The relationship between the structure and function of biological systems is a theme that pervades neuroscience. This idea is something that I have been interested in since I started studying biology particularly because of how structure and function can be examined at so many different levels of organization. In my past research experiences, I have explored this question at the level of circuits as well as at the smaller scale of genetic heterogeneity within a brain region. I am particularly interested in basic science research with translational and clinical implications because the alteration of healthy biological systems, through injury or illness, is a great example of how structural damage impacts the normal functioning of the system. The opportunity to study and research neurobiological disease and injury is a main reason why I am pursuing graduate studies. I believe that these topics align well with the research done by the faculty at the Boston University GPN. The opportunity to engage with patients and clinicians through clinical rounds, as well as the work with both animal and human models are part of what drew me to this program. I believe that both of these aspects of the GPN would enhance my ability to research topics in my fields of interest.

The question of how the structure of a circuit relates to its functional properties was something I explored while working in Fabian Kloosterman's lab in Belgium. I was involved in a project studying the anatomical organization of the subiculum, looking at the input-output relationship of different subiculum cell populations. My role was to try to identify these subiculum inputs primarily through the use of retrograde tracing. I worked fairly independently on this project which allowed me to gain experience in carefully planning out experiments in a way that helps to answer the question being asked. The experiment that I was working toward involved two injections in the same animal: retrograde herpes simplex virus into the retrosplenial cortex, a target of the subiculum, and a glycoprotein-deleted rabies virus into the part of subiculum that projects to the retrosplenial cortex. This involved a lot of experiment troubleshooting and trying to identify the source of error in the experiments. Doing this independently allowed me to think critically about adjusting the injection protocols, whether it was by changing the viruses and retrograde tracers used or the stereotaxic coordinates used for the injections.

The project I worked on in Bernardo Sabatini's lab at Harvard was one that approached the structure-function question from various levels. I worked closely with a graduate student to study the anatomical and molecular heterogeneity in the dorsal raphe nucleus (DRN), a major component of the serotonin (5-HT) system. At the molecular level, the goal was to categorize DRN 5-HT neurons into different subtypes based on transcriptional profiles. To identify candidate molecular markers of the different subtypes, single-cell RNA sequencing experiments were done. SmFISH (single molecule fluorescent in situ hybridization) was then used so that RNA puncta indicating the expression of differentially expressed genes could be quantified. This allowed us to ensure that the marker genes are actually expressed in the DRN as well as examine their spatial distribution. Some of the smFISH experiments were combined with rabies tracing approaches to help us determine if there is a specific subtype that projects to the basal ganglia. The analysis of this smFISH data required pre-processing to convert images from the experiments to a particular format. As most of my recent involvement in this project was on the quantitative image analysis, I wrote macros in Fiji that performed the necessary pre-processing. I also used Fiji to quantify fiber density in the striatum from anterogradely labelled axons and subsequently created visualizations of the data. Anterograde tracing from the DRN was done to

complement the retrograde tracing we did when examining the projection patterns of the subtypes. In thinking about the next steps for the DRN project, I would continue in a direction that is focused on finding connections between neuronal subtypes and specific behaviors implicated in psychiatric illness. Similar approaches, like smFISH and rabies tracing, could be used to identify genetic markers of DRN neurons which project to the amygdala and other brain regions implicated in anxiety. Perturbations of these projections during behavioral tasks could be precisely targeted using the genetic markers and would provide insight into the necessity of these DRN projections in anxiety. Overall, working on this project has given me a good sense of different approaches that can be used to examine the relationship between structure and function. I now appreciate how the use of techniques which span multiple levels of organization, such as smFISH providing both spatial and genetic information, allow for a higher degree of specificity than techniques that address only one level of organization.

Studying the structure-function relationship in the context of the pathophysiology of mild traumatic brain injury (mTBI) is one specific interest of mine. At the molecular scale my interests lie in how the mechanical disruption of membranes seen in concussions alters ion flow into and out of damaged cells. This would demonstrate how molecular pathways and second messenger signaling cascades are affected by injury. To address the cellular level, I am interested in looking at the ability of the injured brain region to send and receive signals to and from the rest of the brain. What is most intriguing to me is how these molecular and cellular changes translate into the clinical symptoms seen in mTBI. A symptom of concussion could be studied at the behavioral level all the way down to a disrupted structure-function relationship of neuronal membranes in a part of the brain implicated in this symptom. Studying a topic of this nature in graduate school would be a great opportunity because I hope to have a career, either in academia or industry, in which I can research biomarkers and therapeutic approaches for patients with brain injuries or mental illness. Continuing to uncover the interrelatedness of structure and function, whether in the field of injury or disease, is something that I feel I would be able to do at Boston University.