Author Spotlight: Dr. Ruth H. Asch, PhD, Assistant Professor, UT Southwestern Medical School

Ruth H Asch, Hernandez Martin N, Garcia-Milian R, Fowles K, DiLeone RJ, Cai Z, Liston CM, Esterlis I. In Vivo PET Imaging of Presynaptic Density Reveals Stress-Associated Synaptic Deficits Related to Behavioral and Molecular Alterations in Rats. *Biological Psychiatry CNNI*, online ahead of print. doi: 10.1016/j.bpsc.2025.09.021.

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Interviewed by Isabelle Rosso, PhD

How did you first start thinking about this research question? What was the spark?

With the advent of PET imaging using radiotracers targeting the synaptic vesicle glycoprotein 2A (SV2A), we now have a way to measure synapses in the living human brain. To me, SV2A PET imaging represents an incredible, untapped opportunity to use the same measure to track synapses in our animal models as we are using in clinical populations. This represents a critical advance towards true mechanistic translational psychiatry research that can facilitate the process from preclinical discovery through to clinical application. I was excited to be able to demonstrate the potential of SV2A PET imaging to serve as this "translational bridge."

Tell us about your work in this paper - what was your study design?

In this study, we used PET imaging with the radiotracer [18F] SynVesT-1 to provide an in vivo measure of SV2A, and by proxy, synaptic density, in male and female rats exposed Chronic Unpredictable Stress (CUS). CUS is a long-established preclinical paradigm for probing the physiological, cellular, and molecular mechanisms subserving behavioral and cognitive changes associated with stress. We also conducted the sucrose preference and novel object recognition tests to assess stress-related behavioral phenotypes. This design allowed us to examine group-level differences in the PET synaptic density measure between CUS and no-stress controls, as well as correlations between our behavioral measures and regional synaptic density. Finally, we

performed label-free quantitative LC-MS/MS proteomics and linear regressions to explore relationships between protein abundance and synaptic density in the prefrontal cortex and hippocampus, providing insight into the greater neuroproteomic landscape underlying the SV2A PET measure.

What was the central finding? Why was this important?

Using in vivo SV2A PET imaging, we demonstrated lower synaptic density in the prefrontal cortex and hippocampus following CUS, which correlated with our measures of stress-related behavioral phenotypes. These findings are consistent with what has been reported using alternative methods, primarily post-mortem approaches, and in studies conducted predominately in male animals. These findings provide proof-of-concept that SV2A PET can be used as a scalable, longitudinal measure of synaptic changes in animal models of stress, and in psychiatric and neurological conditions, as well as a tool to monitor the synaptic impact of novel therapeutic agents.

Is there a little nugget buried in the results section that most readers might not notice?

I hope this is more than a "nugget", but one finding I want to highlight is the difference in the molecular response to stress between males and females. This is reflected by the lack of overlap in the stress-associated differences in protein abundance across sexes. Hopefully this can serve as a reminder that including both sexes in biomedical/biobehavioral research remains critical for advancing our understanding of sex differences in disease, improving diagnosis, and informing the development of targeted and sex-appropriate interventions.

What's next for your research?

Much prior research has focused on the effects of stress experienced in earlier stages of development; yet stress is experienced throughout life and there is clear evidence that the developmental timing of stress shapes its impact. Further, although significant evidence shows that stress accelerates biological aging, the specific mechanisms underlying stress-accelerated brain aging remain poorly defined. As part of my K01 award from the National Institute on Aging, I will be conducting studies to investigate stress- and age- related synaptic decline. My goal is to identify mechanisms that could serve as therapeutic targets to promote later-life stress resilience and healthy aging.

What are you most looking forward to at the next SOBP meeting?

As a brand-new faculty member at UT Southwestern Medical Center, I am excited to use the upcoming SOBP meeting to promote my new lab, receive feedback on our research, identify opportunities for collaboration, and potentially catch the interest of postdoctoral candidates!