Research Narrative for Amar Sahay, PhD
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Background and Current Activities
Dr. Sahay earned his doctorate in Neuroscience in the laboratories of Dr. Alex Kolodkin and Dr. David Ginty at the Johns Hopkins University School of Medicine where he identified distinct roles for semaphorins, axon guidance cues, in establishment of neuronal connectivity in the vertebrate forebrain. During this period Dr. Sahay uncovered one of the first examples of how developmentally prescribed genes, in this case axon guidance cues, are re-used in the adult brain to regulate synaptic functions and seizures. Dr. Sahay then transitioned into Dr. Rene Hen's lab at Columbia for postdoctoral studies to build a foundation in neural circuitry and behavior. As a postdoc, Dr. Sahay published a landmark study where he identified a key function for adult hippocampal neurogenesis in memory. His research garnered national and international recognition, the Career development award from the Society for Neuroscience and four postdoctoral grants including two Brain & Behavior Research Foundation (NARSAD) Young Investigator awards and a NIMH K99/R00. After interviewing at 12 institutions nationwide and receiving several faculty-position offers, Dr. Sahay chose to build a basic neuroscience research program at the Center for Regenerative Medicine, MGH that was grounded in a mission to generate therapeutic insights into memory and mood disorders. In the last 10 years, Dr. Sahay's research program has pioneered a path that integrates molecular, circuit and systems neuroscience to illuminate how neural circuit and network-plasticity mechanisms (adult hippocampal neurogenesis) maybe harnessed to improve memory during aging and calibrate adaptive behaviors. His publications in *Nature*, *Nature Medicine*, *Neuron*, *Nature Neuroscience*, *Nature Communications* and *Cell Reports* are highly cited (over 7300 times), covered by public news outlets, and widely replicated. Based on his work, Dr. Sahay was awarded a US patent to treat memory loss in aging and Alzheimer's disease and memory imprecision in PTSD using gene therapy. His team's science has informed his articulation of transformative ideas in reviews in the most prominent journals in neuroscience: *Neuron* and *Nature Neuroscience* that have profoundly influenced our thinking about the role of neurogenesis and the hippocampus in memory processing and regulation of emotion. Dr. Sahay is recipient of 3 R01s and direct research funding exceeding $8.6 million. His trainees have been awarded nationally competitive postdoctoral fellowships (NARSAD Young Investigator) and the first cohort of trainees have secured independent faculty and principal scientist positions in industry. Dr. Sahay has mentored numerous Harvard College undergraduates who have earned highest honors in neuroscience and the Hoopes prize. Dr. Sahay co-directed the Harvard BBS Program graduate level course on Concepts in Development, Self-renewal and Repair for five years (2014-2018) at MGH. Dr. Sahay is principal faculty of the Harvard Stem Cell Institute and the James and Audrey Foster MGH endowed Research Scholar. Dr. Sahay has been invited to memberships in local, national and international scientific committees. Locally, he serves as member of the Mass General Neuroscience Leadership Council, scientific council of Homebase: a Red Sox Foundation and Massachusetts General Hospital Program for treatment of veterans and PTSD, and Center for Neuroscience of Psychedelics at MGH. Internationally, he is a member of the American College of Neuropsychopharmacology (ACNP) and the Program Committee for the Society for Neuroscience (SFN). He also serves as the sole SFN appointed representative member in the Program Committee for Federation of European Neuroscience Societies (FENS).

Area of Excellence: Investigation

Adaptively responding to the environment is critical to optimal navigation of our world. The hippocampus plays a critical role in this process by generating memories of our experiences and transferring these memories for storage or consolidation to the prefrontal cortex. Memories of past experiences stored in the cortex are re-used by the hippocampus to guide defensive and motivated behaviors (eg: approach, avoidance, reward seeking etc) that are mediated by subcortical circuits (eg: hypothalamus etc). It is intuitive to think how aberrations in hippocampal circuit mechanisms underlying memory processing or consolidation or linkage of mnemonic information with subcortical circuits are the basis for cognitive and mood impairments that characterize memory and psychiatric disorders. Dr. Sahay's lab has generated insights to reverse these aberrations through investigation of molecular, circuit and network plasticity mechanisms supporting hippocampal memory processing and regulation of emotion. This circuit-based focus is particularly powerful and prescient as it is likely that many psychiatric disease genes and risk factors for cognitive decline converge upon these hippocampal circuit mechanisms. As such, his lab's distinguished efforts to discover molecular keys to tune circuits or enhance network plasticity may guide therapeutic strategies to alleviate cognitive and mood impairments associated with aging, Alzheimer's disease and PTSD.

Adult hippocampal neurogenesis or the ability to generate new neurons in the hippocampus is a unique form of network plasticity that has captured the imagination of many over several decades. Building on the seminal paper in *Nature* from his postdoc that defined a canonical function of new neurons in memory discrimination (Cited >1480 times), Dr. Sahay's lab began to investigate the circuit mechanisms that mediate the integration of new neurons into hippocampal circuitry. Dr. Sahay's team engineered a genetic strategy to selectively and reversibly remove synapses on mature neurons. By doing so, Dr. Sahay's group found that they could bias synaptic competition in favor of the new-born neurons. This study in *Neuron* provided definitive evidence for synaptic competition between new and old neurons. Importantly, Dr. Sahay's team then applied their strategy to rejuvenate the hippocampus of aged mice with extra newly integrated neurons. Enhancing the capacity for integration of adult-born neurons in adult, middle-aged and aged mice resulted in more precise and robust memory. At a neural level, mice more with new neurons encoded similar experiences in less overlapping populations of neurons or ensembles. Thus, neurogenesis may facilitate encoding of similar experiences by decreasing interference between experience-associated neuronal ensembles. This study represented a major advance in the field of neurogenesis and memory research as it demonstrated for the first time that increasing hippocampal neurogenesis in aging is sufficient to improve cognition and specifically, through reduction of memory interference. This study was lauded in commentaries in *Nature Reviews Neuroscience* and featured in the *Newsroom* of the National Institute on Aging. Furthermore, this study and Dr. Sahay's 2011 *Nature* study illustrate using two ingenious approaches how to rejuvenate the hippocampus with new neurons and improve memory precision. Importantly, the role of adult-born hippocampal neurons in decreasing memory interference has been widely replicated in at least 12 publications using numerous behavioral paradigms and different approaches to manipulate neurogenesis by many labs around the world.

The success of these studies motivated Dr. Sahay to begin thinking about other approaches to boost neurogenesis in the aging brain or following injury, this time by replenishing the cognitive reserve embodied in the pool of neural stem cells in the hippocampus. To date a large number of transcription factors have been identified that regulate asymmetric self-renewal of adult hippocampal neural stem cells to mediate neurogenesis. In sharp contrast, the identities of transcription factors that regulate neural stem cell expansion (symmetric self-renewal) in the adult hippocampus are not known. Dr. Sahay's lab identified the first transcription factor that regulates neural stem expansion in the adult hippocampus. Although this study which is under revision at *eLife* is still too recent to track its impact and citations, it is likely to have a transformative impact on how we think about preserving cognitive reserve during aging and mobilizing neural stem cells for brain repair following injury.

Complementing his lab's efforts to *rejuvenate* and *repair* brain circuits by targeting neurogenesis, Dr. Sahay pioneered a new approach to improve memory by molecular *re-engineering* of neural circuit connectivity. Key to this strategy is identification of molecular prescriptions of neural connectivity that can be harnessed to re-wire memory circuits and improve cognition. In a study in *Nature Medicine*, Dr. Sahay's laboratory identified one such molecular specifier, Ablim3, that in response to learning regulates neuronal connectivity underlying Parvalbumin inhibitory neuron plasticity and GABAergic inhibition within the hippocampus. Parvalbumin inhibitory neurons, much like orchestral conductors, control the activity of 1000s of excitatory neurons to coordinate the flow of information in the brain essential for encoding and storage of experiences in ensembles or engrams. Dr. Sahay's group leveraged their discovery and showed that targeting Ablim3 in the hippocampus preserved memory precision over time. These findings have important therapeutic implications for PTSD as they created a new neurobiological framework to think about why patients express fear in neutral settings. Specifically, Dr. Sahay's work suggests that inefficient memory consolidation leads to the increased, rather than reduced, generalization of traumatic memories. Targeting Ablim3 represents a connectivity-based strategy to prevent the overgeneralization of fear by maintaining details of the original traumatic experience.

Motivated by a large body of work showing hippocampal hyperactivity in individuals with age-related cognitive decline and Mild Cognitive Impairment, Dr. Sahay's team next examined neuronal connectivity underlying Parvalbumin inhibitory neuron plasticity and GABAergic inhibition within the hippocampus during aging. His group demonstrated for the first time that Parvalbumin inhibitory neuron plasticity in the hippocampus is lost in aging. Importantly, targeting Ablim3 reversed age-related changes in Parvalbumin inhibitory neuron plasticity and restored memory precision in aging. This study was highlighted in *Nature Medicine* and by Dr. Francis Collins, director of NIH, in his commentaries on advances in science and medicine. On the basis of his findings, Dr. Sahay was awarded a US patent for targeting Ablim3 using antisense oligos to dampen hippocampal hyperactivity and improve memory in aging, Alzheimer's disease and PTSD.

A defining feature of Dr. Sahay's arc of discoveries is his sustained incorporation of new techniques to delve deeper into his discoveries. One of the key predictions from the *Nature Medicine* study was that targeting Ablim3 in the hippocampus promotes communication between the hippocampus and the prefrontal cortex. In a recent study that is under revision at *eLife*, Dr. Sahay's team provided evidence showing how targeting Ablim3 in the hippocampus promotes network oscillations and hippocampal-cortical communication. Since network oscillations are biomarkers of cognition and are disrupted in numerous psychiatric disorders, this study provides further support for Ablim3's broad therapeutic potential.

Although the hippocampus expresses receptors for the pro-social hormone oxytocin, the physiological role of hippocampal Oxytocin receptors in behavior has remained elusive for over two decades. Dr. Sahay's group was the first to uncover a physiological role for hippocampal Oxytocin receptors in behavior. In a study in *Nature Communications*, they found that hippocampal oxytocin receptors are necessary for discrimination of social stimuli. His team also identified the neural pathways that links computations underlying social discrimination in the hippocampus to subcortical circuits subserving social recognition. Thus, oxytocin receptors in the hippocampus (of mice and humans) may have evolved to co-opt the same circuitry mediating spatial memory albeit for social experiences. The Boston Globe covered this study and the main findings of this paper have been independently replicated by multiple labs.

Stress is a major risk factor for psychopathologies such as depression and anxiety disorders. Understanding how brain mechanisms support coping behaviors and confer resilience is key to devising novel therapeutic strategies to moderate the effects of stress on the brain and behavior. Dr. Sahay's group was the first to demonstrate how selectively enhancing adult hippocampal neurogenesis was sufficient to prevent chronic stress-induced anxiety-like behavior and promote stress associated

coping behavior. This 2015 study in *Neuropsychopharmacology* has been cited over 350 times. In thinking about how stress affects neural circuity to mediate overgeneralization of fear in PTSD, Dr. Sahay's group identified a transcriptional regulator of resilience to chronic stress-induced overgeneralization of fear. In a study in *Cell Reports*, they showed how changes in levels of a transcription regulator in the hippocampus in response to chronic stress engenders sex specific synaptic and behavioral adaptations.

To begin to understand how alterations in hippocampal functions contribute to irregularities in affective behaviors, Dr. Sahay's team began to investigate the neural pathways that link hippocampally computed mnemonic or contextual information with cortical and subcortical circuits that mediate defensive and motivated behaviors. In two studies published in *Nature Neuroscience* and *Cell Reports*, the Sahay lab illuminated how hippocampal projections to the lateral septum, a major target of the hippocampus, play a critical role in calibration of defensive behaviors. The Sahay lab identified distinct classes of inhibitory neurons as mediators of hippocampal outputs to different subcortical circuits to calibrate defensive behaviors. Based on these ongoing efforts and recognition of his contributions to this field, Dr. Sahay will chair a symposia on the lateral septum and its role in affective behaviors at the 60th Annual meeting of the American College of Neuropsychopharmacology in December 2021.

Scholarship and Recognition

Dr. Sahay's research has garnered tremendous traction in the fields of neurogenesis and memory research and his work has been cited over 7300 times. His findings identifying a role for adult-born neurons in reduction of memory interference remain a landmark milestone in the field of adult hippocampal neurogenesis. Dr. Sahay discoveries have been independently replicated by many different laboratories and continue to kindle deeper enquiries in his own lab and research programs worldwide. Dr. Sahay's work has provided pivotal experimental support to influential theories on the role of the hippocampus and memory such as Hippocampal Indexing theory that posits a continuous role for the hippocampus in accessing details of stored memories. His research program exemplifies how integrating the tools of molecular neuroscience with circuit interrogation techniques allows privileged access to understanding how memories are encoded, stored and deployed to guide behavior. His science has been covered by the Boston Globe, The Scientist, EurekAlert, MIT tech Review, NPR, Fierce Biotech and by the Director of the National Institutes of Health. More recently, Dr. Sahay's science on neurogenesis, memory and aging was prominently featured in a novel entitled "The Memory Thief: And the Secrets Behind How We Remember" released by Simon & Schuster. Dr. Sahay's discoveries have led to formulation of several influential review articles and perspectives published in the most prominent journals of neuroscience: *Nature Neuroscience (2007, 2011, 2019)* and *Neuron (January and August 2020),* and that continue to shape the leading edge of science on adult hippocampal neurogenesis and memory. Notable in these reviews is Dr. Sahay's ability to reach across the aisle to clinicians and relate fundamental neural circuit mechanisms underlying hippocampal memory processing (memory interference, discrimination and generalization) to psychiatric disease endophenotypes, age-related cognitive decline and MCI. Dr. Sahay is regularly requested to review for top journals in neuroscience including *Nature, Nature Neuroscience, Neuron and Cell Stem Cell*. He has served on several NIH special emphasis grant review panels and has reviewed grants for French and Swiss government Neuroscience Funding Agencies.

Dr. Sahay has proven to be a catalytic collaborator to stem cell scientists both locally within Harvard Medical School and internationally. He has engineered genetic tools that were deployed to generate foundational data in several collaborations published in *Nature*. He has part of national collaborative efforts spanning Harvard, UCSF, Stanford, USC and Princeton such as the Simons Collaboration on the Plasticity and the Aging Brain to "discover mechanisms of resilience and

maintenance in the aging brain". He has deposited multiple genetically engineered mouse lines at Jackson Labs for unrestricted access by the neuroscience and stem cell community.

Dr. Sahay has spoken in almost every session on "the functions of adult hippocampal neurogenesis" at major national and international conferences (Keystone symposia, International Fusion Conferences, Eurogenesis meetings, Abcam Neurogenesis meetings). Dr. Sahay co-organized the first international meeting on adult neurogenesis in Asia. He has chaired symposia and given a plenary lecture at the American College of Neuropsychopharmacology annual meeting. Based on his contributions to memory and aging, Dr. Sahay was invited to speak at the National Institute of Aging Cognitive Aging Summit, Neurogenesis and Aging workshop and the Gerontology Society of America. He has spoken at and chaired international Kavli Frontiers of Science Symposia and lectured at numerous universities (UCSF, Johns Hopkins, UTSW, Brown, UC Irvine Center for Learning and Memory, University of. Washington, Seattle, etc) both nationally and internationally (Germany, Japan, India, Israel, France, Sweden etc). He was invited to serve on the Program committee of the Society for Neuroscience where his responsibilities include crafting the program for the largest annual meeting in neuroscience, chairing the program committee for Neurodegenerative disorders and Injury session at the Annual meeting and interfacing with leadership of the American Neurological Association (ANA). In 2020, Dr. Sahay was selected to serve as the sole SFN representative in the 17 european member comprised Program Committee for Federation of European Neuroscience Societies (FENS).

Dr. Sahay's scientific contributions in basic neuroscience are matched by a remarkable track record of research funding. Dr. Sahay has secured grants and philanthropic gifts in excess of $8.5 million in direct costs. He is recipient of 3 R01s, a R35 from the NIH, a $1.1 million grant from the Simons Foundation, multiple Harvard Stem Cell Institute seed and collaborator grants, NARSAD Independent Investigator Award, Ellison Medical Foundation New Scholar in Aging award and an Alzheimer's Association International Research Grant. The incredible breadth of his program is recognized in R level grants from National Institute of Mental Health, National Institute of Aging and National Institute of Neurological Disorders and Stroke. Dr. Sahay was awarded a Career Development Award from the SFN and was named the James and Audrey Foster MGH Research Scholar.

Significant Supporting and Teaching Activities:

Dr. Sahay has been an independent investigator at the Center for Regenerative Medicine at the Massachusetts General Hospital since September 2011. He has proven to be terrific mentor for mentees at all levels of training. His mentorship style has been profiled by the Harvard Stem Cell Institute and is routinely lauded in Harvard undergraduate honors thesis critiques. All three of his first postdocs have successfully transitioned into independent academic faculty and industry scientist positions. Postdoctoral fellows in the Sahay lab have presented independently at national meetings including the Society for Neuroscience meeting and are recipient of multiple internationally competitive fellowships such as the Brain & Behavior Research Foundation (NARSAD) Young Investigator Awards. His first graduate student in the lab transitioned into a successful postdoctoral fellowship where she also secured a Brain & Behavior Research Foundation (NARSAD) Young Investigator Award. Postdoctoral Fellows and graduate students have published in *Nature Medicine*, *Nature Neuroscience*, *Neuron*, *Nature Communications* and *Cell Reports*. The trajectories of current postdoctoral fellows anticipate similar levels of success. Dr Sahay is fully committed to seeing postdoctoral fellows maximize their scientific potential in academia and industry. In 2017, Dr. Sahay launched a startup to create sustainable paths for postdoctoral fellows to biotech and pharmaceutical jobs. Dr. Sahay published a white paper documenting his experience in *Cell Mentor* so that other innovators would benefit from his insights and experience.

Dr. Sahay is fully committed to nurturing undergraduates who express an interest in biomedical research. Of the 5 Harvard undergraduates who have conducted thesis research in the lab, 4 have gone on to medical school (Harvard, UCSF, Case Western Reserve, Cleveland Clinic Lerner College of

Medicine research track) and one to graduate school (UC Berkeley). One was co-mentored by Dr. Arthur Kleinman and was awarded the Hoopes Prize, Harvard University's highest honor for an undergraduate thesis. Another graduated summa cum laude in Neuroscience. All 5 of these students are co-authors on publications from the Sahay lab. In addition to these students, Dr. Sahay's lab has continually supported undergraduates through other mechanisms. These individuals have gone on to be awarded the Barry Goldwater Scholarship and attend MD/PhD programs (Stanford) or join venture capital firms.

Dr. Sahay is conscientious of the importance of diversity and inclusion of underrepresented groups in the scientific enterprise. He is an active member of Cientific Latino's graduate student mentorship initiative (GSMI) program where he mentors minority undergraduates and provides guidance to prospective graduate students on crafting graduate school applications.

Dr. Sahay has made significant contributions to graduate level education at Harvard Medical School. He co-directed the Harvard BBS Program graduate level course on Concepts in Development, Self-renewal and Repair CB226 for five consecutive years (2014-2018). The purpose of this class was to teach G1/G2 and select undergraduate seniors critical thinking about development and regenerative biology. Student involvement in discussions and critique of published work was the core strength of this course. Students were trained to critically assess the current state of the art in stem cell biology, apply the same approaches to their own research and write graduate level fellowship applications. Because this class was held at MGH, it helped increase graduate student presence at the hospital and was tremendously valued by the Executive Committee on Research (ECOR) of Massachusetts General Hospital. He also serves on the thesis committees of a number of graduate students at Harvard Medical School through the Program in Neuroscience and BBS program. Additionally, he provides career guidance to graduate students in the DRB (developmental and regenerative biology) program.

Dr. Sahay also gives lectures to undergraduates and medical residents as part of courses on Regeneration, Neuroscience and Psychiatry at Harvard University and MGH. He participates in the MGH/McLean research track residency program and HMS Clinical and Translational Research Academy that recruit and train psychiatry residents. He reviews postdoctoral fellowships and faculty level applications for endowed Research Scholars for ECOR at MGH. Dr. Sahay provides R01 level grant writing mentorship to Assistant professors at MGH and co-chaired the Harvard Stem cell Institute Annual Retreat that brings together trainees from across the Harvard ecosystem.

Dr. Sahay has been invited to serve on local committees within MGH to foster basic neuroscience research. He serves as member of the Mass General Neuroscience Leadership Council, scientific council of Homebase which is a Red Sox Foundation and Massachusetts General Hospital Program for treatment of veterans and PTSD, and the newly founded Center for Neuroscience of Psychedelics at MGH. He co-founded a monthly seminar series for trainees in basic neural circuit neuroscience at MGH and Massachusetts Eye and Ear Institute and secured a Harvard Brain Science Initiative (HBI) Community Building Grant for it.

Dr. Sahay has contributed to the vibrance of the thematic research centers at MGH. He chaired the faculty search committee at the Center for Regenerative Medicine and served as the external Faculty member for faculty search at the Center for Genomic medicine. Dr. Sahay is an Associate Member of the BROAD Institute and has established productive collaborations to understand inhibitory neuron functions in memory and regulation of emotion.