The relationship of neuroimaging measures to dementia status and cognition in older adults with Down Syndrome

Katherine A Koenig[1] and Pallab Bhattacharyya[1]
[1]*Imaging Sciences, The Cleveland Clinic, Cleveland, OH, United States*

Target audience: This research is of interest to those involved in research with Down Syndrome, Alzheimer's disease, and other dementias.

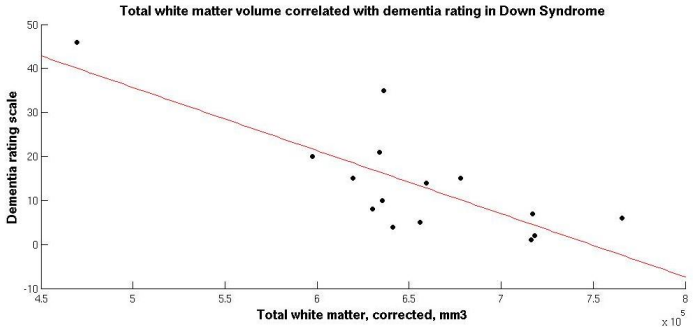
Purpose: Individuals with Down Syndrome (DS) show earlier and more frequent diagnosis of Alzheimer's (AD)-like dementia than the general population[1]. The increased incidence of dementia and the difficulty of diagnosis in this population highlight the need for both markers of disease onset and progression and an understanding of AD pathology in DS. The objective of the current work is to determine if neuroanatomical and proton magnetic resonance spectroscopy (1H-MRS) measures are related to level of cognitive functioning and dementia in individuals with DS.

Methods: 15 adults with Down Syndrome (mean age 44.6 ± 6.9, 6 males) were scanned in an IRB-approved protocol at 3T, in a 12-ch receive head coil. Scans included T1-MPRAGE and single voxel point resolved spectroscopy (TE 30 ms, TR 3000 ms, 96 data averages) at the left dorsal lateral prefrontal cortex (DLPFC) with and without water suppression.

1H-MRS data analysis using jMRUI software package[1] involved (i) zero order phase correction using residual water signal, (ii) residual water suppression using HLSVD filter[3], (iii) apodization with a 5 Hz Gaussian filter, (iv) zero filling and (v) baseline correction. QUEST algorithm[4] was used for metabolite quantification. The basis set for QUEST was calculated using product-operator based NMR-SCOPE[5] with spin Hamiltonian parameters from [6]. Gray matter (GM), white matter (WM) and CSF contribution to the voxel composition was calculated using FAST[7] with the T1-MPRAGE as the base image and used in the calculation of metabolite levels.

Total tissue volume and a volumetric scaling factor were estimated with the FSL program SIENAX[8], and more detailed anatomical volumes were estimated using the program Freesurfer[9]. All volumes were corrected for head size using the volumetric scaling factor.

Cognitive functioning was measured using the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS–IV). The Dementia Questionnaire for Learning Disabled Persons (DLD) was used to determine dementia status.



Results: DLPFC Choline (Cho) is correlated with both the social component of the DLD ($p=0.025$) and inversely related to full scale IQ on the WAIS-IV (FSIQ) ($p=0.045$). There was no relationship between 1H-MRS measures and age. We find substantial inverse correlations between neuroanatomical measures and both age and DLD scores. Total cortical and subcortical grey matter volumes are correlated with age ($p < 0.002$), while bilateral and total white matter volumes ($p < 0.001$) and bilateral ventricular volumes ($p < 0.005$) are correlated with total DLD score (Figure 1). Note that there is one subject with a high DLD score. Our findings remain significant if the outlier is removed.

Discussion: In the current study, Cho is the only measure which shows a relationship with measures of cognition. Prior research has shown increased Cho in individuals with DS, suggesting metabolic abnormalities[10,11], though our study is the first to suggest a relationship with cognition or dementia. We found no relationship between DLPFC *myo*-inositol (mI) and neuropsychological measures, though previous studies suggest hippocampal mI is related to both overall cognitive ability and to dementia status in DS[12,13]. We also find that measures of total white matter and ventricular volume are related to a measure of dementia and that cortical and subcortical grey matter volumes are related to age. The complex relationship between cognition, dementia, and age is highlighted in these results, particularly as subcortical grey matter volume has previously been found to relate to dementia status[14].

Conclusion: In individuals with DS, we find a relationship between DLPFC Cho and dementia status and overall cognitive ability, and between neuroanatomical measures and dementia status. These results highlight the need for longitudinal studies of this population, to clarify the relationship between imaging measures, baseline cognitive ability, and dementia.

References: [1] Roizen, Patterson, Lancet. 2003; 361: 1281-1289. [2] http://www.mrui.uab.es/mrui/ [3] Pijnappel et al., J. Magn. Reson. 1992; 97:122-134. [4] Ratiney et al., Magma. 2004;16(6):284. [5] Graveron-Demill et al., J Magn Reson, Series A. 1993;101:233. [6] Govindaraju et al., NMR Biomed. 2000;13(3):129. [7] Zhang et al., IEEE Trans Med Imaging. 2001;20(1):45. [8] Smith et al., NeuroImage. 2002; 17: 479-489. [9] Fischl et al., Neuron. 2002; 33: 341-355. [10] Huang et al., Am Journal of Psychiatry. 1999; 156(2): 1879-1886. [11] Murata et al., Biol Psychiatry. 1993; 34(5):290-297. [12] Beacher et al., Archives of General Psychiatry. 2005; 62(12):1360-1365. [13] Lamar et al., NeuroImage. 2012; 57:63-68. [14] Haier et al., NeuroImage. 2008; 39(3):1324-1332.
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