Overview / Abstract: Glutamate is the primary neurotransmitter in the brain, used by as many as 90% of brain neurons.[1] It should therefore not be surprising that glutamate dysfunction has been implicated in diseases ranging from major depressive disorder (MDD) to Alzheimer's disease.[2] Magnetic Resonance Spectroscopy (**MRS**), a non-invasive imaging technique, can quantify brain glutamate through acquisitions requiring a few minutes in an MRI scanner. Because of its ease of use and the importance of the research questions it can address, MRS studies of brain glutamate are ubiquitous. For example, a search of NIH reporter for "magnetic resonance spectroscopy" and "glutamate" yielded 2,518 active projects, and there are **twenty-four**[3-26] published MRS studies in MDD. Unfortunately, in MDD, as in most MRS studies of glutamate, there is no consensus on the finding, with *higher* glutamate, *lower* glutamate and *no differences* in glutamate being reported. It was initially thought that these conflicting results occurred due to differences in cohorts examined. While this is not uncommon in science, a recent publication provided a more likely *surprising* explanation for these equivocal results. While it has always been known that **glucose (blood sugar)** and glutamate are related[27-31], this study showed, for the first time, that increasing glucose (i.e., consuming a meal) or decreasing glucose (i.e., fasting) **significantly affects brain glutamate**. This rigorous study showed consistent evidence of a significant effect of glucose variation on brain glutamate levels in experiments ranging from *in vitro* cell analysis, to two photon calcium imaging, to MRS in male rodents and male humans.[32] The implication of such a study is clear – **every estimate of brain glutamate from MRS to date may have been confounded by what the participant ate (or did not eat) prior to imaging!** Having published our own study of glutamate using MRS in MDD[26], this finding had significant implications in our own work. Therefore, using pilot funding, we performed a feasibility MRS study in which a participant received two brain MRS studies on the same day, consuming 75g of glucose before the second scan. Incredibly, the participant's ***brain glutamate increased by 8%*** (from 5.2 mM to 5.6 mM), with a corresponding similar increase in blood glucose***.*** This is a significant change, much greater than has been observed across diagnostic groups. With this knowledge comes a unique opportunity, which, to our knowledge, has not been attempted: We have the ability to determine a normalizing factor, based on glucose levels acquired at the time of the MRS scan. As MRS is acquired by noninvasive MRI imaging, most MRI centers are not equipped to acquire blood sampling (needed to assess glucose) during the MRS imaging. This may be the reason blood sampling was not performed during MRS in humans in the original study. However, we perform such analysis routinely on Stony Brook's simultaneous PET/MRI scanner. We therefore propose to image 18 healthy volunteers twice with MRS. All participants will arrive three hours prior to imaging to control food consumption in that time. Six participants will receive two MRS scans on the same day with no intervention in between. The remaining 12 will be counterbalanced – half the volunteers will consume 75g of glucose before the first scan, half will consume this glucose before the second scan. Both men and women will be included. Blood glucose measurements will be taken throughout the course of both scan sessions for all groups. This study is led by two PIs – a brain imaging expert in mood disorders, Dr. DeLorenzo, who just completed a study of >80 depressed participants using MRS and physicist, Dr. Huang, an expert in MRS acquisition and analysis. Using this data, we can identify **the first relationship between blood glucose and brain glutamate**, which could be used to develop a correction factor for brain glutamate measurements. Such a correction is critically needed in the field, as even if the MRS studies are acquired in a fasting state, differences in blood glucose in this state could still confound all MRS studies. Based on our preliminary data, we would immediately apply for an R01 study to expand the cohort, which would be needed to model non-linear effects and examine participants with blood sugar abnormalities (e.g., diabetes) whose MRS measurements have undoubtedly been confounded by this issue. Due to the widespread use of MRS to measure brain glutamate, and as the only group attempting to correct this significant issue, we would be in a competitive position to receive this funding.