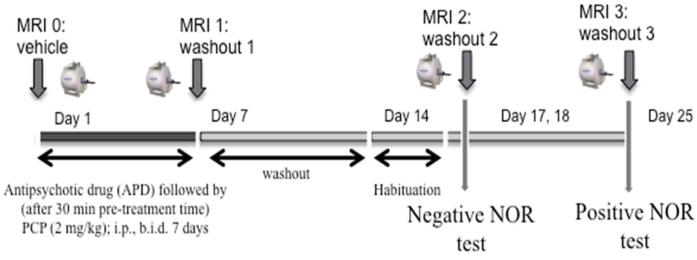
rsfMRI and 1H MRS in sub-chronic phencyclidine (PCP) rat model of cognitive impairment in schizophrenia. A longitudinal study to assess prevention of cognitive impairment deficit

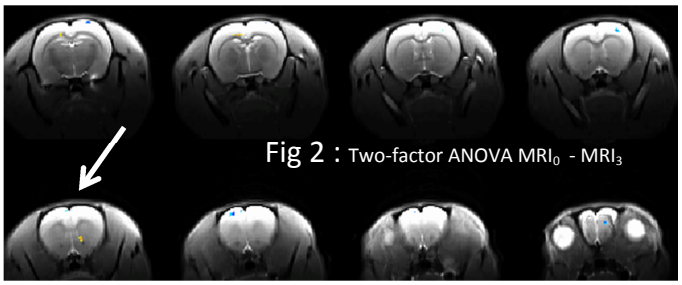
Daniele Procissi[1], Kathleen Anne Williams[1], Lakshmi Rajagopal[2], Yoshihiro Oyamada[2,3], and Herbert Meltzer[2]

[1]*Radiology, Northwestern University, Chicago, IL, United States,* [2]*Psychiatry and Behavioral Sciences, Northwestern University, Chicago, Illinois, United States,* [3]*Dainippon Sumitomo Pharma Co., Ltd, Japan*

BACKGROUND AND PURPOSE: Decreased glutamatergic function and altered brain connectivity are thought to be a major causal factor for the cognitive impairment in schizophrenia (CIS). Sub-chronic (sc) administration of NMDA receptor antagonists such as phencyclidine (PCP) to rats produces putative models of the disorder, inducing an enduring deficit in a variety of cognitive measures, including novel object recognition (NOR)[1]. This deficit can be reversed by treatment with the atypical antipsychotic drug Lurasidone, and recent work (published and unpublished) has shown that giving Lurasidone prior to each scPCP treatment can delay the onset of cognitive deficits[2,3] . In this study, we performed a longitudinal MRI investigation to measure functional connectivity and metabolism in a scPCP model of CIS at different time points during the experiment. The purpose was to assess changes in metabolism and connectivity that reflect the behavioral changes and to evaluate MRI as a potential predictor of successful pharmacological prevention of cognitive impairment.

METHODS 8 Female Long-Evans rats were subjected to scPCP and Lurasidone, as described in the schematic timeline in Fig 1. Animals were scanned at the four time points as diagramed below.





The NOR test was used to assess each animal before and after treatment. For MRI scans, rats were anesthetized using dexmedetomidine hydrochloride and scanned on a 7T Bruker ClinScan. Scan sessions included non stimulated resting state (rs) fMRI and 1H-MRS protocols. FMRI scanning parameters: 300 echoplanar images, 2s TR, 25ms TE, 18 slices, with resolution 0.5x0.5x1mm^3. Single voxel (0.4 mm^3 volume) 1H-MRS was acquired from prefrontal cortex (PFC) in a sub-set of animals pre and post PCP administration (no Lurasidone). The spectra were fitted and metabolite quantitation was extracted in mM using Tarquin software. Rs-fMRI processing used AFNI to perform a seed-based cross correlation (CC) time course of a region of interest in the hippocampus. Two-factor ANOVA was applied to the grouped results, with attention to contrasts between pre-treatment (MRI_0) and each following scan session (MRI_1, MRI_2 and MRI_3), and the presence of NOR deficits.

RESULTS: Shown are the two-factor ANOVA results for the contrast MRI_3-MRI_0 corresponding to pre and post-treatment latest time point. At this time NOR deficit was observed and results reflect the corresponding connectivity differences between the different conditions. Not shown here are the ANOVA maps for the other comparisons. The spectroscopy data, not shown here, for the pre and post PCP cohort was quantified in mM.

DISCUSSION AND CONCLUSION

Using rs-fMRI, we interrogated specifically the interaction of the hippocampus with the whole brain in the context of a sc-PCP-induced NOR-deficit prevention behavioral test. Most significant differences in hippocampal connectivity were reduced in some regions of the brain, but some increased hippocampal connectivity was observed in the latest time point (observed NOR deficit) in respect to earliest time point (pre PCP), as evidenced by white arrow (NAC) in Figure 2. When comparing between the earliest time point and two weeks after washout (no NOR deficit observed), several regions were found to have reduced connectivity. Metabolite analysis showed no alteration in Gln and Glu, contrary to what is expected with ^{1}H-MRS measurements. However, metabolism shift involved with anesthesia may overpower any intrinsic Gln and Glu. We have shown that a dynamic paradigm of scPCP plus Lurasidone administration reflects differences in functional connectivity with the hippocampus across time, mirroring the delay and onset of NOR. This study shows promise for longitudinal fMRI studies of the brain that can track functional brain changes associated with behavioral changes across the course of an experimental paradigm involving pharmacological intervention.

REFERENCES:

[1] Javitt DC et al. *Has an angel shown the way? Etiological and therapeutic implications of the PCP/NMDA model of schizophrenia.*Schizophr Bull, 38(5): 958-996, Sept 2012

[2] Horiguchi M et al *The role of 5-HT1A receptors in phencyclidine (PCP)-induced novel object recognition (NOR) deficit in rats.* Psychopharmacology (Berl)221(2):205-15. May 2012

[3] M. Horiguchi,, et al. *Prevention of the Phencyclidine-Induced Impairment in Novel Object Recognition in Female Rats by Co-Administration of Lurasidone or Tandospirone, a 5-HT$_{1A}$ Partial Agonist.* M Neuropsychopharmacology, 37: 2175-2183 Sept 2012