Comparison of Healthy Young and Elderly: A Study using Automated Whole-Brain *N*-Acetylaspartate Quantification

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Target audience: Neurologists/clinicians; MRI/MRS researchers of normal aging/dementia; the elderly and their caretakers.

Purpose: An estimated 40 million Americans (14% of the U.S. population) are ≥65 years of age, comprising a demographic expected to double in size (to ›20% of the population) by 2040.[1] Since various neurological conditions, including Alzheimer's disease (AD) and the broad spectrum of cerebrovascular disorders, affect the elderly in particular, societal and economic burden to healthcare will likely become staggering. This underscores a need for markers of normal aging to facilitate early detection of abnormalities – during a stage when preemptive treatment may be most effective – and to monitor therapy response. The whole-brain concentration of *N*-acetylaspartate (WBNAA), a marker of global neuronal health, can be used as a surrogate for diffuse neuronal dysfunction and loss, and has been used to monitor neuronal status in AD, normal aging, as well as other brain disorders.[2] Using a manual NAA integration method, we previously showed a significant between-cohort WBNAA variance difference between groups of cognitively-intact elderly and healthy young.[3] Recently, we demonstrated improved WBNAA quantification using a new, automated spectral modeling software that showed ~40% improvement in test-retest reliability.[4] Therefore, in this study we test the hypothesis that, with application of this refinement to the method, we will be able to measure the intrinsic ("true") biological variation associated with healthy young and elderly.

Methods: All MR experiments were performed on 3 T human scanners (Magnetom Trio, Siemens AG, Erlangen, Germany) using the standard circularly-polarized transmit-receive head-coil. Each subject's whole-brain volume was obtained from T_1-weighted sagittal magnetization prepared-rapid acquisition gradient-echo MRI [*TE*/*TR*/*TI*: 3.49/2150/1000 ms, 7° flip angle, 144 slices, 1 mm slice thickness, 256×224 matrix, 256×256 mm^2 field-of-view] using our in-house FireVoxel MRI-segmentation package.[5] The amount of whole-head NAA for each subject was obtained through non-localizing ^{1}H-MRS, *TE*/*TI*/*TR*=0/940/10^4 ms, as described previously.[6] Although lacking explicit spatial localization, this relies on the *implicit* localization of NAA to just the neurons, *i.e.,* to brain only. A novel, automated spectral modeling program was used to fit the NAA peak using parametric metabolite modeling and wavelet filtering of the full MR spectrum, recently shown to improve NAA quantification reliability by ~40% in young controls.[4] Institutional units were scaled via phantom replacement against a reference 3 L sphere of 1.5×10^{-2} mole NAA in water, and NAA peak areas were converted to absolute molar amounts, as described elsewhere.[7] These were normalized to brain size-independent WBNAA concentrations by dividing by brain parenchymal volumes determined using FireVoxel.

WBNAA was determined for 20 healthy young (12 men, 8 women), 32.9±5.0 (mean±standard deviation) years-old, and 41 cognitively-intact normal elderly (23 men, 18 women), 68.9±7.7 years-old. "Normal" for the elderly was established based on neurological and neuropsychiatric examinations as well as age-appropriate, unremarkable MRI. All subjects gave written IRB-approved informed consent. Analysis of covariance was used to compare the two groups in terms of mean WBNAA, adjusting for gender.

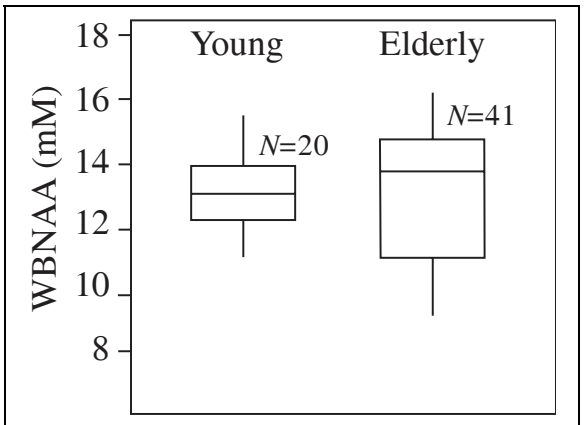

Fig. 1. Box plots showing the first, second (median) and third quartiles (*box*), and ±95 percentiles (*whiskers*) of the WBNAA distribution in healthy young individuals versus in cognitively-intact elderly. Note the similar distributions, especially with respect to medians.

Results: Mean WBNAA in young was 12.8±1.4 mM [coefficient of variation (CV)=11%] compared with 12.8±2.7 mM (CV=21%) for normal elderly, as shown in Fig. 1. Compared with young, elderly WBNAA showed a significantly broader distribution (p‹0.001) (Fig. 1). Compared with manual NAA quantification,[3] the new computer-fitting method (which reduces variability due to operator bias and baseline roll) reduced the within-cohort CVs by 26% (p‹0.03) and 11% (p=0.05) in young and elderly, respectively.

Discussion: Using a novel, automated WBNAA quantification method, we replicated our earlier finding [3] of no significant WBNAA difference between two cohorts with mean age difference ›35 years, despite (normal) brain volume atrophy of 0.33%/year.[8] Similar WBNAA levels over a span of ~four decades of aging suggest brain durability in surviving tissue and functional "quality" of the remaining brain in normal elderly. Broader WBNAA spread in elderly compared with in young, however, suggests divergent, possibly age-related (but still age-appropriate) processes that the elderly encountered over 35 years of normal aging, but which did not adversely affect cognition or overall neuronal health.

Conclusion: Global neuronal health is not compromised with normal aging, though a larger CV in the elderly suggests more divergent processes (possibly age-related) than in young. Moreover, lower reduction in within-cohort CV for elderly versus for young using the new, automated spectral modeling suggests an intrinsic biological variation in elderly, as it does not appear this can be improved further (by instrumental means). This information may be useful for determining proper sample sizes in studies of the elderly to measure desired effects with adequate statistical power.

References: 1. Future Growth. 2013; http://www.aoa.acl.gov/Aging_Statistics/Profile/2013/4.aspx. 2. Rigotti DJ, Inglese M, Gonen O. Whole-brain N-acetylaspartate as a surrogate marker of neuronal damage in diffuse neurologic disorders. *AJNR Am J Neuroradiol.* 2007;28(10):1843-1849. 3. Wu WE, Gass A, Glodzik L, et al. Whole brain N-acetylaspartate concentration is conserved throughout normal aging. *Neurobiol Aging.* 2012;33(10):2440-2447. 4. Soher BJ, Wu WE, Tal A, et al. Automated whole-brain N-acetylaspartate proton MRS quantification. *NMR Biomed.* 2014;27(11):1275-1284. 5. Mikheev A, Nevsky G, Govindan S, Grossman R, Rusinek H. Fully automatic segmentation of the brain from T1-weighted MRI using Bridge Burner algorithm. *J Magn Reson Imaging.* 2008;27(6):1235-1241. 6. Gonen O, Viswanathan AK, Catalaa I, Babb J, Udupa J, Grossman RI. Total brain N-acetylaspartate concentration in normal, age-grouped females: quantitation with non-echo proton NMR spectroscopy. *Magn Reson Med.* 1998;40(5):684-689. 7. Soher BJ, van Zijl PC, Duyn JH, Barker PB. Quantitative proton MR spectroscopic imaging of the human brain. *Magn Reson Med.* 1996;35(3):356-363. 8. Scahill RI, Frost C, Jenkins R, Whitwell JL, Rossor MN, Fox NC. A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. *Arch Neurol.* 2003;60(7):989-994.