Restoration of Abnormal Interconnectivity between Memory and Emotional Processing Circuits in Remitted Late-Life Depression

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Introduction: With increase in life expectancy, late-life depression (LLD) is a growing public health concern in the U.S. and around the globe. LLD is associated with greater morbidity, increased incidence of Alzheimer's disease and premature mortality [1]. Although task-based functional MRI (fMRI) and single-seed functional connectivity MRI (fcMRI) have been extensively used to study the disease, these methods show limited success in simultaneously analyzing multiple brain circuits (or networks). In current study, we use a recently developed method called step-wise connectivity [2] to identify the brain regions that are responsible for the integration of memory encoding and emotional processing networks. We hypothesize that the abnormal interconnectivity between memory and emotional processing networks, which will be seen in LLD, will show recovery towards normal patterns in remitted patients.

Methods: A total of 59 elderly participants (age > 60 yrs) were enrolled in the current study, including 28 controls (CN), 23 LLD, and 8 remitted LLD (rLLD). All participants received a set of MRI scans including a whole resting-state BOLD fMRI (TR=2s, TE=25ms, voxel dimension = 3.75×3.75×4mm^3) followed by a high-resolution SPGR anatomical MRI on a 3T GE Signa LX scanner. ***Data Analysis:*** Step-wise functional connectivity [2] was used to determine the whole-brain direct interconnectivity of the seed regions of interest (ROIs) (amygdala and hippocampus seeds). First, the resting-state fMRI was spatially normalized to MNI space and down-sampled to 6 mm isotropic voxels. Voxels-wise Pearson product-moment correlation coefficient (cc) was calculated between each and every pair of voxels within the brain boundary (cortical and subcortical areas) to obtain a 5971×5971 functional connectivity matrix for individual participant used. Next, a FDR threshold at p = 0.001 is applied to minimize the false positive correlations and eliminating the connections with low temporal coherence. Only significant positive correlations were used to construct a binarized connectivity matrix for further analysis. The direct interconnectivity of a voxel to the seed ROIs was calculated as the sum of the number of pathways, with path length = 1, between that voxel and any of the voxels within the target ROIs [2]. Finally, the resulting voxel-wise interconnectivity map was normalized to values between 0 and 1 for each participant. One-sample t-test was used to obtain the pattern of whole brain interconnectivity map for the CN group ($p < 0.005$, corrected) **(Fig. 1)**. ANOVA and post-hoc t-tests were performed to show group differences among the CN, LLD, and rLLD groups ($p < 0.05$, corrected).

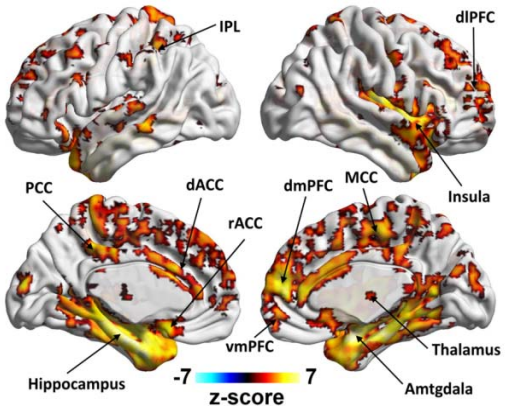

Fig. 1. *One-sample t-test of the direct interconnectivity of hippocampus and amygdala seeds in the CN group ($p < 0.005$, corrected).*

Results and Discussion: Brain regions showed significant direct interconnectivity to the hippocampus and amygdala seeds (**Fig. 1**) include the posterior cingulate (PCC), middle cingulate (MCC), dorsal and rostral anterior cingulate (dACC and rACC), ventral and dorsal prefrontal cortices (vmPFC and dmPFC), inferior parietal lobule (IPL), insula, thalamus, hippocampus, and amygdala. Of these regions, PCC, rACC, dACC, vmPFC, dlPFC, and IPL also showed significantly increased interconnectivity in LLD patients compared to CN (**Fig. 2A**). Interestingly, these brain regions are closely associated with the multidomain cognitive function and emotional processing in the human brain and have been implicated in depression [3, 4]. In rLLD, only MCC, IPL, and rACC showed significantly increased interconnectivity when compared with CN group (**Fig. 2B**). Finally, interconnectivity in the dlPFC, vmPFC, dACC and PCC was significantly decreased in rLLD group compared to LLD, signaling a recovery towards normalcy (**Fig. 2C**). Our results suggest that direct functional interconnectivity analysis is a useful tool to study neuropsychiatric disorders such as LLD, and to monitor the treatment response.

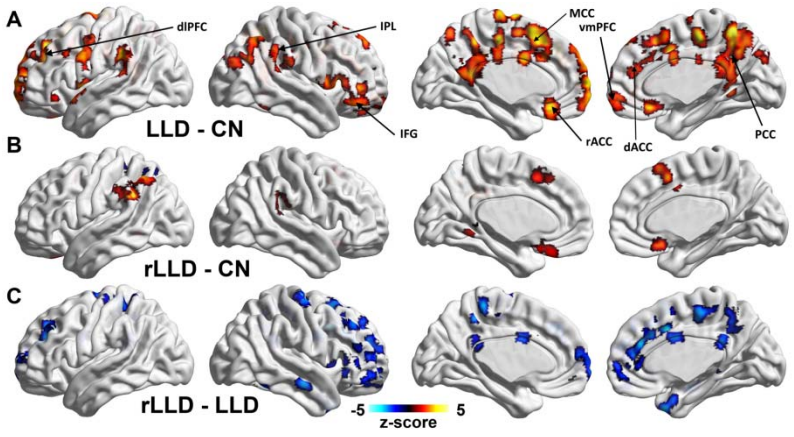

Fig. 2 *Post-hoc t-test of the direct interconnectivity of hippocampus and amygdala seeds among the CN, LLD, and rLLD groups ($p < 0.05$, corrected). The abnormally high interconnectivity in the LLD group is significantly recovered in the rLLD group.*

References: **1**. Alexopoulos GS. Lancet 2005. **2**. Sepulcre J. J Neurosci 2012. **3.** Ajilore O. J Geriatr Psychiatry Neurol 2014. **4.** Mayberg H. Br Med Bulletin 2003. ***Acknowledgement:*** This work was supported by Alzheimer's Association International Research New Investigator (NIRG-11-204070), Extendicare Foundation, Advancing Healthier Wisconsin Research for a Healthier Tomorrow and NARSAD Young Investigator.