Background: Type 2 diabetes (T2D) is associated with poorer cognitive function, accelerated cognitive decline, and higher risk for dementia, accompanied by atrophy in different brain structures. The association of the Transcription factor 7-like 2 (*TCF7L2)* gene with T2D is one of the most reproducible findings in T2D genetics. Since *TCF7L2* is expressed in the brain, we investigated the association between volumes of the hippocampus, amygdala and frontal cortex of cognitively normal T2D elderly. Our hypothesis was that T2D genetic risk variants within *TCF7L2*will be associated with greater brain atrophy among diabetic patients. **Methods:** T2D subjects (n=177) from the Israel Diabetes and Cognitive Decline study who were both genotyped for the *TCF7L2*single nucleotide polymorphisms (SNPs) rs7903146, rs11196205, rs12255372 and underwent brain MRI, were included in this analysis. Images were processed and regional volumes were calculated with SPM software. For each SNP, we used ANCOVA to investigate the association of the T2D risk allele with volume of hippocampus, amygdala and frontal cortex under a recessive model of inheritance - controlling for relevant demographic and clinical variables (sex, age, years of education, duration of T2D, HBA1C, total cholesterol, systolic and diastolic blood pressure, BMI, and ICV [intra-cranial volume]). **Results:** In all three *TCF7L2* SNPs, amygdalar volume was 9-12% lower among carriers of the TD2 risk allele homozygous genotype: rs7903146: TT genotype vs. CT+TT genotypes (p=0.003); rs11196205 CC genotype vs. CG+GG genotypes (p=0.001), and rs12255372TT genotype vs. GT+GG genotypes (p=0.003). These SNPs were not associated with hippocampal or frontal cortex volumes. **Conclusions:** *TCF7L2* genetic variants are associated with smaller amygdalar volume in T2D elderly, suggesting an atrophic process in the amygdala in those with the risk variants. In addition, the amygdala has been implicated in supporting memory processes affected in dementia. Further study of *TCF7L2* role in this region is needed, as amygdalar atrophy has been reported in T2D and the amygdala has been recently reported as a glucose sensing region.

P1-138 DECLINE OF FUNCTIONAL INTERHEMISPHERIC CONNECTIVITY IN AGING: ASSOCIATION WITH PICALM GENOTYPE

Natalya Ponomareva[1], Tatiana Andreeva[2,3], Maria Protasova[2,3], Svetlana Kunizheva[4], Lev Shagam[2], Daria Malina[1], Andrey Goltsov[2,3], Vitaly Fokin[1], Evgeny Rogaev[2,3,5], *[1]Research Center of Neurology, Moscow, Russian Federation; [2]Department of Human Genetics and Genomics, Vavilov Institute of General Genetics of Russian Academy of Science, Moscow, Russia; [3]Center of Brain Neurobiology and Neurogenetics, Institute of Cytology and Genetics of Siberian Branch of Russian Academy of Sciences, Novosibirsk, Russia; [4]2Vavilov Institute of General Genetics, RAS, Moscow, Russian Federation; [5]Brudnick Neuropsychiatric Research Institute, Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA, USA.*
Contact e-mail: ponomare@yandex.ru

Background: Recent genome wide association studies identified a polymorphism in PICALM gene rs3851179 as a risk factor for AD (Harold et al., 2009; Lambert et al., 2009). The normal brain undergoes a substantial decrease of functional connections within resting-state networks during aging, but PICALM-related differences in functional connectivity remain unknown. The present study aimed to determine the possible PICALM genotype -related differences of the alterations of brain functional connectivity in normal aging. **Methods:** We examined PICALM genotype and age-related differences in resting state EEG relative power and functional connectivity assessed by interhemispheric EEG coherence in 145 non-demented volunteers (age range 20-80 years), subdivided into subgroups of those younger and older than 50 years of age and stratified by PICALM rs3851179 genotype. Informed written consent was obtained from all participants. All subjects underwent a neurological examination and cognitive screening. The significance of the differences between the EEG parameters in different groups was estimated using ANOVA in the GLM. The analysis was adjusted for ApoE genotype. **Results:** Interhemispheric coherence of different EEG bands was found to decrease with age in all examined groups. The decline of interhemispheric alpha2 and beta coherence in aging was attenuated in the carriers of PICALM-A protective allele, whereas the homozygous presence of AD risk variant PICALM GG was associated with greater decline in interhemispheric coherence. The PICALM GG genotype was also associated with neurophysiological signs of hyperexcitability and cortical disinhibition, as described previously (Ponomareva et al., 2016). The reduction of alpha interhemispheric coherence of in elderly subjects correlated with the worse performance in verbal memory test. **Conclusions:** The results indicate that altered functional connectivity in normal aging is associated with PICALM genotype. The progressive decline in interhemispheric connectivity contributes to memory decrement and suggests the impact of age-related disconnection process in pathogenesis of AD in the carriers of PICALM GG genotype. Supported by Russian Science Foundation grant No 14-44-00077 (Aging-related genetic-EEG association study); in part by Russian Science Foundation grant No 14-15-01121 (genotyping of AD-gene), the grants from the Government of the Russian Federation (No14.B25.31.0033), and NIH/NIA AG029360, by RFBR grant No 15-04-08744-a.

P1-139 PATHWAY-SPECIFIC GENETIC RISK SCORE ASSOCIATED WITH ALZHEIMER'S DISEASE AND WHITE MATTER LESIONS IN COGNITIVELY NORMAL SUBJECTS

Shahzad Ahmad[1], Christian Bannister[2], Sven J. van der Lee[1], Dina Vojinovic[1], Hieab H. H. Adams[1], Alfredo Ramirez[3,4,5], Valentina Escott-Price[2], Rebecca Sims[2], Peter Holmans[2], Meike W. Vernooij[6], M. Arfan Ikram[6], Najaf Amin[1], Cornelia M. van Duijn[1], *[1]Department of Epidemiology, Erasmus Medical Centre, Rotterdam, Netherlands; [2]MRC Centre for Neuropsychiatric Genetics & Genomics, Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, United Kingdom; [3]Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany; [4]University Hospital Cologne, Cologne, Germany; [5]Human Genetic, University of Bonn, Bonn, Germany; [6]Erasmus MC University Medical Center Rotterdam, Rotterdam, Netherlands. Contact e-mail: s.ahmad@erasmusmc.nl*

Background: Alzheimer's Disease (AD) is a heterogeneous disease from a genetic and clinical perspective. Our genetic research revealed seven pathways that play a role in AD pathogenesis including *immune response, endocytosis, cholesterol transport, hematopoietic cell lineage, hemostasis, clathrin/AP2 adaptor complex* and *protein folding*. How these pathways associate to the clinical expression of AD is an area of research unexplored. We evaluated the association of each of these pathways to AD and its early related phenotypes such as mild cognitive impairment (MCI) and magnetic resonance imaging (MRI) phenotypes in a population-based study, the