Recent studies using an advanced diffusion model, Free Water Imaging (FWI), have demonstrated that fractional anisotropy (FA) reductions in schizophrenia (SZ) patients were mostly associated with increases in extracellular free-water (FW) in the early stages of the illness, while patients with chronic SZ predominantly showed decreases in FA of the tissue (FAt). Conversely, a study comparing patients with chronic bipolar disorder (BP) and healthy individuals (HC) reported that FW was increased in BP subjects suggesting a different trajectory compared to the one found in SZ patients. The present study is the first to investigate WM properties in adolescent-onset SZ and BP together. Utilizing conventional diffusion tensor imaging and FWI, we aim to identify imaging biomarkers that could help differentiate the biological nature of these two disorders.

**Methods:** Forty-eight (20F/28M) SZ patients (mean age: 16.28, 15 (7F/8M) BP patients (mean age: 15.52) and 35 (18F/17M) HCs (mean age: 15.65) were included in the study. The mean duration of psychosis (DOP) was 0.97 years in BP subjects and 1.84 years in SZ subjects. All participants underwent diffusion MRI scanning (1.5 T Siemens Magnetom Sonata, 60 gradient directions with b = 1000 m/s² and 5 images with b = 0 m/s²). Each scan was repeated three times to increase the signal-to-noise ratio and was subsequently corrected for motion and eddy currents before getting averaged. FA, FAt, and FW maps were calculated and then skeletonized using Tract-Based Spatial Statistics (TBSS). Voxel-wise, non-parametric statistics were conducted with 5000 permutations and threshold-free cluster enhancement controlling for age, sex and motion.

**Discussion:** Our results are in line with previous studies suggesting a perturbation of WM health in individuals suffering from BP and SZ. The use of FWI in the present study allows for the further clarification of the biological nature of FA reductions: while SZ patients showed only reductions in FAt compared to HCs, the BP group also had marked increases in FAt compared to HCs and the SZ group. These increases in FAt spatially overlapped with FA decreases, suggesting that an extra-cellular pathology is driving the observed FA reductions. The present alterations of WM properties in adolescent-onset BP are similar to those previously described in chronic BP and indicate that FW increases might be a biomarker of BP disorder. Interestingly, the adolescent SZ group, unlike recent-onset or first episode adult SZ cohorts, show no FW alterations, but instead FAt reductions similar to those previously reported in chronic SZ subjects. This could be explained by the longer illness duration, or different disease trajectories between adult and adolescent-onset psychosis. Taken together, we show differential patterns of WM aberrations in adolescent-onset SZ and BP, which lend support to the presence of distinct pathologies underlying the neurobiological development and manifestation of these disorders.

**Background:** Several neuroimaging studies have attempted to characterize the contribution of glutamatergic dysfunction to functional dysconnectivity of large-scale brain networks using ketamine models. However, findings from blood oxygen level-dependent (BOLD) imaging studies have been conflicting, in part because the signal stems from a complex interaction between blood flow, blood volume, and oxygen consumption.

**Methods:** We obtained multimodal neuroimaging in a group of healthy volunteers (n = 15) during a saline and during a ketamine infusion (0.27 mg/kg bolus over 10 minutes, followed by a continuous infusion of 0.25 mg/kg/hour for 50 minutes). We acquired 2D pCASL scans (TR/TE = 5200/35 ms, excitation flip angle = 90°, in-plane resolution = 3.75 x 3.75 mm², matrix = 64 x 64, slice thickness = 5.0 mm, label time 1s, delay time 1s, labeling offset 8cm) with 30 pairs of labeled and unlabeled images to measure regional cerebral blood flow (rCBF) and MR spectroscopy scans in the left hippocampus (TR/TE = 2000/80ms; 1200 Hz spectral bandwidth; 1024 points; 640 averages, and 8 with no water suppression, voxel size: 2.7x 1.5x 1.5cm) to measure glx (glutamate+glutamine). We examined changes in rCBF and metabolic connectivity, as well as their associations with clinical symptom severity (measured with the Brief Psychiatric Rating Scale [BPRS]) and glx levels.

**Results:** Voxelwise analysis comparing rCBF during a saline infusion and ketamine challenge demonstrated regionally selective increases in the prefrontal, orbitofrontal and cingulate cortices as well as the insula, angular gyrus, caudate, putamen, thalamus and hippocampus. No areas showed a decrease in rCBF. Metabolic connectivity analyses revealed a complex pattern of ketamine related rCBF changes. Positive correlations between the anterior cingulate/ frontal pole and insula decreased. Negative correlations between the hippocampus and the dorsolateral prefrontal cortex as well as the putamen decreased. We also found that the increase in rCBF in the bilateral putamen and left hippocampus was positively correlated with psychosis severity during the ketamine challenge while change in anterior cingulate cortex rCBF was negatively correlated with change in hippocampal Glx. 

**Discussion:** Here we find regionally selective patterns of rCBF changes, and metabolic connectivity changes at the level of large-scale brain networks that are thought to be central to the schizophrenia psychopathology. Our study adds to the efforts to confirm putative links between an imbalance in glutamate metabolism and dysconnectivity of large-scale brain networks. Development of glutamatergic compounds that alleviate disease burden, possibly through normalizing glutamate excess related increased rCBF, are direly needed.