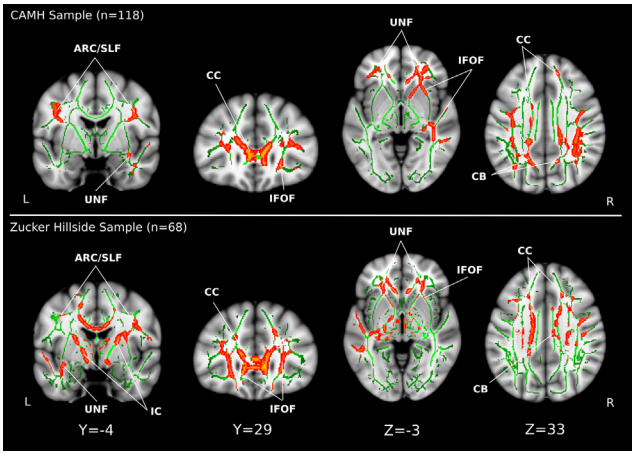
and HWE filters and population stratification were assessed. Association between genetic markers and cerebrospinal fluid protein levels was assessed using linear regression after adjustment for age, gender and the principle components from EigenSoft analysis. Analysis was performed in each sample independently; results were combined in a metaanalysis using METAL. We applied additional filters to find a set of associated markers that are the highest priority for follow-up. SNPs from these loci were tested for association with AD status in data from the Alzheimer's Disease Genetics Consortium. **Results:** 69 phenotypes were analyzed after QC filtering. We 12 identified candidate loci for 11 phenotypes including cis-effects for Angiotensin Converting Enzyme (rs4968782 P=3E-12), Interleukin 6 Receptor (rs61812598 P=5E-63) and Matrix Metalloproteinase 3 (rs679620 P=5E-44) and trans effects for CD-40 antigen (rs7250371 P=7E-09), Chemokine CC-4 (P=8E-22; P=5E-09), Macrophage Inflammatory Protein-1 beta (rs6808835 P=1E-13), Monocyte Chemotactic Protein 1 (rs2228467 P=3E-18), Osteopontin (rs11076196 P=2E-08), Prostatic Acid Phosphatase (rs3844501 P=2E-23), Sortilin (rs1708487 P=3E-09) and Trefoil Factor 3 (rs7280100 P=1E-08). Of these loci, SNPs in ACE (p=0.003), MMP3 (p=0.01) and PAP (0.03) showed association with AD risk. **Conclusions:** We have identified 12 loci with strong and replicable genetic associations with levels of 11 different proteins in the cerebrospinal fluid. Associations with AD status for ACE, MMP3 and PAP indicate a possible role for these markers in AD risk. These findings illustrate the utility of an endophenotype based approach to understanding disease risk and identify these genes and important therapeutic targets for modulating risk for AD and other disorders related to these proteins.

O4-01-02 EFFECTS OF THE SORL1 ALZHEIMER'S DISEASE RISK GENE ACROSS THE HUMAN LIFESPAN

Daniel Felsky[1], Philip Szeszko[2], Lei Yu[3], William G. Honer[4], Philip De Jager[5], Julie Schneider[6], Anil Malhotra[7], Toshikazu Ikuta[2], Jon Pipitone[1], Mallar Chakravarty[1], Nancy Lobaugh[1], Benoit Mulsant[1], Bruce Pollock[1], James Kennedy[1], David Bennett[6], Aristotle Voineskos[1], *[1]Centre for Addiction and Mental Health, Toronto, Ontario, Canada; [2]Feinstein Institute for Medical Research, North Shore-LIJ Health System, Manhasset, New York, United States; [3]Rush Alzheimer's Disease Center, Chicago, Illinois, United States; [4]University of British Columbia, Vancouver, British Columbia, Canada; [5]Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, United States; [6]Rush University Medical Centre, Chicago, Illinois, United States; [7]The Zucker Hillside Hospital, Glen Oaks, New York, United States. Contact e-mail: dfelsky@gmail.com*

Background: Variants within a 5′ haplotype of the sortilin-related receptor, L-class, A repeat-containing (SORL1) gene have been repeatedly implicated in late-onset AD. To characterize risk posed by these variants across the lifespan, we analyzed their effects on 1) white matter integrity using diffusion tensor imaging (DTI), 2) prefrontal SORL1 mRNA levels, and 3) postmortem amyloid plaque and tau tangle pathology. **Methods:** Imaging-genetics analysis was performed on two samples: 118 healthy subjects (CAMH, age 18-86) on a 1.5T GE scanner with 23 directions, and 68 healthy Caucasian subjects (Zucker Hillside, age 8-40) on a 3T GE scanner, with 31 directions. TBSS was used to assess the effect of genotypic group on voxel-wise fractional anisotropy (FA), co-varying for age, sex, and APOE-ε4 status where possible. Prefrontal SORL1 mRNA was quantified in the BrainCloud dataset (access through dbGaP, NCBI, n=269) using Illumina microarrays. Immunohistochemical analysis was performed on a sample of postmortem Caucasian HC, MCI, and AD brains (Rush University Memory and Aging Project/Religious Orders Study, Chicago, Il, USA: n=782) to quantify amyloid plaque and paired helical filament-tau separately for mesial temporal and neocortical structures. All samples were genotyped for risk SNPs within the SORL1 5′ haplotype. **Results:** rs689021 was associated with reductions in fronto-temporal WM FA in both the CAMH and Zucker Hillside samples, at a 5% FWE corrected threshold (See Figure). The effects were independent of age, manifesting as early as childhood and adolescence. In BrainCloud, the rs689021 risk genotype significantly predicted a period of reduced gene expression in Caucasians during adolescence (F=7.03, p=0.0003). Postmortem pathology analysis revealed associations of rs668387 with amyloid plaques in the whole sample (t=4.84, p=0.028) and neocortical tangles in healthy subset only (t=9.03, p=0.0027). **Conclusions:** Our results suggest that 1) variation in the SORL1 gene may confer risk for AD via temporo-frontal WM circuitry long before the onset of AD symptoms, 2) SORL1 variation predicts a dynamic period of mRNA expression during development, and 3) SORL1 genetic risk may stem from altered amyloid plaque and tau tangle pathology in the whole brain and neocortex, respectively.



O4-01-03 GENOME-WIDE ASSOCIATION STUDY AND ADMIXTURE MAPPING OF AGE-RELATED COGNITIVE DECLINE IN AFRICAN-AMERICANS

Towfique Raj[1], Lori Chibnik[1], Cristin McCabe[2], Barbara Stranger[1], Lisa L. Barnes[3], David Weir[4], Richard Mayeux[5], Tatiana Foroud[6], David Bennett[3], Kathleen Steele Hall[7], Jill Murrell[7], Denis Evans[3], Philip De Jager[1], *[1]Brigham and Women's Hospital/Harvard Medical School, Boston, Massachusetts, United States; [2]Broad Institute, Cambridge, Massachusetts, United States; [3]Rush University Medical Center, Chicago, Illinois, United States; [4]University of Michigan, Ann Arbor, Michigan, United States; [5]Columbia University, New York, New York, United States; [6]Indiana University School of Medicine, Indianapolis, Indiana, United States; [7]Indiana University, Indianapolis, Indiana, United States. Contact e-mail: traj@rics.bwh.harvard.edu*

Background: To leverage genome-wide data from several cohorts so as to identify genetic determinants of age-related cognitive decline among older African-American (AA) people. **Methods:** We examined genome-wide genotyping data for 4,426 unrelated older AA subjects who had at least two repeated measures of cognition from six (CHAP, IIDP, ROS, MAP, MARS, and WHICAP) prospective community-based studies. We compared them to 2,703 unrelated non-Hispanic European Americans (EAs) from the ROS, MAP and CHAP studies. Within each cohort, individual cognitive tests were combined to form an aggregate measure of global cognition. We used linear mixed effects models to characterize individual paths of change in cognition, controlling for age, sex and education as fixed effects. After quality control, imputation was performed using the 1000 Genomes Project Phase I combined reference panels of EA and AA ancestry. Common variants were meta-analyzed across cohorts using weighted fixed-effect models. HAPMIX software was used to estimate ancestry at each locus, and MIXSCORE software was used to test whether individuals with faster or slower rates of global cognitive decline had a proportion of ancestry different from the genome average. **Results:** APOE ε4 haplotype was strongly associated with rate of cognitive decline in AAs (P= 1.92 x 10 -14) but the magnitude of the effect was weaker in AAs (β= -0.01) compared to EAs (β= -0.05). In AAs we replicated previously known loci in EAs including ABCA7 (P= 4.13 x 10 -4), PICALM (7.35 x 10 -4), and EPHA1 (P= 8.06 x 10 -4). We discovered one genome-wide significant association at the TRPS1 locus (chr 8q23), and replicated that association in EAs (P(DISC) = 2.52 x 10 -7; P(REP) = 9.79 x 10 -3; P(JOINT) = 1.37 x 10 -8). We also found another variant at the TEK locus (chr 9p21) with suggestive evidence of association (P(DISC) = 4.10 x 10 -7). Using admixture mapping, we did not detect any significant admixture peak. **Conclusions:** These results suggest that genetic factors alone may not explain differences

in age-related cognitive decline between AAs and EAs. Further large-scale admixture mapping studies will be necessary to validate our findings.

O4-01-04 PREDICTORS OF MEMORY PERFORMANCE IN A LARGE, STRATIFIED, RANDOM POPULATION SAMPLE OF OLDER AMERICANS: CLINICAL, DEMOGRAPHIC, LIFESTYLE AND GENETIC FACTORS

Vijay Ramanan[1], Kwangsik Nho[1], Li Shen[1], Shannon Risacher[1], Sungeun Kim[1], Tatiana Foroud[1], David Bennett[2], Andrew Saykin[1] For The Alzheimer's Disease Neuroimaging Initiative (ADNI)*[1]Indiana University School of Medicine, Indianapolis, Indiana, United States; [2]Rush University Medical Center, Chicago, Illinois, United States. Contact e-mail: vramanan@iu.edu*

Background: Human episodic memory is a complex trait with substantial estimated heritability (30-60%) (Pappassotiropoulos et al. TICS 2011). However, the factors impacting memory in cognitive aging and in dementia are not well-characterized. Using the Health and Retirement Study (HRS), a large, population-based sample of older Americans (N =16,261), we aimed to identify variables predictive of memory performance, assess candidate memory genes for replication of association, and use an unbiased genome-wide approach (GWAS) to discover additional genes and pathways related to memory. **Methods:** Cross-sectional data from HRS wave 3 was analyzed. Stepwise linear regression was performed using recall on a 10-word list learning task as the outcome and variables indicating demographic, cognitive, health, behavioral, occupational, socioeconomic, and marital status as potential predictors. SNP genotypes (Illumina HumanOmni2.5 array) passing standard quality control including 1% minor allele frequency were tested for association to memory score using PLINK (N =6,695). Post-GWAS pathway analysis was performed using GATES/GSA-SNP. Independent replication samples included the Religious Orders Study/Rush Memory and Aging Project (ROS/MAP) and Alzheimer's Disease Neuroimaging Initiative (ADNI) datasets. **Results:** Immediate and delayed recall were highly correlated (r =0.79) and explained by identical predictor variables. The 13 variables significantly associated with immediate recall accounted for 36% of its variance (See Table). Controlling

Table1
Ramanan et al., "Predictors of memory performance in a large stratified random population sample of older Americans: clinical, demographic, lifestyle, and genetic factors"

A. Clinical, demographic, and lifestyle factors associated with immediate memory recall on a 10-word list learning task (N=16,261)

Variable	% Variance Explained	Std. β	*P*-Value
Mental status score	17.56%	0.233	2.62×10^{-193}
Age (years)	11.33%	-0.316	2.54×10^{-241}
Vocabulary score	2.79%	0.132	1.17×10^{-69}
Gender (0=male, 1=female)	2.29%	0.168	5.39×10^{-116}
Education (years)	1.15%	0.098	3.06×10^{-35}
Self-rated memory*	0.76%	-0.078	3.43×10^{-32}
Depression score (CESD scale)	0.26%	-0.046	1.44×10^{-11}
Vigorous activity 3+ times/week**	0.08%	0.026	8.50×10^{-5}
Number of years worked**	0.05%	0.022	4.00×10^{-3}
Ever had diabetes**	0.04%	-0.022	8.97×10^{-4}
Total household assets	0.03%	0.017	8.02×10^{-3}
Ever had high blood pressure**	0.03%	0.018	6.95×10^{-3}
Currently working for pay**	0.02%	0.019	0.016

B. Candidate genes interrogated for replication of association to immediate memory recall on a 10-word list learning task (N=6,695)

Candidate Gene	Previous Association with AD or Memory	Top *P*-Value < 0.05
BCHE	Ramanan et al., *Mol Psychiatry*, 2013 (In Press)	1.04×10^{-4}
CAMTA1	Huentelman et al., *HMG*, 2007	2.99×10^{-4}
WWC1	Papassotiropoulos et al., *Science*, 2006	1.12×10^{-3}
DISC1	Carless et al., *Mol Psychiatry*, 2011	1.15×10^{-3}
PICALM	Barral et al., *Neurology*, 2012	5.80×10^{-3}
MS4A6A	Naj et al.; Hollingworth et al., *Nat Genet*, 2011	8.92×10^{-3}
SCN1A	Papassotiropoulos et al., *Mol Psychiatry*, 2011	0.012
BDNF	Cathomas et al., *Int J Neuropsychopharmacol*, 2010	0.015
CR1	Chibnik et al., *Ann Neurol*, 2011	0.016
DTNBP1	Zhang et al., *Biol Psychiatry*, 2010	0.021
CTNNBL1	Papassotiropoulos et al., *Mol Psychiatry*, 2011	0.036
ABCA7	Hollingworth et al., *Nat Genet*, 2011	None identified
APOE‡	Corder et al., *Science*, 1993	None identified
BIN1	Wijsman et al., *PLOS Genetics*, 2011	None identified
CD2AP	Naj et al.; Hollingworth et al., *Nat Genet*, 2011	None identified
CD33	Naj et al.; Hollingworth et al., *Nat Genet*, 2011	None identified
CLU	Jun et al., *Arch Neurol,* 2010	None identified
COMT	Barnett et al., *Biol Psychiatry*, 2006	None identified
MS4A4E	Naj et al.; Hollingworth et al., *Nat Genet*, 2011	None identified
TOMM40	Caselli et al., *Alzheimer's Dementia*, 2012	None identified

*1=excellent to 5=poor.
**0=no, 1=yes .
‡SNPs characterizing APOE ε2/ε3/ε4 alleles (rs429358, rs7412) were not genotyped