The effects of ketamine on default mode connectivity in major depression

J.W. Evans¹, A. Nugent¹, C.E. Chang², C. Zarate¹

¹Experimental Therapeutics and Pathophysiology Branch, NIMH, NIH, Bethesda, MD, USA, ²Advanced MRI Section, NINDS, NIH, Bethesda, MD, USA

Background: Major depressive disorder (MDD) carries the heaviest burden of disability among mental and behavioral disorders according to the World Health Organization (WHO, 2010). Novel drugs such as ketamine have garnered interest because they can relieve depressive symptoms within hours (Zarate, 2013). Investigations of its mechanism of action could help identify biomarkers of response and of depression, which would greatly speed and reduce the cost of drug development and patient treatment. In the current study, a cohort of MDD patients and healthy controls each had five resting state fMRI scans over the course of a double blind randomized placebo controlled cross-over ketamine infusion study. The resting state default mode network is used here to investigate differences after the infusion of ketamine in MDD patients.

Methods: 30 MDD subjects (unmedicated, ages 20-65, 17 female), 20 healthy controls (20-50, 10 females) are included in this analysis. Montgomery–Asberg Depression Rating Scale (MADRS) ratings and resting state fMRI scans were obtained at baseline and 2 and 10 days post each infusion. Scans were 10 minutes long with the subject's eyes closed. Cardiac and respiration data were also recorded. The data was processed using AFNI (Cox, 1996). The default mode was defined by taking the average timecourse from a 6mm radius sphere placed at the posterior cingulate cortex, MNI coordinates (0,-52,27)(Raichle, 2011). A group analysis using a linear mixed effects model (GroupxScan*MADRS) with contrasts of pairwise differences between each scan and baseline as well as drug–2day with placebo-2day was implemented using 3dLME (Chen, 2013). The effect of the drug was isolated by performing a conjunction analysis among the drug>baseline and drug>placebo contrasts at threshold of p<0.1.

Results: The MDD group MADRS scores over the course of the study curve reproduces what has been seen in the literature (Zarate, 2006), and the first scan after the drug infusion has the largest difference in MADRS score change, or improvement in depression. The conjunction analysis illustrating locations of the insula, thalamus/pulvinar, MT and anterior cingulate at a threshold of 0.1 (two-tailed) are found to be affected by the drug infusion. Several of these regions are part of the salience network which is implicated in the processing of negative information in MDD (Hamilton, 2012).

Conclusions: The results indicate that ketamine may affect the interplay of the salience network and the default mode, and following the triple-network model of depression (Menon, 2011) could underlie the improvement of depression symptoms. Expanding the seed set beyond the standard seed ROIs to more depression specific regions and investigating the inter-network connectivity changes as well as those in healthy controls will clarify the roles of these regions in the response to ketamine in major depression.