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Lifetime Stress Accelerates Epigenetic Aging

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Background: Psychological stress is associated with accelerated cellular aging and increased risk for aging-related diseases, but the underlying molecular mechanisms are unclear.

Methods: We examined the effect of stress on a DNA methylation age predictor that was shown to correlate strongly with chronological age across human tissues (Horvath 2013). Genome-wide DNA methylation was measured in peripheral blood using the 450K Illumina array in three independent cohorts: the Grady Trauma Project/GTP (N=366); a panic disorder case/control sample recruited at the Max Planck Institute of Psychiatry/MPI-P (N=318); and the Conte Center for the Psychobiology of Early-Life Trauma/Conte (N=42). Age acceleration was calculated by subtracting chronological age from age predicted by DNA methylation. Psychiatric symptomatology and stressors were assessed using standard questionnaires.

Results: DNA methylation age strongly correlated with chronological age in all samples ($r=0.9$, $p=2.5\times10^{-133}$). Cumulative lifetime stress but not childhood or current stress predicted age acceleration in GTP ($p=0.012$) and MPI-P ($p=0.021$). Moreover, epigenetic age acceleration predicted depression (GTP: $p=0.002$; Conte: $p=0.014$) and panic disorder ($p=0.007$). In secondary analyses, we examined the effect of lifetime stress on individual CpGs of the DNA methylation age predictor. After correcting for multiple comparisons, we identified in both GTP and MPI-P a stress-regulated CpG near *MCAM*, a gene implicated in aging-related diseases, including cardiovascular disease and cancers.

Conclusions: Cumulative lifetime stress, but not childhood or current stress, and psychiatric phenotypes are associated with accelerated epigenetic aging. Our findings may explain the accelerated cellular aging and increased disease risk associated with chronic stress and psychiatric disorders.

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