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**LCNE neurons in motor learning and Rett Syndrome**

**Project Overview:**

Rett Syndrome (RTT) is a severe neurodevelopmental disorder predominantly affecting females and occurs in approximately 1 in every 10,000 live births. The majority of classic RTT cases are caused by loss-of-function mutations in the gene that encodes the methyl-CpG-binding protein 2 (MeCP2). One of the most devastating symptoms of RTT is the disruption of motor function. Patients lose purposeful use of their hands and develop stereotypical, repetitive movements such as hand wringing and flapping (Banerjee et al., 2016, 2019; Chahrour & Zoghbi, 2007; Ip et al., 2018; Tillotson & Bird, 2020). The primary motor cortex (MC) plays a critical role in the voluntary control of movement as well as the emergence of goal-directed, reliable responses during motor learning (Chen et al., 2015; Dombeck et al., 2009; Dura-Bernal et al., 2023; Komiyama et al., 2010; Lee et al., 2022; Makino et al., 2017; Peters et al., 2014). MeCP2 mutations disrupt the excitatory-inhibitory (E/I) balance and synaptic plasticity of circuits in the MC (Banerjee et al., 2019; Tropea et al., 2009; Wood & Shepherd, 2010; Yue et al., 2022; Zhang et al., 2022), and could thereby lead to motor deficits. Locus coeruleus noradrenergic neurons (LCNE) have been heavily implicated in the learning and execution of motor tasks . I shall be working with my mentor to elucidate the effect of LCNE neurons in motor learning and RTT, specifically in the MC, during a motor learning reinforcement task.

Motor Learning in the Motor Cortex.. Goal directed motor movements, such as a lever press in response to a tone, become increasingly stereotyped in mice over a training period. Studies have demonstration that training decreases the trial-by-trial variability of these movement, and they become faster and more temporally compressed (Peters et al., 2014). A similar pattern is reflected in MC neural activity, with activity onsets of movement-related excitatory neurons arriving earlier and overall sequential activation patterns being temporally compressed (Makino et al., 2017; Peters et al., 2014). Likewise, excitatory, although not inhibitory, neurons showed higher dynamism and larger, more variable populations of distinct neurons recruited across trials during initial learning (Peters et al., 2014). In motor learning, mice reassociate neuron activation patterns to updated movements (Sun et al., 2022). Expert mice ultimately develop reliable, attractor-like activation sequences of a consistent population of neurons (Jensen et al., 2022; Recanatesi et al., 2022). This learning is thought to result from plasticity and potentiation of functional, motor-task related neuronal ensembles in the MC (Bacmeister et al., 2022; Hedrick et al., 2022).

Locus Coeruleus and Motor Task Learning. The locus coeruleus (LC) is a small neuromodulatory structure located in the brainstem that has low density noradrenergic projections to most cortical and subcortical structures. LCNEneurons have been implicated in a wide variety of brain functions such as stress (Likhtik & Johansen, 2019), learning (Breton-Provencher & Sur, 2019; Takeuchi et al., 2016), decision making, attention (Aston-Jones & Cohen, 2005), arousal (Sara & Bouret, 2012), and wakefulness mediation (Carter et al., 2010). As the primary source of norepinephrine (NE) in the brain (Breton-Provencher et al. 2022), the LC is comprised of a dense core of noradrenergic neurons that establish far projections, as well as a shell that is made up of mostly glutamatergic and GABAergic neurons that receive various inputs and project locally to mediate LCNE neurons (Breton-Provencher & Sur, 2019; Waterhouse et al., 2022). LC activation has been shown to play a critical role in increasing circuit plasticity and learning, including novelty-induced memory enhancement (Takeuchi et al., 2016), place cell reorganization (Kaufman et al., 2020), auditory processing learning (Glennon et al., 2023), and cortical engram tagging for fear memory (Fan et al., 2022). Recent studies have focused on the role of LCNE neurons in behavior reinforcement learning (Basu et al., 2022; Breton-Provencher et al., 2022; Mu et al., 2019). Midbrain LCNE activity over a cued motor task (lever press after a specific tone) was shown to have two major components: 1) a transient prior to behavioral execution (Breton-Provencher et al., 2022; Inagaki et al., 2022) and 2) another transient after receiving reinforcement of either reward or punishment (Basu et al., 2022; Breton-Provencher et al., 2022). These signal components were also shown to be differentially represented in different brain regions, with the pre-behavior transient being higher in the MC and the reinforcement signal being more widely distributed across cortices, being in both MC and prefrontal cortex (PFC). Moreover, these LCNE signals to the MC are necessary for successful learning of the motor task (Breton-Provencher et al., 2022). These results suggest that LCNE projections to the MC may play a crucial role in learning a motor task .

LC and Motor Task Learning in RTT. RTT knockout (), which have impaired LCNE signaling MeCP2 knockout (KO) mouse models have been shown to have reduced tyrosine hydroxylase (TH), a rate-limiting enzyme in the catecholamine biosynthesis pathway, expression in the LC and reduced basal levels of NE in cortex (Ide et al., 2005; Taneja et al., 2009). This is mirrored by findings of substantially lower NE, and dopamine (DA), levels in post-mortem cortical tissue from RTT patients (Hanefeld, 1985). LC activation has been shown to rescue motor learning deficits in other neurodevelopmental disorders (Yin et al., 2021). Moreover, A β2-adrenergic agonist improves motor coordination in MECP2 null mice (Mellios et al., 2014). Therefore, it may be possible that rescuing LCNE neuron specific RTT deficits may help to ameliorate the disease motor deficits.

**Personal Responsibilities & Goals:**

**1) How do LC and RTT modulate self-initiated rewarded motor movement learning?**

To study motor learning in an initial, simple behavioral task, we will have water-restricted mice learn to press a lever for water reward delivered through a (solenoid-controlled) lickspout. A successful lever press will involve the unidirectional crossing of two thresholds. These lever presses will not be cued, and all lever presses for a 100 press “binge” will be rewarded with water. A single session will be run per day. The lever displacement curves will be measured, and individual lever presses will be identified. The movement path variability, total jerk (a measure of movement smoothness), lever press speeds, and lever press rate throughout the session will be analyzed across days.

This “binge” lever press task will be conducted on mice with LC neurons inhibited or stimulated to uncover the role of LC in self-initiated motor movement learning.To look at how RTT specifically may affect self-initiated motor movement learning, this “binge” lever press task will then be run with either heterozygous MECP2 KO or LC-specific shMECP2 mice.

**2) How do LC and RTT modulate cued rewarded motor learning?**

Self-initiated movements, especially sub-second mouse lever press movements, may be difficult to study in the context of separating preparatory versus concurrent movement versus reinforcement neural processing phases. However, I am interested in the temporal separation of such behavioral phases due to the existence of distinct temporal components of LC🡪MC activity in past studies of learned behavior (Breton-Provencher et al., 2022). Moreover, learning spontaneous, self-initiated movements may not utilize LC signaling as much or in the same manner as learning more complex cued directed and task specific movements. Therefore, in addition to the self-initiated lever press “binge” task, I will also have a tone-cued lever press task. In this task, a 500ms audio tone cue will be presented after which mice will have a 10 second window to lick for reward. Failure to press the lever at the tone will not be punished. However, to avoid constant lever pressing, lever presses outside prior to the tone/start of the trial will result in an elongated inter-trial interval (ITI) and the trial will not start until the mouse stops pressing.

LC is known to modulate cue detection and cue association learning which may present a confounding variable in our study of motor movement learning. Moreover, our preliminary results have found that heterozygous MECP2 KO mice have lower hit rates than WT mice. This suggests that MECP2 may also affect either cue detection, cue association learning, and/or other aspects of physical movement unrelated to the learning of the motor movement itself. To compensate for this while studying motor movement learning, I will have each mouse complete 100 total hit trials per day of learning. Thus, if mice with MECP2 deficits, or LC inhibition, have lower hit rates due to failing to detect the cue, failing to learn a strong cue-lever press association, or subthreshold lever press attempts due to physical weaknesses, they will still have more overall movement practice. Our preliminary data suggests that even with these settings of erring on more movement practice, heterozygous MECP2 KO mice still have more variable and jerkier “hit” lever press movements, regardless of their ability to successfully create the tone-lever press association, and ultimately show deficits in learning the stereotyped “hit” lever press movement present in expert WT mice.

For this tone-cued lever press task, the experimental groups will consist of the following: LC chemogenetic inhibition, LC chemogenetic activation, LC🡪MC optogenetic inhibition, LC🡪MC optogenetic activation, MECP2 KO, LC shMECP2, and MECP2 KO + LC MECP2 rescue (possibly also with RNAi).

Potential Pitfalls: These methods assume that the lever press-water reward association is much easier for mice to learn and will not be different between MECP2 KO and WT mice.

**3) How do LC and RTT modulate the maturation of MC motor ensemble activation sequences?**

To further investigate the neural mechanisms underlying the role of LC in motor learning, I will image MC layer 2/3 and layer 5 neurons with GCaMP. We will study how LC manipulation or RTT related mouse models may affect the development rate of a stereotyped neural pattern activation sequence under the same several conditions. Specifically, I am interested in the correlation and stereotypy, neural identity stability, and temporal dynamics of activation sequences. Because LC activity sends differential signals to different cortical modalities, with the MC receiving a stronger movement preparation signal compared to reinforcement signal than the PFC, I am also interested in how changes to these activation sequences may differ between intracortical versus projection neurons. We plan to differentiate these by looking at differences in layer 2/3 (more intracortical) neurons and layer 5 (more projection) neurons. Finally, because adrenergic receptors are significantly enriched on neuron derived neurotrophic factor (NDNF) and vasoactive intestinal peptide (VIP) expressing neurons, I am also interested in looking at differences in how motor pattern activation sequences may change in these populations of neurons following LC manipulation.

**Research Characteristics and Timeline**

* Mouse line (purchased from JAX labs)
  + Adult C57BL/6J wild type
  + Adult heterozygous MECP2-
* Surgery
  + Performed under isoflurane in a stereotaxic frame.
  + Viruses
    - pAAV-hSyn-DIO-hM4D(Gi)-mCherry for cell specific chemogenetic inhibition of neuronal activity.
    - pGP-AAV-syn-jGCaMP7f-WPRE to image calcium activity in neuronal populations
  + Cranial window glued on the skull allowing a view to the motor cortex.
  + Recovery was monitored for 72 hours.
* Training

After recovery mice will be put on a water restriction schedule receiving 25mL/kg water per day, gradually decreasing from ad libitum to 25mL/kg water per day over the course of one week. The mice will be monitored weekly throughout the experiment to for signs of distress and a weight loss of no more than 10% of its original body weight will be allowed.

* + Mice will be trained to associate either a self-initiated or cued lever press with reward until mouse made 100 successful consecutive lever press trials.
* Two-photon imaging
  + Imaging will be recorded with a Prairie Ultima IV two-photon microscopy system.
  + Calcium transients will be imaged and recorded by Two-photon excitation of GCaMP7f at 920nm wavelength.
* Histology
  + After perfusion and extraction brain will be sliced with a vibratome at 100µm
  + Slices will be washed with Phosphate buffer solution before application of antibodies.
  + Antibodies:
    - anti-c-Fos (1:500 dilution, Cell Signaling), anti-TH (1:500 dilution, Aves), anti-MeCP2 (1:500 dilution, Invitrogen)
  + Slices will be mounted in mounting medium with DAPI.
* Confocal imaging
  + Utilized to capture fluorescence of cells.
* Two-photon imaging and electrophysiology spike data analysis
  + Two-photon data will be analyzed with software “Suite2p” and data run on IDE Spyder with an environment and code provided by post-doc Jennifer Shih.
  + Spike data will be preprocessed and analyzed in MATLAB with software developed and provided by Gabrielle Drummond.

I, as an undergraduate student, will be working directly with the training, imaging, data collection and data analysis. Training of mice will be done primarily over the winter semester while analysis of collected data will occur throughout the year as needed.My participation in the project should be completed in the first week of August.

**Personal Statement:** Why I am interested in this UROP is to learn to be a real neuroscientist and hopefully help publish something.

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