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RPPR Final Report

as of 20-Feb-2018

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Final Report for Period Beginning 01-Sep-2014 and Ending 31-Aug-2017

Title: Warfighter Neuroendocrinology: Modeling Stress Response, PTSD, and TBI

Begin Performance Period: 01-Sep-2014

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Major Goals: Stress related disorders affect multiple biological functions from endocrine system regulation to brain circuitry connectivity. Identifying the mechanisms that lead to the development of such disorders has been an active area of research, with a particular emphasis placed on understanding the dynamics of post-traumatic stress disorders (PTSD).

Although many advances have been made, how PTSD emerges and evolves is still unclear. Experimental studies are challenged by incongruent diagnostic criteria and confounding treatment protocols. Understanding PTSD is not a simple task as there is no reliable biological predictor or marker for PTSD and diagnoses are heavily reliant on self-reporting. Current treatments include psychotherapy and pharmacotherapy: it is not very clear how the two intervention methods inform each other and they are not always very successful. In part, these challenges are due to the lack of a comprehensive understanding of the biological processes and systems that are affected by PTSD and how they respond and interact with each other under stress. The goal of this research is to develop and analyze a mathematical model that includes the relevant physiological features involved in stress response regulation. Among the many promising avenues of investigation is the study of the hypothalamus-pituitary-adrenal (HPA) axis, that receives input from stress and that regulates cortisol production in the body. Cortisol is one of the main hormones of the body and helps regulate metabolism, mood, and sexuality among other functions. It is also observed that often, PTSD patients suffer from hypo-cortisolism, so that cortisol levels can be used as a possible biomarker, although not all PTSD patients suffer from low cortisol expression. Existing models for the HPA axis in the mathematical literature are not comprehensive and do not reproduce all the rich features that are instead observed in the medical literature. Furthermore, we would like our model to allow for bistability: the existence of two stable states such that an individual can exist in either of the two, one with high levels of cortisol (normal, not affected by PTSD) and one with lower levels of cortisol (diseased, affected by PTSD). Finally, we would like to compare and contrast our model with experimental data on patients to reproduce the effects of medications, exposure therapy and other physiological or psychological intervention methods.

Accomplishments: Over the course of this project we formulated a more complete and realistic model for the HPA axis where hitherto neglected processes were included. Specifically, we were distinguished the (slow) process of cortisol-mediated CRH biosynthesis from the (fast) process of CRH secretion. Our multi-time scale model was thoroughly analyzed using dynamical system and numerical methods. We were able to reproduce known oscillatory behavior patterns and we uncovered the existence of two basins of attraction, one marked by "normal" cortisol levels, the other by hypocortisolism, which we consider to be the "diseased" state as is observed in PTSD patients. We found that external distress, such as due to traumatic events, can lead to transitions from the normal to the diseased state. This is important because it means that the emergence of hypocortisolism in PTSD patients can be due **solely** to psychological trauma and not necessarily because of physical injuries. The latter would change the

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physiological parameters of our model, which here stay unmodified. Given that external distress can cause normal-to-diseased transition we also asked whether the reverse transition could be stimulated. Indeed, we found that by carefully tuning external stress, the reverse transition from diseased to normal state could be triggered. This result implies that exposure therapy, i.e. subjecting patients to stressful events in a clinical setting with the purpose of alleviating PTSD symptoms, may indeed help normalize HPA axis functionality. Our analysis provides a causative rationale for improving treatments and guiding the design of new psychological protocols. Finally, we show that timing and intensity of the external stress play a crucial role in determining how and if transitions occur.

We also performed parameter sweeps and found different behavioral regimes. This may be useful in determining the effects of physical trauma on the HPA axis functionality, where parameters are changed due to brain injuries, for instance. We also find that bistability emerges only under some parameter combinations that while defining a significant portion of parameter space are not exhaustive. This means that the subgroup of individuals that are represented by parameters that do not lead to bistability may be less susceptible to the onset of PTSD, compared to others. Finally, we used our model to better understand the mechanisms underlying current clinical protocols used to probe patient stress response. Specifically, we addressed dexamethasone (DEX) and ACTH challenge tests, which probe the response of pituitary and adrenal gland responses, respectively. Our model shows that adrenal hypo-sensitivity can give rise to the responses seen in ACTH challenge tests, and enhanced cortisol-mediated suppression of the pituitary in subjects with PTSD is not necessary to exhibit the responses observed in DEX stress tests. Finally, we proposed new two-stage DEX/external stressor protocols to better understand pituitary hormone suppression.

Training Opportunities: The PI and coPI organized a session at SIAM by the title “Computational Psychiatry: Mechanisms, Diagnosis, and Treatment of Depressive Disorders”. They also mentored 1st year Biomathematics student Alexander Fisher for the Spring quarter of 2017 and the Summer of 2017.

Results Dissemination:

1. Lae Un Kim, invited talk -- SIAM Conference on Applications of Dynamical Systems (DS17), Snowbird, Utah. (May 2017)
2. Lae Un Kim, invited talk -- Matador Math Society Colloquium, California State University, Northridge. (November 2015)
3. Lae Un Kim, poster -- 61th Biophysical Society Annual Meeting, New Orleans, Louisiana (February 2017)
4. Lae Un Kim, poster -- SIAM Life Sciences, Boston, Massachusetts (July 2016)
5. Lae Un Kim, poster -- 1st QCBio Annual Retreat, Institute for Quantitative and Computational Biosciences, Lake Arrowhead, California (September 2015)
6. Maria R. D’Orsogna, invited talk -- IMPA Mathematical models and modeling of biophysical phenomena Rio de Janeiro, Brazil (November 2017)
7. Maria R. D’Orsogna, seminar -- Hong Kong University, Faculty of Education, Hong Kong, China (December 2016)?
8. Maria R. D’Orsogna, invited talk -- Mathematical modeling and computation in medicine and biology, TSIMF, Sanya, China (December 2016)
9. Maria R. D’Orsogna, seminar --Interdisciplinary Research Institute at the California State University at Northridge, (October 2016)
10. Maria R. D’Orsogna and Tom Chou, organizers of SIAM conference on dynamical systems, Snowbird, UT (May 2017)?
11. Tom Chou, invited talk -- The Fields Institute for Research in Mathematical Sciences, Multi-scale Modeling of Wave Structures in Tissues, Toronto, Canada (September 2017)
12. Tom Chou, seminar -- University of Toronto, Physics Department (August 2017)
13. Tom Chou, seminar -- University of Pennsylvania, Mathematics Department (April, 2017)
14. Tom Chou, seminar -- National Taiwan University, Mathematics Department (December, 2015)

Honors and Awards: Nothing to Report

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Technology Transfer: Nothing to Report

PARTICIPANTS:

Participant Type: Graduate Student (research assistant)

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Participant: Lae Un Kim

Person Months Worked: 12.00

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Project Contribution:

International Collaboration:

International Travel:

National Academy Member: N

Other Collaborators:

Participant Type: Graduate Student (research assistant)

Participant: Bhaven Mistry

Person Months Worked: 1.00

Funding Support:

Project Contribution:

International Collaboration:

International Travel:

National Academy Member: N

Other Collaborators:

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Paper Title: Perturbing the Hypothalamic-Pituitary-Adrenal Stress Response System: Mathematical Modeling to Improve Diagnosis of Post-Traumatic and Related Stress Disorders

Authors: Lae Un Kim, Maria R. DOrsogna, Tom Chou

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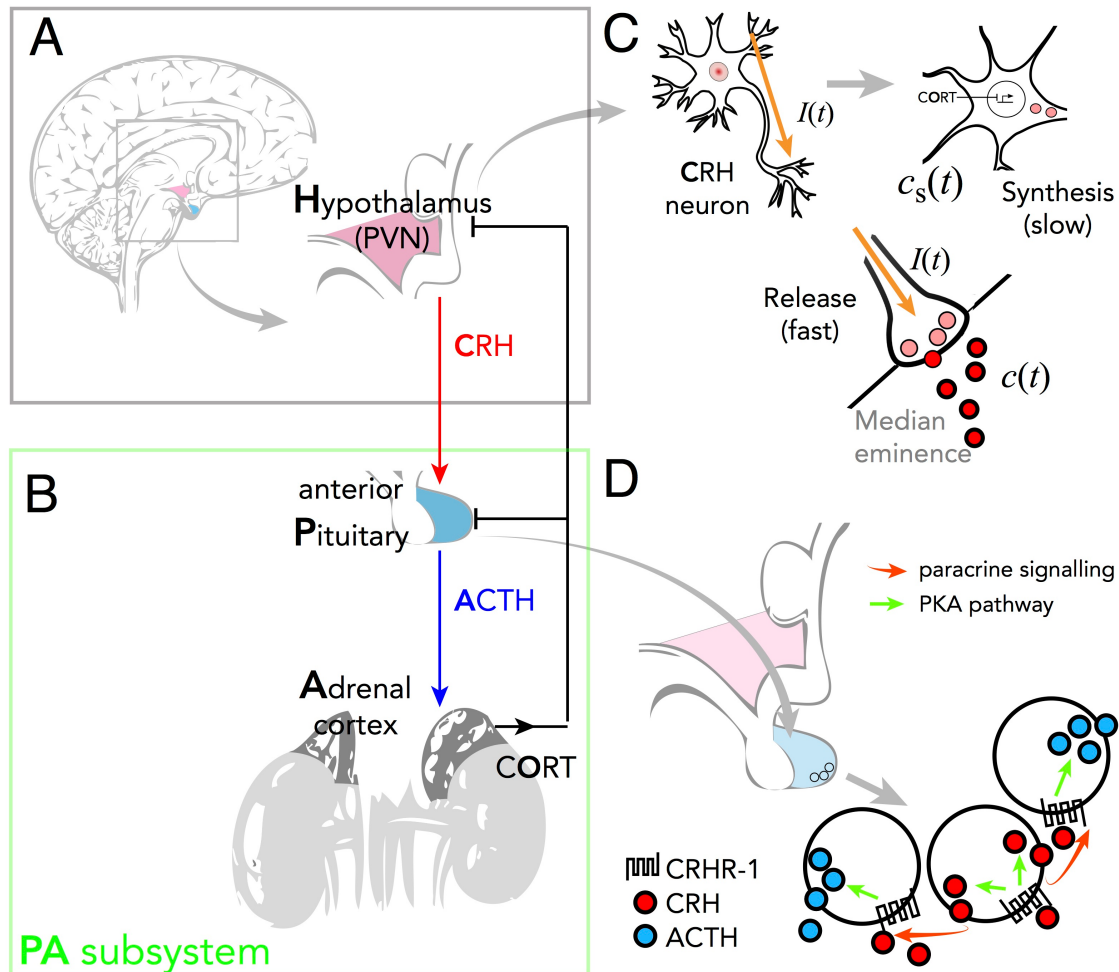
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Authors: Lae Un Kim

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Schematic of the HPA axis: (A) Stress is processed in the central nervous system (CNS) and a signal is relayed to the paraventricular (PVN) in the hypothalamus to activate CRH secretion into the hypophyseal portal system. (B) CRH diffuses to the pituitary gland and activates ACTH secretion. ACTH travels down to the adrenal cortex to activate cortisol (CORT) release. Cortisol inhibits both CRH and ACTH secretion to down-regulate its own production, forming a closed loop. (C) Negative feedback of cortisol suppresses CRH synthesis in the PVN, ultimately reducing the amount of stored CRH and its subsequent release. External inputs such as stressors and circadian inputs directly affect the release rate of CRH at the axonal terminal. (D) CRH released by the PVN stimulates the protein kinase A (PKA) pathway to activate release of CRH by the anterior pituitary, contributing to ACTH secretion in a auto/paracrine fashion.