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Adult Human Hippocampal Neurogenesis and Depression: Are We Closer to Solving the Puzzle?

Dr. Mirjana Maletic-Savatic is the Investigator at the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital and Associate Professor of Pediatrics, Neurology, and Neuroscience at Baylor College of Medicine. She is a Board- certified neurologist specialized in Child Neurology. Born in Belgrade, Serbia, Dr. Maletic-Savatic earned her medical degree and started her PhD at the University of Belgrade. Due to the outbreak of war in then Yugoslavia, she immigrated to the United States and completed her PhD degree in biophysics and neurobiology at Stony Brook University. Following a brief but very productive postdoctoral fellowship at Cold Spring Harbor Labs (her work on activity-dependent brain plasticity was a runner up for the Best Publication of the Year in Science), she pursued residency in child neurology at Stony Brook Hospital. Shortly after, she received a prestigious Phillip R. Dodge Young Investigator Award from the Child Neurology Society and was subsequently recruited by Dr. Huda Zoghbi to Baylor College of Medicine and the Duncan Neurological Research Institute. Dr. Maletic-Savatic has made important discoveries in the fields of learning and memory, adult neurogenesis, and NMR-based biomarker discovery. She has been recognized with many honors including the Neuroscience Brain Research Award from the McKnight Foundation, Brain Immuno-imaging Award from the Dana Foundation, NASA/TRISH Human Tissue Avatars grant, and Best Doctors in America among others. She is an avid supporter of women in science, technology, engineering and math, and actively mentors young women across the globe as part of the New York Academy of Sciences (Next Global Scholars, 1000 Girls, 1000 Futures).

Abstract: Adult hippocampal neurogenesis has been strongly associated with mood control in animal models. However, in the human brain, the extent and the functional significance of neurogenesis continues to be debated, in large part because the field has lacked a non-invasive method to measure the phenomenon in living organisms. Using magnetic resonance spectroscopy (MRS), we identified a fatty acid-related biomarker that is highly enriched in neuroprogenitors and visible on the MRS spectrum. We discovered, using a panel of biophysical, chemistry, and pharmacological tools, that neuroprogenitors are particularly abundant in mono-unsaturated fatty acid, one of which is an endogenous ligand for nuclear receptor NR2E1, required for their self-renewal, proliferation, and neurogenesis. We then developed an automated algorithm that allows objective quantitation of the fatty-acid

enriched neurogenic biomarker in the live human brain. The MRS neurogenic biomarker distinguishes neurogenic and non-neurogenic areas (N=35 subjects; Wilcoxon V=55, p=0.01) and is positively associates with pattern separation and response to antidepressant treatments (N=34; p=0.0029), while it declines with age (N=300; Rpartial=-0.23, p=0.004; df=224). In depressed individuals receiving electroconvulsive treatment (N=20), an early two-fold signal increase predicts subsequent hippocampal plasticity (R=0.70, p=0.0026) and clinical outcome (R=-0.53, p=0.036). We thus now have the means to study neurogenesis in the live human brain and in patients who suffer from depression. Moreover, we have a new druggable target that may lead to development of more effective therapies for depression, as we can stratify patients in whom pathology may depend on the rate of hippocampal neurogenesis.