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Review

Animal models of transcranial direct current stimulation: Methods and mechanisms

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HIGHLIGHTS

- We provide a comprehensive description of methodology for studying cellular mechanisms of tDCS.
- *In vivo* and *in vitro* tDCS animal studies are contextualized by examining experimental methodology.
- We discuss clinical tDCS at single cell, synaptic, and network levels from studies of animal tDCS.

ABSTRACT

The objective of this review is to summarize the contribution of animal research using direct current stimulation (DCS) to our understanding of the physiological effects of transcranial direct current stimulation (tDCS). We comprehensively address experimental methodology in animal studies, broadly classified as: (1) transcranial stimulation; (2) direct cortical stimulation *in vivo* and (3) *in vitro* models. In each case advantages and disadvantages for translational research are discussed including dose translation and the overarching "quasi-uniform" assumption, which underpins translational relevance in all animal models of tDCS. Terminology such as anode, cathode, inward current, outward current, current density, electric field, and uniform are defined. Though we put key animal experiments spanning decades in perspective, our goal is not simply an exhaustive cataloging of relevant animal studies, but rather to put them in context of ongoing efforts to improve tDCS. Cellular targets, including excitatory neuronal somas, dendrites, axons, interneurons, glial cells, and endothelial cells are considered. We emphasize neurons are always depolarized and hyperpolarized such that effects of DCS on neuronal excitability can only be evaluated within subcellular regions of the neuron. Findings from animal studies on the effects of DCS on plasticity (LTP/LTD) and network oscillations are reviewed extensively. Any endogenous phenomena dependent on membrane potential changes are, in theory, susceptible to modulation by DCS. The relevance of morphological changes (galvanotropy) to tDCS is also considered, as we suggest microscopic migration of axon terminals or dendritic spines may be relevant during tDCS. A majority of clinical studies using tDCS employ a simplistic dose strategy where excitability is singularly increased or decreased under the anode and cathode, respectively. We discuss how this strategy, itself based on classic animal studies, cannot account for the complexity of normal and pathological brain function, and how recent studies have already indicated more sophisticated approaches are necessary. One tDCS theory regarding "functional targeting" suggests the specificity of tDCS effects are possible by modulating ongoing function (plasticity). Use of animal models of disease are summarized including pain, movement disorders, stroke, and epilepsy.

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Contents

1. Meaningful animal studies of tDCS

This review is an update, with permission, of a previously published work (Bikson et al., 2012).

The basic motivation for tDCS research using animals is similar to other translational medical research efforts: to allow rapid and risk free screening of stimulation protocols in research and clinical settings, and to address the mechanisms of tDCS with the ultimate goal of informing clinical efficacy and safety of tDCS. To have a meaningful relevance for clinical tDCS, animal studies must be designed with consideration for: (1) correctly emulating the delivery of DCS into the brain; and (2) measuring responses which can be used to draw clinically relevant inferences. Before reviewing the main insights drawn from animal studies, we outline the basis for translational animal research on tDCS, as well as their limitations.

What is the role of translational animal models of tDCS within the broader context of tDCS science and clinical application? Like any model, using DCS on animals is intended to reproduce some relevant features for human applications with the goal of: (1) retrospectively providing a mechanistic explanation for findings in human; and (2) prospectively informing rational effort to optimize tDCS. In these senses the need for an animal model is evident given the current state of understanding of tDCS, including a highly limited understanding of how to customize tDCS for any given application. The parameter space in designing tDCS is large, spanning dose selection (electrode montage, current intensity, duration), potential use of biomarkers to titrate and customize dose, subject selection, and pairing of tDCS with adjunct interventions such as cognitive training or rehabilitation. It is impractical to test this parameter space comprehensively in human. Therefore, animal models are intended to guide human research by informing how improved protocols are discovered.

In addition to an exhaustive iterative search of published papers (forward and backward citations, prior review), candidate papers were identified through a PubMed search including key words: *in vivo*, *in vitro*, animal model, tDCS, direct current, polarizing current, rodent, rat, cat, ferret, rabbit.

1.1. Stimulators, nomenclature, and electrode techniques

To ensure reproducibility and precision during tDCS, clinical and animal studies should always use current controlled stimulation. The electrode-tissue interface represents an unknown and changing impedance in series with brain tissue, but current control