Establishing an anatomically constrained model of the visual thalamus for optogenetic vision restoration

1. Context

Vision loss affects an ever-increasing number of people worldwide, making it one of the main challenges for healthcare. Gene transfer based on recombinant Adeno-associated viruses (AAVs) is emerging as a major therapeutic path for these defects. Recently, groundbreaking results demonstrated, for the first time **partial visual restoration with optogenetic gene therapy** in a blind patient affected by retinitis pigmentosa*(1)*. This clinical success directly resulted from our pre-clinical study enabling Sorbone team (SO) to select the best genetic construct (AAV2.7m8-CAG-ChrimsonR-tdTomato)*(2)*. In this study, we confirmed that **gene therapy by intravitreal AAV injection primarily targets the retinal ganglion cells of the fovea (f-RGCs).**

Following this first preclinical study, we measured the activity in the primary visual cortex (V1) of non-human primates (NHP) following the optogenetic activation of AAV-transduced retina*(3)*. These optogenetic responses showed significantly different kinetics, polarity and amplitudes compared to photoreceptor-mediated light responses. The recorded differences reflect distinction in upstream and downstream processing, raising major questions of direct clinical relevance: **how does the optogenetic signal differ in its integration and perception by the visual system between the natural light response?**

On its way to V1, visual signal passes and is transformed in the lateral geniculate nucleus (LGN). The role of the LGN in term of computation on the visual information stream is, to this day, not clearly defined. While the LGN is classically described as a relay toward the cortex, mounting evidence start to question its previously assumed role: a simple gating process, directing relevant information to the visual cortex. Indeed, properties of LGN cells showed indication of emerging properties, such as size tuning or binocular modulation, that might have an origin in the LGN internal computation.

Hence, to understand the difference in optogenetic vs. light signal propagation from retina, it is essential to develop a **system level understanding** of information propagation from the eye to LGN to V1. To address this, we propose to develop a **biologically detailed large-scale model of the early visual pathway,** that heavily relies on previous experimental work by the SO and modeling of Charles University team (CU).

Objectives

In this project we propose to address two fundamental questions: (1) the role of LGN **in optogenetic vs. natural light signal integration**, (2) how does the **LGN response in these two conditions impact the next stage of visual processing** in primary visual cortex (V1).

Approach

To answer this question, we will rely on a pre-existing corpus of data available at SO. First, we have recordings of the primate retinas treated with optogenetic, or not, and can compare f-RGCs activity in response to different light levels. Second, we developed a multicolour labeling technique (called 3A-Brainbow) that, if used with the same gene therapy vector as the optogenetic gene therapy, similarly labels f-RGCs population. 3A-Brainbow allows the expression of a vast amount of hues making it possible to distinguish and reconstruct a complete population of neurons. Using that labeling we imaged the f-RGCs terminals in the LGN and are currently performing exhaustive 3D reconstruction of the axonal organization of f-RGCs terminals in the different LGN layers. Furthermore, thanks to immunohistochemical labeling, we also have access to the position of the synaptic contact on the f-RGCs axons in the LGN.

The work in this project will be based on a previous large-scale biologically detailed spiking network model of early visual pathway from retina to V1*(4)*, and optogenetic stimulation*(5)* developed by CU, which has been extensively validated against a wide range of measures under different stimulation protocols ranging from artificial stimuli such as sinusoidal gratings to naturalistic movies*(6)*. While the

cortical stage of the current model is biologically detailed, at the level of LGN the model utilizes a simplified phenomelogical model of neurons that approximates the entirety of retino-thalamic processing. Using information from existing literature, and crucially relying on the unique 3A-Brainbow reconstruction data in the LGN provided by SU, in this project we will build a state-of-the-art model of retino-thalamo-cortical pathway. We will model On and Off visual stream from midget and parasol RGCs inputs to the 4 parvocellular (P) and 2 magnocellular (M) LGN layers, respectively. We will take in account in our model the 3 M, P and K (koniocellular) neural types, as well as, local LGN inhibitory interneurons and inhibition from the peri-geniculate nucleus. Following the implementation and validation of the model against existing literature and additional physiological data from LGN recordings provided by SO, we will study the differences in the type and layer specificity of recruitment of neurons through visual or optogenetic stimulation of the retinal pathway. Our goal will be to identify which factors (such as neural type or spatial specificity of stimulation) could contribute to minimizing the differences between the visually and optogenetically evoked LGN responses. In the final stage of the project we will connect the new LGN model to the existing biologically detailed model of V1, and simulate the specific cortical response recordings previously performed by SU under the two stimulation conditions. These simulations will serve to validate the entire retino-thalamic-V1 pathway model, and crucially allows us to understand the underlying factors that contribute to the differences in the responses under the two stimulation conditions, and in turn allows us to propose strategies for improving the next generation of optogenetic based retinal therapies.

This is project necessitates collaboration between theoretician (CU) and experimentalists (SU) to conceive and implement the model as well as provide data to constrain it. The SU team is perfectly fitted for this project demonstrably running world leading research program in optogenetics based retinal therapies, and developing the new 3A-Brainbow LGN labeling methods. Likewise, CU team has extensive experience in modeling visual system and has developed the state-of-the-art model of early visual pathway that is at the core of the proposed project. It is expected that this project will generated substantial impacts, both in terms of basic science by developing the most detailed model of LGN processing in V1 to date, as well as in terms of societal impact through advancing research on vision restoration through optogenetic based retinal treatments.

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