Division of Integrative Neuroscience

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Overview

The Division of Integrative Neuroscience is a research division aimed at understanding the pathophysiology underlying psychiatric illnesses using approaches that span multiple levels of neurobiological analysis. Accordingly, we combine molecular and cellular neurobiological techniques with analyses of the behavior of neural circuits and neural systems in order to fully understand animal models of psychiatric illnesses such as anxiety disorders and schizophrenia. Consisting of three main research programs (laboratories led by Dr. Rene Hen, Dr. Holly Moore, and Dr. Joshua Gordon) and several additional faculty members and fellows, Integrative Neuroscience maintains close ties with the Center for Neurobiology and Behavior and various other neuroscience laboratories in the department.

Faculty and Staff

Director: Rene Hen
PIs: Susanne Ahmari, Peter Balsam, Alex Dranovsky, Karen Duff, Josh Gordon, Dave Leonardo, Holly Moore.
K awardees: Mazen Kheirbek (Hen lab), Ben Samuels (Hen lab).

Current Research

The overarching theme of the division is to use genetic and circuit-based approaches to study specific endophenotypes of psychiatric disorders. This mechanistic approach is aimed at stratifying these disorders in order to develop novel treatment strategies.

Examples of genetic approaches:

Modeling the rs6295 polymorphism in the human 5-HT1A promoter associated with depression and impaired response to SSRIs: Rene Hen, Dave Leonardo, Zoe Donaldson, Ben Samuels.

Modeling the 22q11 deletion associated with schizophrenia: Josh Gordon, Holly Moore, in collaboration with Joseph Gogos and Maria Karayiorgou.

Examples of circuit-based approaches:

Testing the hypothesis that over-generalization is an endophenotype of depression and anxiety disorders that is caused by a dysfunction of the ventral

hippocampus: Rene Hen, Mazen Kheirbek, Alex Dranovsky, in collaboration with Blair Simpson, Abby Fyer, Dev Devanand, Maura Boldrini, and Scott Small.

Testing the hypothesis that repeated stimulation of specific cortico-striatal projections is sufficient to generate OCD-like behaviors: Susanne Ahmari in collaboration with Blair Simpson.

Divisional Highlights

To achieve better circuit control we have successfully implemented the latest pharmacogenetic and optogenetic strategies. Our first paper using optogenetics in freely moving mice came out in Neuron (Kheirbek et al, 2013).

Our second paper using optogenetics is currently in press at Science (Ahmari et al, 2013). We report a novel animal model of Obsessive Compulsive Disorder that will enable us to study the specific circuit dysfunction underlying this disorder.

To translate our findings into clinical populations we have embarked on a series of studies in collaboration with the Anxiety Clinic (Blair Simpson and Abby Fyer) and the Taub Imaging Facility (Scott Small). Specifically we are designing human tests that are similar to the tests we use in rodents and that are aimed at assessing pattern separation and overgeneralization in humans.

Future Directions:

To further our ability to study brain circuits in behaving mice, we plan on importing a new technology that allows the high resolution imaging of large ensembles of neurons while mice are performing a specific behavioral task (Barretto et al, 2011). To achieve this goal we hope to hire a new assistant professor with expertise in fluorescence microendoscopy.

In collaboration with the Anxiety Clinic, we will initiate proof of concept clinical trials with the compounds that we are currently testing in rodent models of over-generalization.

We will also expand our translational studies into additional endophenotypes of psychiatric disorders such as: an interneuron deficit and an abnormal synchrony between the hippocampus and the prefrontal cortex in a model of schizophrenia (Holly Moore and Josh Gordon); a new model of anorexia nervosa (Nesha Burghardt in collaboration with Tim Walsh); a potential new model of autism (Zoe Donaldson).

Publications (Selected)

Sahay A, Wilson DA, Hen R. (2011) Pattern separation: a common function for new neurons in hippocampus and olfactory bulb. Neuron.70(4):582-8. Review. PMCID: PMC3109085.

Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, Fenton AA, Dranovsky A, Hen R. (2011) Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature. 472(7344):466-70. PMCID: PMC3084370.

Dranovsky A, Picchini AM, Moadel T, Sisti AC, Yamada A, Kimura S, Leonardo ED, Hen R. (2011). Experience dictates stem cell fate in the adult hippocampus. Neuron. 70(5):908-23. PMCID: PMC3124009.

Barretto RP, Ko TH, Jung JC, Wang TJ, Capps G, Waters AC, Ziv Y, Attardo A, Recht L, Schnitzer MJ. Time-lapse imaging of disease progression in deep brain areas using fluorescence microendoscopy. Nat Med. 2011 Feb;17(2):223-8.

Kheirbek MA, Klemenhagen KC, Sahay A, Hen R. (2012). Neurogenesis and generalization: a new approach to stratify and treat anxiety disorders. Nat Neurosci. 15(12):1613-20. PMID: 23187693.

Kheirbek, MA, Drew, L, Burghardt NS, Costantini DO, Tannenholz L, Ahmari SE, Zeng H, Fenton AA, Hen R. (2013) Differential control of learning and anxiety along the dorso-ventral axis of the dentate gyrus. Neuron. 77, 955-68.

Ahmari SE, Spellman T, Douglass N, Kheirbek MA, Deisseroth K, Simpson B, Gordon JA, Hen R (2013). Repeated corticostriatal stimulation generates persistent OCD-like behavior. *Science* (*in press)*