Of mice and men: a translational approach to studying dopamine dysfunction in schizophrenia

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Abstract: The concept of cortical hypodopaminergia in schizophrenia (SCZ) has been widely accepted for years, with little empirical evidence for decreased dopamine release in patients. We have combined PET and fMRI methods in the same patients with SCZ, to measure cortical DA release capacity, using [11C]FLB457 with the amphetamine paradigm, and BOLD fMRI activation during a working memory task. We measured decreased capacity for DA release in dorsolateral prefrontal cortex (DLPFC), confirming the hypothesized cortical hypodopaminergia in schizophrenia, and a significant relationship between DA release capacity and BOLD activation in DLPFC. Surprisingly, we also observed a widespread decrease in DA release encompassing most cortical and extrastriatal regions, including the ventral midbrain (Slifstein, van de Giessen et al. 2014). The decrease of DA release in the midbrain is an unexpected and intriguing finding, in light of the well replicated findings of excess release in the striatum. This complex DA phenotype can be modeled in transgenic mice to shed light on its mechanisms and design better treatments.