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Rapid telomere erosion in schizophrenia

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Telomeres are DNA repeats located at the ends of chromosomes, which progressively shorten with each cell division, thus serving as a molecular biomarker of physical aging in many organisms.[1] Unexpectedly, telomere dysfunction was recently described in psychological stress[2] and mood disorders.[3] These intriguing findings suggest a molecular link between neural activity and aging, and raise the possibility that telomere maintenance may be impaired in other psychiatric disorders.

Here, we tested the hypothesis that telomere dynamics are altered in schizophrenia, a severe psychotic disorder. Subjects with schizophrenia were recruited from two cohorts, A and B, and were evaluated using structured interviews (Supplementary Methods). Telomere lengths were measured in a total of 51 individuals with schizophrenia, 52 unaffected, unrelated individuals, and 24 unaffected family members. Genomic DNA was isolated from peripheral blood lymphocytes and telomere length was measured using quantitative PCR.[4] Significance was evaluated using analysis of variance (ANOVA) or analysis of covariance (ANCOVA) where necessary (Supplementary Methods). Since telomere lengths were quantitated in two independent laboratories, the results were analyzed separately, as described below.

We first examined telomere lengths in 31 individuals diagnosed with schizophrenia (DSM-IV), recruited from the two separate cohorts (A, $n=13$; B, $n=18$), 41 unrelated individuals screened as having no major psychiatric disorder (Control) and 24 unaffected family members (Family), most of whom were first-degree relatives of cohort B (Figure 1a; Supplementary Table S1A). As expected, there was a negative correlation of telomere length with age ($r=-0.28$, $P=0.01$). Since age and sex can affect telomere length,[5] the data were analyzed using an ANCOVA, controlling for the effects of these two variables. We observed a significant main effect of diagnosis ($F=6.44$, $df=2$, $P=0.002$), but there was no main effect of age or sex within this analysis. No significant difference in telomere lengths was observed between the two schizophrenia cohorts, although they were evaluated using different struc-

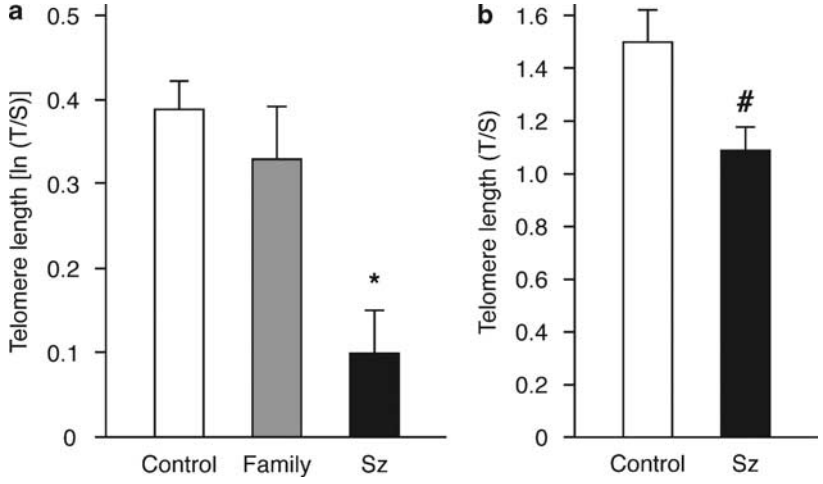

Figure 1 Reduced telomere length in peripheral blood lymphocytes of individuals with schizophrenia. A measure of telomere length, T/S,[4] was determined for individuals in various diagnostic groups. (**a**) Comparison of unrelated, unaffected individuals (Control, $n=41$), unaffected individuals related to individuals with schizophrenia in cohort B (Family, $n=24$) and individuals diagnosed with schizophrenia combined from two cohorts, A and B (Sz, $n=31$). T/S was transformed to natural logarithms to permit comparisons of normally distributed values within each diagnostic group (Supplementary Table S1A). $^{*}P=0.002$ for Control vs Sz using ln(T/S). (**b**) T/S was determined for unrelated, unaffected individuals (Control, $n=26$) and individuals with schizophrenia (Sz, $n=33$) in an age-matched data set containing only male subjects (Supplementary Table S1B). $^{\#}P=0.008$ for Control vs Sz. Means ± s.e.m. are depicted.

tured diagnostic interviews. In *post hoc* analyses, individuals with schizophrenia had significantly shorter mean telomere lengths than controls ($P=0.002$) (Figure 1a; Supplementary Table S1A).

In a second study, we analyzed a group in which age was matched and all individuals were of a single sex, male. Our rationale was that telomere attrition is not linear at all ages and can differ between the sexes.[5] Thus, we recruited 20 additional male individuals with schizophrenia and added them to cohort A (total $n=33$). In addition, we recruited 12 unaffected males and added them to the existing male controls (total $n=26$). Telomere lengths were measured and analyzed separately from the previous study. Again, we observed that individuals with schizophrenia had significantly shorter mean telomere lengths than unaffected controls ($P=0.008$) (Figure 1b; Supplementary Table S1B).

Chronic antipsychotic treatment could affect telomere length. However, there was no correlation between current antipsychotic dose ($r=-0.071$, $P=0.66$) and estimated lifetime antipsychotic dose ($r=0.045$, $P=0.78$) with telomere length (Supplementary Figure S1).

Telomere erosion appears to be occurring rapidly in individuals with schizophrenia. By their mid- to late 30's, the mean T/S (a measure of telomere length[4]), of individuals with schizophrenia was lower than controls by about 0.37–0.41 (Figures 1a and b; Supplementary Tables S1A and B), which corresponds to approximately 1580–1750 bp telomeres (see Supplementary Methods). Since telomere lengths were measured after about 20 years of illness in schizophrenia (mean age 36.2–38.8 years), we estimate that the rate of telomere loss has more than doubled with the onset of schizophrenia, and that lymphocytes in individuals with schizophrenia had aged the equivalent of at least 25 years more than their control counterparts. It should be noted that these estimates are based on cross-sectional studies, and longitudinal measurements carried out on the same individuals over time would be required to obtain a more accurate rate of telomere erosion.

The presence of significant telomere loss in schizophrenia implies an abnormal aging component in this disorder. Although the cause is unknown, rapid telomere loss can be caused by stress,[2] oxidative damage[5] and DNA instability,[1,5] mechanisms that have been implicated in schizophrenia pathology.[6,7] These findings therefore suggest new directions of research that may illuminate the neuropathology of this enigmatic disorder.

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Chronic fluoxetine treatment alters behavior, but not adult hippocampal neurogenesis, in BALB/cJ mice

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Chronic antidepressant treatment has been shown to increase adult hippocampal neurogenesis.[1] In recent years, it has been widely suggested that the clinical effects of antidepressants may be mediated through an increase in adult hippocampal neurogenesis.[2] This hypothesis is attractive because the delay between stimulating cell proliferation and the production of mature neurons might explain the delayed onset of the clinical effects of antidepressant drugs. In support of this hypothesis, it has been shown that hippocampal