non-invasive probing of brain electrical activity at a very high temporal resolution is a key advantage in using scalp EEG for studying neurological disorders [1–4]. Scalp EEGs have largely been limited to diagnostic applications in clinical settings, but more recently have gained attention for Brain Computer Interface (BCI) and virtual reality-based research as well as development of neurorehabilitation and assistive technologies [5–7].

Despite the growth of non-invasive EEG solutions in clinical settings [8], awake EEG in pre-clinical settings is mostly dominated by invasive solutions such as the use of intra-cortical implantable electrodes [9], which require restraint, surgery and tethering to a recording device [10],[11]. Awake EEG recording in small animal models requires invasive surgical procedures for electrode grid placements [12], or screw placement for EEG cap fixation [13].

Furthermore, the fast-paced growth-rate of small animals such as rats during the early stages of brain maturation has not been properly considered [14],[15]. The use of anesthesia/analgesic compounds for brain activity recording in animal models has shown to challenge a direct interpretation of EEG measurements [16–18]. Long sessions of training and possible behavioral alterations resulting from the use of current EEG technology are among the barriers to obtain recordings from awake animals [19].

This study introduces a novel design, hereon referred to as the Axial Dependent Modular Electrode Mount (ADMEM) system, which forms a non-invasive and modular electrode mounting solution. This device allows EEG technology to be utilized for awake, chronic recording of brain electrical activity in a developmental small animal model. Section II describes the design objectives and constraints, as well as the architecture of the proposed ADMEM solution. Section III demonstrates tests for the practical utilization of ADMEM in the developing rat, followed by discussion and concluding remarks.

II. AXIAL DEPENDENT MODULAR ELECTRODES MOUNT

A. Design objective and constraints

The design objective was specified to provide pre-clinical researchers with a non-invasive electrode mounting solution for chronic scalp EEG recording in a developing rat. An additional design challenge was the rapid head growth that occurs during brain maturation. Accommodations for this head growth included a possible increase in the number of

recording electrodes, as well as adjustments in electrode locations. To obtain reliable scalp EEG recording, electrodes must maintain solid contact with the scalp. Priority in the constraint set was given to the animals' safety and comfort by using a non-toxic, flexible material that minimized risk of injury or abrasion. Other considerations include reducing the weight of the ADMEM integrated with a recording system to prevent animal discomfort and any behavioral confounds.

B. ADMEM system architecture

A three-dimensional (3D) architecture of the ADMEM system is depicted in Figure 1. The outer frame is mounted on the scalp and seemed with silicone glue and dental acrylic. Each hexagonal electrode module is designed to house miniaturized EEG electrodes.

A plastic sliding bar is used as a flexible arm to secure the electrode holders in location. The sliding bar is also utilized as a base for securing the electrode module at specific locations via plastic screws. The elastic sliding bar was included to satisfy the need for potential re-adjustment of electrode locations as the animal grew. The sliding bar allows the electrode module to move almost to any position within the frame along the bar. The overall dimension shown in Figure 1 were chosen based on the measurements performed on rat pups in the age range of 17 to 25 postnatal days.

Three-dimensional drawing of the design was initially created using Autodesk Fusion 360 (www.autodesk.com). The first prototype was 3D printed out of thermoplastic polyurethane (TPU) using a fused deposition modeling (FDM) 3D printer (Luzbot Taz 6). TPU was chosen for its material properties, which satisfy the design constraints. It has a 60 Shore A hardness rating, making the device flexible enough to conform to the shape of the rat scalp surface, but durable enough to withstand the stress induced by the rat grooming behavior. Studies done with TPU polymers confirm that its byproducts are nontoxic, with one study in particular specifically testing the effect of TPU on Sprague Dawley rats [20–23]. Furthermore, TPU is a widely accessible material for 3D printing purposes, making the mount inexpensive to manufacture.

III. IN-VIVO EVALUATION OF ADMEM SYSTEM

Bio-compatibility and performance of the ADMEM system were evaluated on a group of male, Sprague Dawley (SD) rat pups (postnatal age 21 days, body weight 624.63 g; Charles River, MD). Animals were randomized into ADMEM and control groups (n=5/group). All procedures performed were reviewed and approved by the University of California Los Angeles (UCLA) Chancellor's Animal Research Committee, and were in conformity with the National Institutes of Health (NIH) Guide for Care and Use of Laboratory Animals [24]. Animals were maintained on a 12-h light/dark cycle with food and water given *ad libitum*. All rats were anesthetized with isoflurane (induction: 3-4%; maintenance: 2.5-3% vaporized in oxygen flowing at 0.61/min), maintained at 37°C with a homeostatic temperature-controlled blanket, and monitored for respiration, muscular relaxation and toe pinch response. After the head was shaved, all rats were immobilized in a stereotaxic surgical frame, and the mounting site on the skin was then prepared using aseptic technique, including three alternating preparations with betadine and alcohol. The mount prototype was

mounted on the animals from ADMEM group. All rats were then transferred to a temperature-controlled recovery enviromnent to reach a normal, awake state before being returned to their home cage. All animals were monitored daily for their weight, activity level, and scalp condition under the mount. To assess possible anxiety and stress induced by the mount, an open field activity test was conducted one day after the ADMEM installation.

The open field test allows evaluation of anxiety and locomotor behavior [25]. The apparatus, shown in Figure 2 (a), is a rectangular box (dimensions 50.8 centimeters length, 33.6 centimeters width, and 32.6 centimeters height). During the test, each animal was placed on the starting point, centered and facing the wall (the upper one in relation to the recording camera mounted on the ceiling and centered to the field), and was video recorded while freely exploring the test apparatus for five minutes. The test measures spontaneous locomotor activity in different areas of the arena. Since rats tend to spend more time near the edges of open areas, they are expected to spend lower percentages of time and distance traveled within the central region of the apparatus, defined as the middle cell when the arena area is divided by a 3×3 grid of cells. Video processing was completed in MATLAB R2016b (www.mathworks.com) to calculate the percentage of time in the center, and the total distance traveled. A heat map was also calculated for each group for mean time spent at each location. We studied two time-points over a 4-day period: an acute time-point at postnatal day (PND) 22 and a sub-acute time-point at PND 26.

IV. RESULTS

Animal from both Control and ADMEM groups showed a very similar rate of weight gain (1.07±0.00% and 1.07±0.01% of prior days weight for Control and ADMEM groups, respectively). The group weight changes are shown in Figure 2. (d). The similarity of trends demonstrates that ADMEM does not interfere with nutritional intake. Groups representations of open field test heat maps for both PND 22 and PND 26 test days are shown in Figure 2. (b)

Visual inspection of the maps reveals that both groups of animals spend a greater percentage of their time exploring the corners and wall-side pathways. Estimation of total traveled distances, a representation of locomotor behavior, did not reveal any effect for the mount. The percent of time spent in the center was not different between ADMEM and Control groups on PND 22 test day. However, the ADMEM group of animals showed a reduced preference for exploring the central region when compared to the Control group for PND 26 test day. The results are promising for the use of ADMEM for non-invasive scalp EEG recording in awake animals. In particular, we observed no obvious signs of distress and anxiety in the sub-acute stage after mounting ADMEM system. However, the late-induced anxiety raises a potential confound that needs to be fully addressed on the next version of the ADMEM prototype for chronic recording.

V. Conclusion

Our proof of concept prototype contains design features specifically tailored to the study of juvenile rats. The modular feature of ADMEM provides for flexibility in electrode

placement because researchers can shift modules as necessary to target shifting areas of study during rat development. The material used in the design of ADMEM, TPU, provides safe, adjustable and comfortable solution for the non-invasive monitoring of brain electrical activity for developing animal models. It also is compatible with magnetic resonance imaging [26]. This material property can be capitalized on in future studies by incorporating ADMEM with wireless circuitry for the purpose of simultaneous fMRI and EEG recordings. Another alternative to this approach is to include radiofrequency coils with ADMEM. A statistically significant difference between ADMEM and control groups in the amount of time spent in the center of the open field on was not observed on PND 22 but was observed on PND 26, suggesting the presence of late-induced anxiety. Since the current ADMEM prototype covers the rodent extensively, it could act to prevent head grooming, an innate body care behavior instrumental in rodent stress coping and de-arousal [27]. Reducing the size of the ADMEM as well as making certain parts removable to expose certain parts of the rat head can potentially mitigate this late-induced anxiety. Other future directions include reduction of mount size and integration with EEG circuitry and electrodes.

Revealing characteristics of electrical signals in the brain is critically important since it will directly lead to a broader understanding of how the brain functions as well as clinical applications for patients with neurological disorders. Our headmount, when fitted with appropriate recording circuitry as well as electrodes, could aid researchers in conducting comprehensive studies to provide impactful insights and improved treatments for neurological disorders.

Acknowledgment

The authors would like to acknowledge the support provided by UCLA Department of Bioengineering.

VII. References

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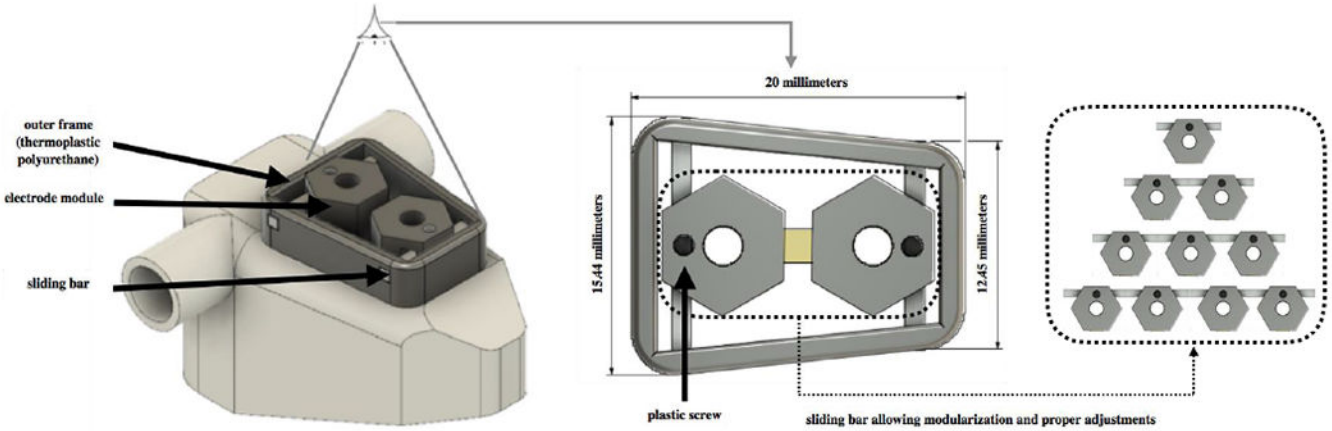

Figure 1.

Three dimensional architecture of Axial Dependent Modular Electrode Mount (ADMEM) system, overlaid on a 3D model of rat head. Thermoplastic polyurethane (TPU) is used for printing the design. Inclusion of sliding bar allows modularization as well as proper adjustment of electrode locations within the frame.

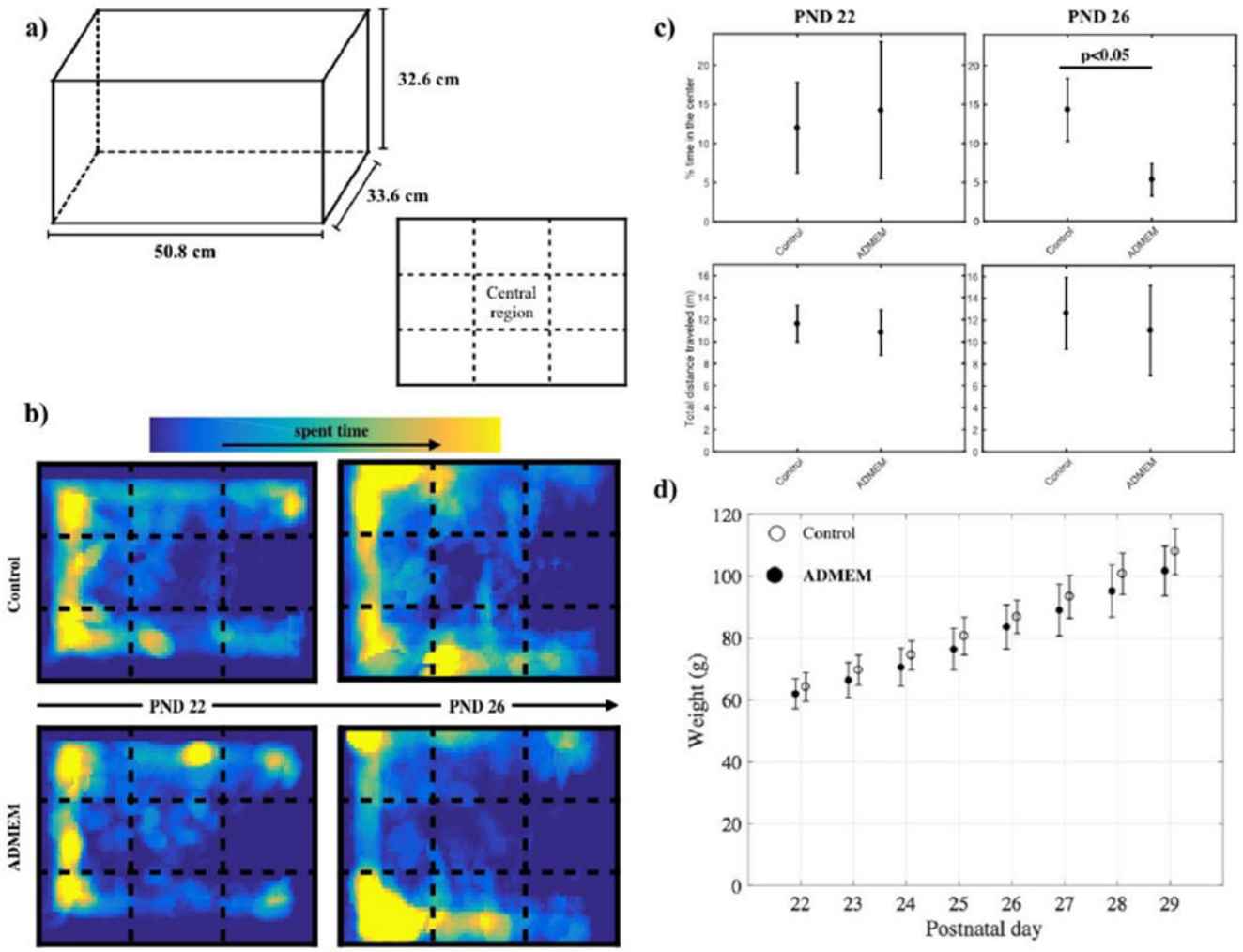

Figure 2.

(a) The dimensions of the open field test apparatus are shown. The field is divided into 9 sub-fields, and the time spent in each field is recorded. (b) Open field test results for PND 22 and PND 26: Group representative heat maps for Control and ADMEM group, along with (c) bar graphs (mean and standard deviation) representing group-wise percent time spent in the center quantification across both Control and ADMEM groups for test days, and group-wise measured total distance traveled for Control and ADMEM groups. (d) Control and ADMEM group trend of weight changes on PND 22-29.