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Neuronal number and size display concordance with disease phenotype in primary progressive aphasia with TDP-43 pathology

G. KIM¹, I. A. AYALA², S. LAMERAND³, R. SHAHIDEHPOUR⁴, T. GEFEN⁵, *S. WEINTRAUB⁶, E. BIGIO², M.-M. MESULAM⁷, C. GEULA⁸;

¹Stanford Univ., Stanford, CA; ²Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; ³Cognitive Neurol. and Alzheimer's Dis. Ctr., Chicago, IL; ⁴MCCNAD, Northwestern Univ., Chicago, IL; ⁵Cognitive Neurol. and Alzheimer's Dis. Ctr., Feinberg Sch. of Medicine, Northwestern Univ., Chicago, IL; ⁶Northwestern University, Feinberg Sch. of Medici, Chicago, IL; ⁷Norrthwestern Univ., Mesulam Ctr. For Cognitive Neurol. and Alzheim, Chicago, IL; ⁸Mesulam Cogn Neurol & Alzhei Dis Cent, Northwestern Univ. Med. Sch., Chicago, IL

Primary progressive aphasia (PPA) is a neurodegenerative disorder in which loss of language function is the most salient clinical feature. PPA is characterized by significant atrophy in the perisylvian language network in the language dominant hemisphere (LDH). A proportion of PPA brains present with TDP-43 containing inclusions in the brain at autopsy (PPA-TDP). We previously showed that the density of TDP-43 inclusions and activated microglia in PPA-TDP display concordance with disease phenotype; they are more prominent in language cortical regions and show significant asymmetry favoring the LDH. TDP-43 inclusions also predominate in areas of greatest atrophy. The purpose of this experiment was to determine whether neuronal number and size display similar concordance with disease phenotype. The density of Nissl-stained cortical pyramidal neurons were determined in the language cortical areas including inferior frontal gyrus (IFG), inferior parietal lobule (IPL) and superior temporal gyrus (STG), and the memory-related entorhinal cortex (EC), in a cohort of PPA-TDP brains using unbiased stereological counting techniques. Perikaryal area of neurons in layers III and V of these regions was also determined in both LDH and the non-language dominant hemisphere (NLDH), using the Image J software. Across regions, the number of neurons was slightly but consistently lower in the LDH compared to same regions in NLDH. Size of layer V neurons showed more consistent asymmetry and was smaller in the LDH in the language-related IPL and STG, but not in the memory-related EC. The hemispheric asymmetry of layer V pyramidal neuronal size reached statistical significance in STG ($p < 0.02$). A case with language function localized to the right hemisphere by functional MRI showed consistently smaller neuronal size in the right hemisphere across all regions ($p < 0.0001$). These preliminary findings suggest that neuronal size and to a lesser extent neuronal number show alterations in PPA-TDP that are consistent with regional specificity and asymmetry of language function.

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