25.2 TELOMERE LENGTH AND PRO-INFLAMMATORY CHEMOKINE AS PATHOLOGICAL AGING BIOMARKERS IN SCHIZOPHRENIA: RELATIONSHIP WITH EPISODIC MEMORY PERFORMANCE AND TOTAL GRAY VOLUME

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Background: Schizophrenia (SZ) is associated with increased somatic morbidity typically related to processes of aging, such as cardiovascular disease and metabolic abnormalities. Furthermore, individuals with SZ have increased mortality and reduced life span. These observations of increased somatic morbidity and mortality, in addition to cognitive impairments similar to those seen in normal aging, may indicate that subjects with SZ have a pathological accelerated aging. However, although there is evidence supporting this hypothesis, the neurobiological underpinnings are still unclear. Therefore, this presentation aims to suggest possible mechanisms to this hypothesis. A suggested biomarker of aging is the length of telomeres (TL), which are DNA-protein structures that protect the ends of chromosomes and progressively shorten with each cell division. Inflammatory processes, such as dysregulation in cytokines, may influence TL. The pro-inflammatory chemokine CCL11, a type of cytokine, was described as an age-related systemic factor associated with decreased neurogenesis in hippocampus and impaired memory in mice, that was increased in chronic but not in recent onset individuals with SZ. Thus, these biomarkers could be associated with brain volume loss and memory impairments, which might be behavioral and structural outcomes of aging.

Methods: We included 48 individuals with SZ and 64 healthy subjects (HC). Participants had the same socioeconomic and educational background. They underwent clinical and memory assessments, structural T1 MRI 1.5T, and had their peripheral blood drawn for biochemical analysis. Comparisons of group means and correlations were performed. We aimed to evaluate the relationships of TL and CCL11 (aging and inflammatory biomarkers, respectively), gray matter (GM) volume, and episodic memory performance in individuals with SZ compared to HC.

Results: Our results showed that SZ had shorter TL and increased CCL11 compared to HC. Additionally, individuals with SZ had reduced GM volume and worse episodic memory performance than HC. In SZ, shorter TL was related to increased CCL11, and both biomarkers were related to reduced GM volume, all of which were related to worse memory performance. Older age was only associated with reduced GM, but longer duration of illness was related with all the aforementioned variables. TL mediated the effects of duration of illness to memory performance. In HC, there were no significant correlations except for the expected relationship between memory and GM.

Conclusions: We saw associations between increased CCL11, shorter TL, reduced GM volume, and decreased episodic memory in SZ, which were all related to longer duration of illness. These results suggest that it is not age itself, but the impact of the disease associated with a pathological aging that might lead to a worse outcome. Chronic pro-inflammatory processes could influence the body's capacity to absorb damage over time. This could have impacts on the brain that might lead to structural and functional consequences, such as loss of GM, which in turn could elicit behavioral impairments, such as memory deficits. Although preliminary, our data point to potentially important mechanisms related to neural and cognitive impairment associated with psychosis consistent with the hypothesis of accelerated aging in SZ.

25.3 IMAGING ACCELERATED AGING MACHINE-LEARNING BASED MULTIVARIATE PATTERN ANALYSIS OF STRUCTURAL MRI IN SCHIZOPHRENIA AND ULTRA-HIGH-RISK SUBJECTS

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Background: Brain structural changes in schizophrenia parallel some age-associated changes. Previous studies were often limited to cross-sectional analyses of interacting effects of diagnosis and age, while pointing to frontal and (superior) temporal cortical alterations being most prone to progressive brain structural changes associated with age. The use of machine-learning based approaches has allowed the estimation of age in individual brain scans based on comparison to normative data sets. One of these strategies, the BrainAGE (brain age estimation gap) approach provides a metric describing the deviation of an individual’s brain from the physiological age trajectory, thus yielding an indicator of accelerated brain aging based on multivariate pattern analysis (rather than univariate statistics of single brain regions).

In this presentation, we include a systematic evaluation in samples with chronic schizophrenia, first-episode schizophrenia, ultra-high-risk (UHR) subjects for schizophrenia, as well as phenotypic (schizotypy) and genetic (polygenic risk) factors in large healthy cohorts.

Methods: We include four different data sets to test the hypothesis of accelerated brain aging in schizophrenia, based on high-resolution anatomical 3T MRI scans. We used the BrainAGE algorithm (Franke et al., 2011; Gaser et al. 2013) applying machine-learning based on a separate training data set to calculate the gap between estimated and chronological brain age. This includes a pilot BrainAGE study on a total of 70 subjects with chronic schizophrenia patients compared to healthy controls and bipolar patients, and a comparison data set (n=72) with major depression patients and matched healthy controls; a 112 subject study comparing ultra-high risk (UHR) subjects with first-episode schizophrenia patients and healthy controls, and finally two analyses from the FOR2107 multi-center cohort study on the association of BrainAGE with psychometric schizotypy and polygenic risk for schizophrenia.

Results: First, we find that BrainAGE scores are elevated in chronic schizophrenia (compared to bipolar disorder and healthy controls), and that BrainAGE is not elevated in major depression. Second, we find that BrainAGE is elevated also in first-episode schizophrenia and with a trend in UHR. Third, we find that subgroups within UHR differ on BrainAGE scores: those with genetic risk show elevated BrainAGE, while those with UHR status based only on attenuated psychotic symptoms do not show elevated BrainAGE. Currently, additional replication studies are being performed to corroborate genetic findings (also being extended to polygenic risk).

Conclusions: We find elevated BrainAGE scores, indicative of accelerated brain aging, in schizophrenia (both chronic and first-episode), but not other major psychoses, as well as UHR subjects with genetic risk. These findings suggest that surrogate markers of accelerated aging are not (only) an epiphenomenon of disease duration or medication but might reflect an inherent and possibly genetically influenced acceleration or progression of structural changes in schizophrenia. While ongoing replication studies are also aiming at extending our findings to molecular genetic markers, our findings demonstrate a consistent pattern across multiple stages of the disease. At the same time, progress is being made to understand a potential genetic overlap of (physiological) processes regulating brain maturation and aging and those implicated in schizophrenia.

25.4 ACCELERATED AGING OF FUNCTIONAL BRAIN NETWORKS SUPPORTING COGNITIVE FUNCTION IN PSYCHOTIC DISORDERS

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Background: Brain structural changes in schizophrenia parallel some age-associated changes. Previous studies were often limited to cross-sectional analyses of interacting effects of diagnosis and age, while pointing to frontal and (superior) temporal cortical alterations being most prone to progressive brain structural changes associated with age. The use of machine-learning based approaches has allowed the estimation of age in individual brain scans based on comparison to normative data sets. One of these strategies, the BrainAGE (brain age estimation gap) approach provides a metric describing the deviation of an individual’s brain from the physiological age trajectory, thus yielding an indicator of accelerated brain aging based on multivariate pattern analysis (rather than univariate statistics of single brain regions).

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Conclusions: We find elevated BrainAGE scores, indicative of accelerated brain aging, in schizophrenia (both chronic and first-episode), but not other major psychoses, as well as UHR subjects with genetic risk. These findings suggest that surrogate markers of accelerated aging are not (only) an epiphenomenon of disease duration or medication but might reflect an inherent and possibly genetically influenced acceleration or progression of structural changes in schizophrenia. While ongoing replication studies are also aiming at extending our findings to molecular genetic markers, our findings demonstrate a consistent pattern across multiple stages of the disease. At the same time, progress is being made to understand a potential genetic overlap of (physiological) processes regulating brain maturation and aging and those implicated in schizophrenia.