NENS Exchange Grant Final Report

Mandy Meijer, PhD Student

Training period: 26/06/'19 – 20/12/'19
Home Institution: Department of Human Genetics, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, The Netherlands
Host Institute: Laboratory of Behavioral Genetics, Brain Mind Institute, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland
Project Title: Linking the environment and genome by DNA methylation in aggressive behaviour in a rat model of peripubertal stress-induced pathological aggression

Background

Aggressive behavior is largely heritable, but environmental adversities, such as (early life) stress, also play an important role. Moreover, there is an interplay between these external and internal factors and one way to study them is via DNA methylation. The interplay of these two factors can be investigated by studying epigenetic mechanisms, which can alter gene expression levels and eventually behavior. The host department developed a rat model, in which the inter-individual differences in response to the stress hormone, corticosterone, have a genetic background. More importantly, the animals with different genetic background response differently to stress in terms of aggressive behavior, making this a perfect model to study the interplay between genome and environment.

Research and training

During my training period, I was taught how to handle the animals and how to perform the peripubertal stress protocol in order to investigate the effect of stress (as environmental factor) on the genome. During this period I have been taught several behavioral paradigms to induce stress and to measure anxiety-like behavior as well as sociability and aggressive behavior. Moreover, I have experience with analyzing the behavioral data now and know the advantages and disadvantages of the type of tests and analyses.

One of the behavioral experiments we performed, was the elevated plus maze. This is a paradigm to test for anxious-like behavior. It is important to evaluate anxious-like behavior to assess whether results seen in the aggression test might be driven by other behavioral domains. Animals spent more time in the open arms of the elevated plus maze are thought to be less anxious. We observed that the animals from the low corticosterone responding group (low line) are less anxious than the animals from the high corticosterone responding group (high line). Peripubertal stress has no effect on the time spent in the open arms (**figure 1**).

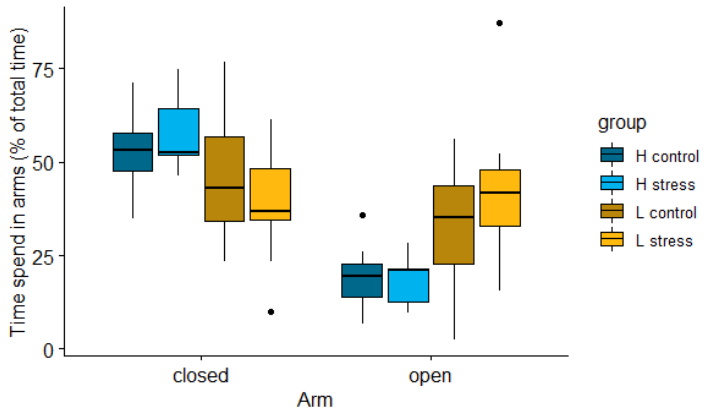

Figure 1 Anxious-like behavior is not affected by the peripubertal stress protocol. *Animals with the different genetic backgrounds (high (H) and low (L) corticosterone responding group) were allocated to*

the control or stress group and during adulthood tested in the Elevated Plus Maze. Time spend in open and closed arms was measured and calculated as the percentage of the total time spend in the apparatus (ten minutes).

During my training period I was also involved in the breeding and subsequent validation of the genetic lines. Due to the fact that the experienced people in the lab were involving in me practical aspects of this type of research, I feel like I gained a lot of experience and knowledge.

After the behavioral tests, we harvested brains and experienced people in the lab taught me how to use brain atlases to punch specific subnuclei of brain regions and how to isolate DNA from these subnuclei to perform DNA methylation analysis.

Implementation home institute

DNA methylation is tissue specific and therefore we expect DNA methylation changes in aggressive individuals in brain regions instrumental to aggression (i.e. prefrontal cortex, amygdala, hippocampus). In human studies, DNA methylation studies are mainly focusing on accessible tissue, such as blood and saliva. Previous research projects during my PhD focused on DNA methylation in human cohorts. By comparing different species, we want to integrate the findings across species to identify the underlying biological mechanisms of aggressive behavior.

Professional development

The NENS Exchange Grant made it possible for me to experience a training period at the Laboratory of Behavioral Genetics, where I not only learned about behaviour, but also had the opportunity to work in an international environment. Since the lab is originally part of an technical university, I had the change to exchange ideas and knowledge with researchers in a broad area of expertise.