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T122. Telomere Length in Schizophrenia as a Function of Age and Illness Duration

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Background: Schizophrenia is associated with a substantially increased risk of early mortality even after accounting for lifestyle factors and suicide, raising the possibility that it may be associated with accelerated biological aging. One index of biological aging is leukocyte telomere shortening, which can happen with repeated mitoses as seen with chronic exposure to inflammation or with oxidative stress. Leukocyte telomere length (LTL) is reportedly shortened in depression and certain anxiety disorders, although not all studies agree, and some suggest a 'dose-response' relationship with illness chronicity. LTL has not been well studied in schizophrenia, and published results differ across studies, with individual studies reporting shortened, lengthened or equivalent LTL. Individual determinants of LTL shortening in schizophrenia, including the possible roles of age and illness chronicity, have been poorly characterized. In this study of demographically well-matched individuals with schizophrenia and healthy comparison subjects, we hypothesized that LTL would be shorter in schizophrenia in proportion to the individual's age (reflecting 'accelerated cellular aging') and the individual's chronicity of illness.

Methods: Thirty-one individuals with schizophrenia (14 men and 17 women; mean age 51.2 yrs+SD 11.1, range: 26–64 years) and 31 matched healthy comparison subjects (14 men and 17 women; age 51.5+11.8, range: 23–65 years) were studied after providing informed consent. The duration of schizophrenia was estimated by subtracting the age of onset of illness from the age at time of study participation. The mean illness duration in this sample was 25.7 years+13.9 (SD), range: 1.1–53.1 years. Severity of psychotic symptoms was rated with the Scales for Assessment of Positive and Negative Symptoms (SAPS and SANS). LTL was determined from buffy coat cells by qPCR as previously described (Cawthon RM, Nucleic Acids Res, 30: e47, 2002). All statistical analyses are reported as two-tailed tests and are covaried for age, gender, ethnicity, and education.

Results: Within the schizophrenia group, there was a highly significant age-associated decrease in LTL (r=−0.60, p=0.001), but this relationship was not statistically significant in the healthy comparison group (r=−0.18, NS). Comparison of the regression coefficients relating age to LTL revealed a near-significant trend toward greater decreases in LTL with increasing age in the schizophrenia group compared to the healthy comparison group (Fisher r-to-z test: Z=1.9, p<0.06). The average LTL in the schizophrenia group (mean+SD=5328.6 base pairs+378.2) was 92 base pairs shorter than that in the healthy comparison subjects (mean+SD=5420.6 base pairs+378.2), representing approximately three years of accelerated leukocyte aging in the schizophrenia group, although this difference was not statistically significant (F=0.78, NS). However, lifetime duration of schizophrenia, corrected for age, gender, ethnicity, and education, was strongly inversely correlated with LTL (r=−0.53, p=0.009), consistent with a cumulative effect of schizophrenia chronicity on LTL shortening. LTL was not

significantly correlated with the current severity of positive or negative psychotic symptoms (SAPS: r=−0.03, NS; SANS: r=0.15, NS).

Conclusions: These data provide additional insight into possible accelerated cellular/biological aging in schizophrenia. The data suggest that schizophrenia is not intrinsically associated with shortened LTL, and that LTL shortening does not antedate the onset of schizophrenia or represent a risk factor for developing it. Rather, the data suggest that chronicity of schizophrenia is associated with a progressive acceleration of certain cellular aging processes. This pattern of a 'dose-response' relationship between chronicity of illness and LTL shortening has also been reported in depression, certain anxiety disorders, and psychological stress, suggesting common trans-diagnostic biological underpinnings such as chronic inflammation and oxidative stress, both of which have been reported to be increased in schizophrenia. Future studies will be needed to distinguish between the effects of advanced age and duration of illness in predicting LTL in schizophrenia and to assess the relationship between LTL and treatment history, since the observed correlation could represent effects of psychotropic medication rather than the illness itself. Longitudinal studies will be necessary to assess trajectories of LTL change over the lifespan. The present findings are early results of an ongoing large-scale study of accelerated biological aging in schizophrenia (NIMH Grant: R01 MH094151; Dilip V. Jeste, PI). If replicated, the current results may help explain the surfeit of physical aging disorders among individuals with schizophrenia.

Keywords: schizophrenia, psychosis, telomeres, aging, leukocytes.

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