CONCLUSION

In this thesis we investigated the functional role of the cerebellothalamocortical (CTC) circuit in the context of skilled reaching. Our findings have contributed to a growing body of knowledge regarding how this circuit supports multiple functional roles, including movement initiation and motor planning. The experimental paradigm employed in this thesis has proven invaluable in demonstrating that tightly controlled behavior and *in vivo* electrophysiological identification of sub-regions of the motor thalamus allow us to tease apart previously unresolved questions concerning the role of cerebellar input to the primary motor cortex (M1).

This thesis work was introduced by contextualizing the work within the broader study of motor control. We begin by discussing the relevant neuroanatomy, which is complex and dependent on the animal model under study. We then highlight a combination of behavioral, neurophysiological, and computational modeling studies and provide the overarching framework for studying the CTC pathway.

In Chapter 2, we specifically examined the contribution of the macaque cerebellar thalamus to movement initiation. Our findings are broadly consistent with the idea that cerebellar input to the motor cortex drives initiation activity in M1. We found further evidence that the cerebellar thalamus may be acting as a critical junction in the sensorimotor transformation between stimulus and action, which has not been reported in motor areas. Our task was designed to fully dissociate motor planning and initiation, and it revealed a complex timecourse of directional encoding in the cerebellar thalamus. In general, the strength of directional encoding during movement execution is weaker in the cerebellar thalamus than it is in M1, which has been observed in previous work. However, the dynamics of encoding in the cerebellar thalamus during the delay period and reaction interval suggested a time-varying flow of directional information from the cerebellar thalamus to M1 following the instruction. The cerebellum may be relaying the task instruction to M1 at the beginning of the trial but does not maintain a representation of the motor plan throughout the delay, and the component of activity that is consistent with the role of movement initiation is not directional. Together these findings suggest that the cerebellar thalamus may be performing different functional roles like motor planning and initiation via different patterns of activity.

In Chapter 3, we adopted an approach to identify M1 neurons that receive excitatory disynaptic input from the cerebellum, denoted M1-Cb+, and compared their activity to that of the larger M1 network recording during the planning, initiation, and execution of reaches. In general, we found that cerebellar input to these units raises their baseline and task-dependent firing rates. We examined how the upcoming reach was encoded in the activity of these neurons and observed substantially larger directional encoding in these neurons throughout the task relative to M1 neurons that were not labeled as receiving cerebellar input. We validated our Cb-input identification approach to ensure that these findings were not a byproduct of our selection approach.

The findings we report in Chapter 2 and 3 are surprising because the directional encoding observed in the cerebellar thalamus during reach execution is far weaker than in M1, yet cerebellar input appears to drive directionality and higher firing rates within M1 itself. Though it remains speculative, there are several ways in which disparity could arise. The simplest concern is that we may have under sampled parts of the cerebellar thalamus with the most directional encoding and thus underreported the true strength of directional encoding. Given the high neuron count and spread of recordings used in our analysis, this seems less likely. The primary concern is that the degree of cerebellar input may be associated with other factors that drive directionality, leading us to incorrectly presume the role of cerebellar input. M1-cb units are unlikely to be characterized just by their Cb-recipient nature. For example, tt may be that layer 5 pyramidal tract neurons are the type of M1 neuron most likely to receive Cb input and those PT neurons receive directional information from some other source (e.g. PMd). The network of M1 neurons could be composed of non-PT neurons, which have low directionality tend to not receive Cb input, and PT neurons, which have high directionality and tend to receive Cb input. There are two other network-level explanations that make it biologically plausible. The CTC pathway provides excitatory feedback to the motor cortex even at rest or baseline conditions. Even if the cerebellar input to M1 plays no functional role, the additional e4xcitoatyr input and resulting higher firing rates in the M1-Cb+ neurons may be increasing the sensitivity of those neurons to other inputs. The other idea concerns the cerebellar thalamus. Weakly tuned inputs may converge in cortex to amplify their effect, such that directional information is more strongly represented at the single neuron in M1. We reasoned that very few neurons in the cerebellar thalamus actually have directional information at the epochs where this mattered (end of delay, reaction interval). Additional work is needed to address the questions posed by this thesis.

As we move forward, the findings from this thesis will serve as a foundation for future research on the cerebellothalamocortical circuit. We hope that this work, including the posed conceptual frameworks, will spur additional discussion and insights into the behavior and functional role of cerebellar inputs to cortex. We aim to understand how cerebellar input shapes cortical firing so that we can understand the neurophysiological consequences of cerebellar dysfunction and motivate neuromodulatory strategies.