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A physiologically plausible spatiotemporal model of bold allows deconvolution of hemodynamic and neuron response components

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Abstract

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EFFICIENT DELIVERY OF SIRNA TO NEURONS USING LAYERED DOUBLE HYDROXIDE NANOPARTICLES

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Purpose: Small interfering RNAs (siRNAs) are capable of targeting and destroying specific mRNAs, making them particularly suited to the treatment of neurodegenerative conditions such as Huntington's Disease. However, the delivery of unprotected siRNAs is ineffective due to their susceptibility to degradation by ubiquitous nucleases. Layered double hydroxide nanoparticles (LDHs) are now emerging as a potential drug delivery system as they exhibit low cytotoxicity and are highly biocompatible. This study aims to develop LDHs as an efficient and safe siRNA delivery system for the central nervous system. **Methods**: Initially, fluorescently tagged dsDNA-cy5-LDH complexes were injected into the lateral ventricles of C57BL/6 mice (n=3) to determine the extent of penetration. Effectiveness of gene targeting was then assessed by injecting siRNA-EGFP-LDH complexes into the ventricles of EGFP expressing mice (n=3). Coronal sections of C57BL/6 mice were processed for fluorescence analysis and EGFP levels were assessed by Western Blotting. **Results**: The fluorescence intensity observed in the brain of the dsDNA-cy5-LDH group was significantly higher than that injected with dsDNA-cy5 alone (Student t test, $p<0.05\%$). The Western Blot results showed that the EGFP protein level in the siRNA-EGFP-LDH group was lower than in the siRNA-EGFP only group (Student t test, $p<0.05\%$). **Conclusion**: Our study demonstrated that intraventricular injection of dsDNA-loaded LDHs resulted in widespread distribution in the forebrain. Injection of siRNA-loaded LDHs into the lateral ventricle resulted in knockdown of the target gene. These studies therefore suggest that LDH particles have great potential as an siRNA delivery system for patients suffering from neurodegenerative disease.

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CONSCIOUS, SIMULTANEOUS RECORDINGS OF RODENT VISUAL ELECTROPHYSIOLOGY: IMPROVED CLINICAL TRANSLATABILITY

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PURPOSE: Electroretinogram (ERG) and visually evoked response (VEP) in rats are commonly measured under physiology-altering anaesthetics. We employ conscious, telemetric ERG and VEP recordings to investigate the effect of laboratory anaesthetics on visual functions. METHODS: We implanted Physiotel transmitters (DataSciencesInternational, U.S.A.) in Long-Evans rats (n=9), with the active ERG electrode affixed onto the superior sclera and the active VEP to the visual cortex. ERG and VEP were recorded in conscious animals up to 28 days post-surgery. Electrophysiology under ketamine:xylazine (k:x) or isoflurane were measured in the same cohort at days 7 and 14. All data are expressed as mean (±SEM) and parameters between groups are compared via mixed linear analysis. RESULTS: Conscious ERG returned maximal a-wave (-15±1μV), rod b-wave (39±5μV) and cone b-wave (17±2μV) amplitudes, which were significantly smaller than that under k:x (a-wave -22±4μV; rod b-wave 56±9μV; cone b-wave 24±3μV) but larger than responses under isoflurane (a-wave -10±2μV; rod b-wave 24±5μV; cone b-wave 8±2μV). Isoflurane produced less sensitive a-waves compared to conscious (1917±334 vs 398±126 $m^2.cd^{-2}.s^{-3}$).VEP amplitudes were similar in all conditions, with only P2-N1 amplitude larger in k:x (15±2μV) compared with conscious (12±2μV) and isoflurane (14±2μV). Isoflurane yielded significantly slower VEP (implicit times: P1 25±3ms, N1 53±4ms, P2 81±6ms) than conscious (P1 18±1ms, N1 34±1ms, P2 62±1ms). P2 implicit times were slowed under k:x (72±1ms) compared to conscious. CONCLUSIONS: This is the first study to record wireless ERG and VEP in conscious rats. We show anaesthesia affects both retinal and cortical electrophysiology. This technology can potentially improve translatability of functional assessments from rodent models to humans.

ORAL-17-03

DEEP BRAIN STIMULATION AND CORTICAL ACTIVATION

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Purpose: Deep brain stimulation (DBS) is an evidence-based treatment for Parkinson's disease (PD) and essential tremor (ET), in which small quadripolar electrodes are implanted into the subthalamic nuclei (STN) or ventral intermedial thalami, respectively. The aim of this study was to investigate whether scalp maps resulting from DBS can help identify functionally and differentially-connected subregions of the STN and thalami for optimal placement of electrodes. Methods: DBS was carried out in three PD and three ET patients. Each electrode had 4 contacts, spaced with 1.5mm interelectrode distance (lead model 3389, Medtronic, Meerbusch, Germany). Different combinations of these contacts were activated to stimulate distinct subregions in the STN or thalami. EEG was recorded concomitantly with DBS. Independent component analysis and spectral analysis were applied to estimate the scalp map of the DBS pulses. Results: In both PD and ET patients, the stimulation pulses were pronounced over the motor cortex and frontal areas, however sparse in the parieto-occipital regions. Choosing different DBS contacts resulted in activation of different areas of the cortex, indicating strong ipsilateral subcortico-cortical connectivity. Some combinations of contacts activated only a small area of the cortex while others activated widespread cortical areas. Conclusion: This study provides first evidence that the cortical representation of the DBS pulse may depend on the subcortico-cortical connectivity of distinct narrowly-spaced subregions in the target nuclei. Whether this might be of help to guide electrode localisation and programming can be addressed in larger cohorts by combined clinical, electrophysiological and imaging studies.

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A PHYSIOLOGICALLY PLAUSIBLE SPATIOTEMPORAL MODEL OF BOLD ALLOWS DECONVOLUTION OF HEMODYNAMIC AND NEURONAL RESPONSE COMPONENTS

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Purpose: Functional MRI (fMRI) experiments rely on precise characterization of the blood oxygen level dependent (BOLD) signal. As current hardware allows fMRI in the submillimeter range, the need for quantitative modelling of the spatiotemporal properties of this signal becomes pressing. Here, we find that a detailed physiological theory for cortical tissue predicts hemodynamic waves that travel several mm across the cortical surface. This understanding allows a solution to the inverse problem and thus a more precise estimate of the underlying neural activity. We apply this model to high resolution (1.5mm) and super high resolution (0.8mm) fMRI data. **Methods:** A model of spatiotemporal hemodynamics derived from physiology (Aquino et al. PLoS 2012) is used to predict the spatiotemporal hemodynamic response function (stHRF) – the BOLD response to an impulsively local neural drive. The properties of the stHRF were then tested on four subjects. Subjects viewed an evoked visual paradigm, while fMRI was recorded at 1.5 mm or 0.8mm resolution. Spatiotemporal neural activity was estimated by inverting fMRI data using Wiener deconvolution and the stHRF. **Results:** Our predicted hemodynamic waves were validated, traveling 5–10 mm across the cortical surface at an average speed of 4±2 mm/s (S.E.M.) and damped at a average rate 0.8±0.2 /s (S.E.M.). Furthermore, these responses can be separated into a local and a propagating component transitioning at ~ 1 mm. These estimates confirm the prediction of our spatiotemporal model, and the measured features agree with parameter estimates derived from physiology. Deconvolution of these data yields a localized neural activity of ~1 mm that agrees with independent measures of the neuronal point spread function. **Conclusion:** We demonstrate the first successful spatiotemporal deconvolution of the hemodynamic components of BOLD revealing the underlying neural dynamics. Thus demonstrating a method that can be incorporated with existing experiments and models of neural activity.