Introduction: The power of fMRI in assessing neural activity and detecting group differences is often hampered by variations in fMRI responses across individuals. Previous studies have established that fMRI signal is modulated by a number of physiologic parameters including baseline venous oxygenation ($Y_v$) (1), cerebrovascular reactivity CVR (2,3), resting state BOLD signal fluctuation (4) and baseline cerebral blood flow (5). Normalization of fMRI signals with these parameters may be useful in reducing variations and improving sensitivity. However, none of the previous studies have tested this utility in patient populations. In the present work, we conducted an event-related fMRI study in three groups of participants. Schizophrenia volunteers on medication, Schizophrenia volunteers off medication, and healthy controls. We studied how fMRI normalization using baseline $Y_v$ may affect the detection of group differences. It was observed that un-normalized fMRI signals showed no differences across subject groups. After $Y_v$-normalization, however, significant group differences were identified in visual and motor regions. Further investigation by comparing each pair of groups suggested that untreated schizophrenia individuals manifested lower activations in visual and motor areas, and these deficits were mitigated by medication treatment, consistent with the hypothesized pathophysiology in this disease. The present study provides the first clinical demonstration that fMRI normalization using venous oxygenation in human disease studies can enhance detection power with relatively little added cost.

Methods: A total of 49 subjects were studied on a Philips 3T MRI scanner, with 20 Schizophrenia volunteers in the “off-medication” group (41.2±10.3 years), 14 Schizophrenics in the “off-medication” group (35.4±8.9 years), and 15 age-matched healthy controls (41.6±11.5 years). Each subject received 2 fMRI runs with 60 pictures in each run. Each picture appeared for 3s with jittered fixation time between the pictures. There were face and fish in each picture and the subjects were instructed to determine if the face and fish was the same matched pair as they saw during the treatment session before the fMRI scan, and to press buttons accordingly. Standard BOLD fMRI imaging parameters were used: TR/TE=1500/30ms, voxel size 3.4x3.4x5mm$^3$, duration 7.38 min per run. The baseline venous oxygenation ($Y_v$) was determined in the sagittal sinus using a TRUST MRI technique (7) with the following parameters: voxel size 3.4x3.4x5mm$^3$, TR=8000ms, TE=1200ms, four effective TEs: 0ms, 40ms, 80ms and 160ms, scan duration 4.5 min. FMRl signal was calculated as the contrast between picture viewing and fixation. The fMRI modulation effects were assessed in five foci ROIs, including the early visual areas, bilateral sensorimotor areas, ventral lateral prefrontal cortex (DLPFC), ventral lateral prefrontal cortex (VLPFC) and thalamus. To focus our analysis on activated voxels, only the top activated voxels within anatomic masks (from PickAtlas software) of those regions were included in the signal averaging. The fMRI signal amplitude was determined as the percent signal change. Data processing of TRUST followed methods used previously (7). FMRl signal normalization was based on a previous report and was simply scaling the signal using $Y_v$, i.e. $fMRI = fMRI/(1 Y_v)$ (8). ANOVA test on the three groups were performed before and after normalization. When the ANOVA showed there was significant difference among the groups, two sample t test was performed to assess individual group pair.

Results and Discussion: Group-level analysis showed robust activations (Fig. 1) in the five ROI areas. Fig. 2 shows a significantly correlation between $Y_v$ and fMRI signal in visual and sensorimotor ROI ($p=0.003$ and 0.002, respectively) across the subjects. Other ROIs also showed a trend of negative correlation between $Y_v$ and fMRI signal, although not significant ($p>0.08$). This inverse correlation was in agreement with previous studies in healthy controls (1,6), i.e., an individual with lower baseline $Y_v$, tends to have a greater BOLD fMRI signal. Since our measure of $Y_v$ is a global one and not region-specific, the current observation of a correlation in multiple brain regions confirms the previous finding that global measure of baseline $Y_v$ is sufficient for the purpose of fMRI normalization (6). There’s no group difference in baseline $Y_v$, among the three groups (ANOVA $p=0.91$). The ANOVA analysis on the fMRI signal showed no significant difference among the control and two patients groups in all five ROIs ($p=0.06$, 0.13, 0.13, 0.87 and 0.57 for visual, sensorimotor, DLPFC, VLPFC and thalamus ROI, respectively). However, after normalization of the fMRI signal to the baseline $Y_v$, the early visual areas and sensorimotor area showed significant difference among the three groups (Fig 3, $p=0.02$ and 0.03 for visual and sensorimotor ROI, respectively). Further two sample t test between the groups showed the normalized fMRI signal of the off-medication group is significantly lower than that of control group in early visual area ($p=0.01$) and in the sensorimotor area ($p=0.03$). In the sensorimotor area the off-medication group also showed lower normalized fMRI signal than the on-medication group.

Studies specifically designed to examine the functional integrity of primary visual cortex, primary motor and somatosensory regions in schizophrenia have provided mixed results, as some found diminished activation (9,10) while some found intact functional activation(11,12). Our result suggested the failure to find functional deficit in Schizophrenia may be due to the “normal variations” in the Schizophrenia which reduced detection power. After accounting for the baseline $Y_v$ difference, the patient groups, especially the off-medication group, are found to have lower brain activity than the control group. It also confirmed the previous finding that medication would help schizophrenia patients maintain their brain function.

In summary, this work extends previous findings in healthy controls, and showed a modulation effect of physiologic parameters on fMRI signals in a diseased population. The results demonstrated that, by accounting for basal physiologic parameters, the sensitivity of fMRI in differentiating patient population from healthy controls can be enhanced with relatively little cost. Since the global measures of baseline $Y_v$ is sufficient for the purpose of normalizing fMRI signals in multiple brain regions, this non-invasive, fast, and reliable approach may benefit a spectrum of fMRI studies.