CHARACTERIZING CEREBELLAR-DEPENDENT MOVEMENT PARAMETERS IN PRIMATES

To assess the efficacy of therapeutic interventions developed by the Raynor Cerebellum Institute (RCI), it is essential to establish a model animal system that: (1) enables rapid, quantitative testing with minimal latency, cost, and administrative burden, (2) allows for robust behavioral measurements with minimal within- and across-subject variance, and (3) maximizes the potential generalizability of findings to the human brain. This project presupposes that the motor system of nonhuman primates (NHPs) serves as an ideal model for testing RCI-developed interventions due to the strong correspondence between human and NHP neuroanatomy.

As discussed at the recent RCP 2024 summit, the motor system provides a well-suited behavioral framework for developing quantitative and objective behavioral assays for cerebellar involvement and therapeutic efficacy. While rodent models offer genetic accessibility and low costs, their cerebellar projections for motor control differ significantly from primates. Rodents, as quadrupedal mammals, rely primarily on rubrospinal limb control via the red nucleus, whereas primate movements are more dependent on the corticospinal tract. These fundamental differences suggest that NHPs likely provide a more generalizable model for testing preclinical therapeutic interventions. This proposal aims to develop a robust battery of cerebellar-dependent motor tasks in NHPs to facilitate quantitative assessments of NHP models of cerebellar dysfunction and the potential restoration of function via RCI-developed therapeutics.

Short-term Goals

In the short term, we aim to design a battery of motor control and learning tasks in NHPs that ensure: (1) high reproducibility within and between subjects, (2) readily quantifiable task-relevant metrics, and (3) a strong correspondence to cerebellar deficits and severity scales (e.g., ICARS) measured in human patients.

Our task battery will rely on multiple movement tasks, primarily of the upper limbs. These tasks will include:

- The conventional center-out reaching tasks commonly used in NHP motor studies.
- A 3D out-and-back reaching tasks akin to pellet retrieval /reach-to-consume tasks in rodent models.
- A planar manipulandum task requiring rapid back-and-forth tracking of a moving target (analogous to the “Finger Chase” SARA task and the “Finger-to-Nose” task used in the ICARS assessment).
- A task involving rapid pronation/supination of the hand while grasping a 3D manipulandum (akin to the “Pronation-Supination” task from the ICARS assessment).

Across these paradigms, we will quantify kinematic metrics such as dysmetria (assessed via endpoint error), movement trajectory deviations (efficiency), reaction time, variance, and task duration. Our objective is to establish precise, quantitative definitions of baseline NHP movement patterns, improving upon existing studies that focus on a single behavioral task, outcome variable, and/or limited number of NHP subjects.

We will also investigate limb motor learning characteristics by having NHPs adapt to force-field perturbations, a well-established cerebellar-dependent task. Additionally, we will assess responses to imposed visuomotor rotations, a task with partial cerebellar dependence in humans, to explore its relevance in NHPs, where explicit task-based strategies may differ from human subjects.

Medium-term Goals

Beyond characterizing cerebellar-dependent execution and motor learning in NHPs, our medium-term goal is to develop a reversible model of cerebellar dysfunction that allows for the rapid, quantitative assessment of potential therapeutic approaches. To achieve this, we will employ DREADD (Designer Receptors Exclusively Activated by Designer Drugs) technology with the goal of transiently inactivating the cerebellar circuits that support accurate limb movements.

Our initial approach will involve *rAAV-retro*-mediated expression of inhibitory DREADDs under the L7 promoter, targeting Purkinje cells. Following viral administration within the interposed and/or dentate nuclei, manganese-enhanced MRI will be used to assess viral vector and vehicle spread. Following an incubation period, systemic administration of DCZ should transiently inactivate broad regions of the cerebellar cortex (which we will assess via simultaneous extracellular recordings and, potentially, functional imaging), allowing us to evaluate the resulting motor deficits using our established task battery. This approach, in tandem with invasive or non-invasive therapeutic strategies developed by other RCI investigators, should enable us to quantitatively assess intervention efficacy.