Investigating the Role of Brain Stem in Alzheimer's Disease using Directional Brain Networks derived from Resting State fMRI

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Introduction: Connectivity analysis of resting state fMRI has been widely used to identify biomarkers of Alzheimer's disease (AD) based on brain network alterations. Specifically, seed-based functional connectivity and whole brain analysis revealed decreasing connectivity and network integrity in AD compared to healthy aging, with the Default Mode Network being the hardest hit system [1]. On the other hand, directional connectivity models have reported distributed increases as well as decreases in causal relationships among brain regions in mild cognitive impairment and AD [2]. It is difficult to interpret these connectivity results because traditionally, our knowledge of brain function is anchored on regions (activations and morphometric changes) and not connections. Further, from an interventional standpoint, it is easier to functionally modulate the activity of regions (using brain stimulation, neurofeedback etc) rather than connections. Therefore, Venkataraman et al [3] recently introduced a method for identification of disease foci based on non-directional functional connectivity differences between populations. Here we extend this concept for identifying focal directional connectivity deficits in AD as compared to matched controls.

Method: Resting state fMRI data from 98 control participants (NC) and 61 patients with AD were acquired from the Alzheimer's disease Neuroimaging Initiative (ADNI) database [4]. The data was subjected to standard resting state preprocessing pipelines using SPM8 [5] and DPARSF [6] toolboxes. Mean time series were then extracted from 200 functionally homogeneous regions of interest (ROIs) identified via spectral clustering [7]. Latent neural signals underlying these time series were obtained using blind hemodynamic deconvolution using a Cubature Kalman filter [8] and input into a multivariate autoregressive model (MVAR) in order to obtain measures of directional influence between brain regions using correlation-purged granger causality (CPGC) [9]. A generative model was formulated based on CPGC path weights, characterizing disordered connectivity emanating from or driving into the affected foci. Variational expectation-maximization algorithm was used to fit the model, identifying foci that were affected mostly by the disease. This is an adaptation of a similar previous approach described for non-directional functional connectivity [3]. Finally, paths which were statistically different between the groups for the identified foci were obtained.

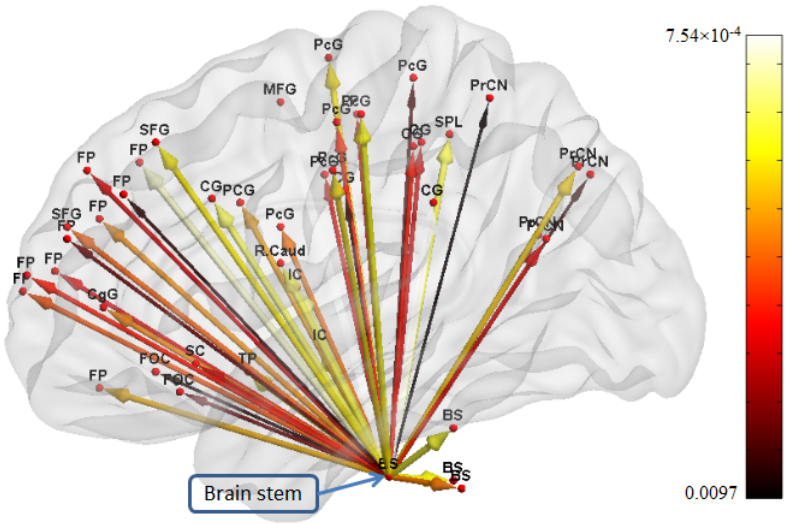

Fig.1 *Directional influences out of the identified disease focus of brain stem. Note that all paths had significantly higher connectivity in controls compared to AD*

Results and Discussion: Brain stem was found to be sole focus whose directional connectivity was significantly ($p<0.05$ FDR corrected) affected by AD. As shown in Fig.1, 43 such paths were identified as having significantly higher connectivity in controls as compared to AD. Interestingly, all paths represented the directional influence of the brain stem on mostly cortical (and few sub-cortical) regions. This is in accordance with previous studies that have shown progressive damage [10] in brain-stem during early periods of AD. Further, Locus Coeruleus in the brain stem is the largest repository of Norepinephrine (NE) in the human brain [11]. Noradrenergic neurons in LC project to many parts of the brain including olfactory, limbic and prefrontal areas. NE is known to suppress neuroinflammation [12]. This purported role has been hypothesized to be a protective factor against AD. In fact, Heneka et al [13] showed that NE stimulation of mouse microglia suppressed Aβ-induced cytokine and chemokine production and increased microglial migration and phagocytosis of Aβ. Induced degeneration of brain stem increased expression of inflammatory mediators in APP-transgenic mice and resulted in elevated Aβ deposition. This indicates that decrease of NE in brain stem facilitates the inflammatory reaction of microglial cells in AD and impairs microglial migration and phagocytosis, thereby contributing to reduced Aβ clearance. These findings indicate that depletion of NE in LC is an etiological factor in the development of MCI and progression to AD. Our identification of brain stem as the disease focus in AD supports the above observations and suggests that functional MRI studies of AD, which have been very cortico-centric, must in future investigate the role of this structure in AD

References: **[1]** Dennis *et al,* Neuropsychol Rev, 24:49-62, 2014 **[2]** Liang *et al*, *PLoS One*, 9(3): e88476, 2014 **[3]** Venkataraman *et al*, *IEEE Trans Med Imaging*, 32(11), 2012 **[4]** http://www.loni.ucla.edu/ADNI **[5]]** Friston *et al*, *Human Brain Mapping*, 2(4), 189-210, 1995 **[6]** Chao-Gan et al, *Front Syst Neurosci*, 4(13), 2010 **[7]** Craddock *et al*, *Hum Brain Mapp*, 33(8): 1914-28 **[8]** Havlicek *et al*, *NeuroImage,* 56(4): 2109-2128, 2011 **[9]** Deshpande *et al*, *IEEE Transactions on Biomedical Engineering,* 57(6):1446:1456, 2010 **[10]** Kienzl, *et al*, *Life Sci*, 65(18-19): 1973-6, 1999 **[11]** Herregodts *et al*, *Brain Research*, 542: 300-306, 1991 **[12]** Weinshenker *Current Alzheimer Research*, 5: 342-345, 2008 **[13]** Haneka *et al*, *Journal of Neurochemistry*, 85: 378-398, 2003.