Microstructural changes in the penumbras of cerebral small vessel disease lesions are associated with cognition and sleep.

Joel Ramirez1,2†, Kirstin Walker1†, Melissa McSweeney1, Hassan Akhavein1, Melissa F Holmes1, Miracle Ozzoude1, Christopher JM Scott1, Fuqiang Gao1, Seyyed MH Haddad2, Paula McLaughlin4,5,6, Brian Levine2,6, Donna Kwan2, Manuel Montero-Odasso2, Elizabeth Finger2, William E McIlroy10, Anthony E. Lang11, Maria C. Tartaglia12,13, Jennifer Mandzia9, Bradley J MacIntosh1,2,14, Morris Freedman2, Jennifer Rabin1,15, Stephen C. Strother4,14, Mario Masellis11,16, Sean Symons17, Robert Bartha3,18, Andrew Lim11,16, Richard H Swartz2,16, Sandra E Black2,16, Maged Goubran1,14, ONDRI Investigators

1Hurvitz Brain Sciences Program, Sunnybrook Research Institute, University of Toronto (UofT), 2Heart and Stroke Foundation Canadian Partnership for Stroke Recovery (Sunnybrook site), 3Centre for Functional and Metabolic Mapping, Robarts Research Institute, University of Western Ontario (UWO), 4Centre for Neuroscience Studies, Queen’s University, 5Nova Scotia Health Authority, Dalhousie University, Department of Medicine – Geriatrics, 6Ratman Research Institute, Baycrest Health Sciences, 7Department of Psychology and Medicine (Neurology), UofT, 8Department of Medicine, Division of Geriatric Medicine, Parkwood Hospital, UWO, 9Department of Clinical Neurological Sciences, Schulich School of Medicine & Dentistry, UWO, 10Department of Kinesiology, University of Waterloo, 11Edmond J. Safra Program in Parkinson’s Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, 12Tan Centre for Research in Neurodegenerative Diseases, UofT, 13Division of Neurology, Toronto Western Hospital, University Health Network, 14Department of Medical Biophysics, UofT, 15Harquail Centre for Neurodemolulation, Sunnybrook Health Sciences Centre (HSC), 16Department of Medicine (Neurology), Sunnybrook HSC and UofT, 17Department of Medical Imaging, UofT, Sunnybrook HSC, 18Department of Medical Biophysics, UWO

Purpose
To investigate microstructural changes of the penumbra layers surrounding different cerebrovascular disease lesion sub-types and associations with cognition and sleep quality.

Methods
Participants: 146 individuals with CVD from the Ontario Neurodegenerative Disease Research Initiative (ONDRI).
Periventricular and deep white matter hyperintensities (p/dWMH), lacunes, and MRI-visible perivascular spaces (PVS) were segmented. From diffusion MRI, fractional anisotropy (FA) and mean diffusivity (MD) were estimated from the penumbra layers surrounding each lesion sub-type. Linear regression models were used to examine diffusion metrics within each lesion type (central), outermost penumbra layer (distal), across the penumbra gradients (slope), and for all NAWM (global).

Associations with Processing Speed, Executive Function, Memory, Visuospatial Reasoning and sleep quality (PSQI) were examined, controlling for demographics, vascular risk factors, sleep medications and sleep apnea.

Results
FA and MD were significantly different between penumbra layers of all lesion sub-types (all p<0.0001).
Central: Linear regressions revealed FA within pWMH was associated with memory (β=−0.19, p=0.04); MD within dWMH with processing speed (β=−0.23, p=0.03), and memory (β=0.2, p=0.05). Sleep analysis revealed MD within dWMH was associated with PSQI (β=−1.22, p<0.001).
Distal: FA in the outermost NAWM layer of BG-PVS was associated with visuospatial (β=0.31, p=0.04), processing speed (β=0.4, p=0.004), and executive function (β=0.29, p=0.02); and FA in the outermost NAWM layer of lacunes was associated with executive function (β=0.52, p=0.005).
Slope: FA slope of pWMH penumbra was associated with memory (β=0.22, p=0.02) and executive function (β=0.19, p=0.02); and, MD slope of dWMH was associated with processing speed (β=0.26, p<0.01), and executive function (β=0.18, p=0.04). Sleep analysis revealed the MD slope of dWMH was associated with PSQI (β=1.13, p<0.001).

Conclusion
These findings suggest that white matter alterations that extend beyond the vascular lesions demarcated on standard structural MRI may be associated with poor sleep quality and cognitive dysfunction.