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The aged rhesus macaque hippocampus exhibits previously undetected pathological tau

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Keywords

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Abstract

Due to their genetic, behavioral, and physiological similarities to humans, rhesus macaques (Macacca mulatta) have long been used as a translational model in biomedical research. However, studies using very old monkeys have been impeded by lack of access to animals of advanced age. As the average lifespan of a rhesus macaque is reported to be 25 years, acquiring animals of this age can be both time- and cost-prohibitive. Our laboratory, via a collaborative pooling of resources, has access to postmortem tissue from a cohort containing some of the oldest known macaques in the world, with three animals having lived more than 40 years. Due to this unique resource, we are able to examine whether specific normative or pathological brain aging processes occur in the macaque brain. Specifically, we are interested in whether the rhesus monkey naturally develops Alzheimer's disease (AD) phenotypes. For decades, it has been known that macaque species naturally accumulate amyloid beta plaques as they age, similarly to both healthy humans and those with AD. These plaques, however, are controversial in terms of their contribution to cognitive deficits involved in aging and AD. Tau is another major hallmark of AD, with intracellular hyperphosphorylated tau tangles correlating much more strongly with declining cognition, and is historically undetected in even the oldest monkeys. Here, using immunohistochemistry with clinically-validated antibodies against phosphorylated tau, we present novel evidence of multiple forms of clinically relevant tauopathy in the aged rhesus macaque entorhinal cortex and hippocampus. Taken together, the rhesus monkey exhibits far more of the human brain aging condition than previously presumed. Therefore, it represents a highly appropriate translational animal model in which to investigate mechanisms that underlie the normal and pathological human brain aging, as well as to test pharmacologic, metabolic, and lifestyle interventions aimed at targeting physiological AD etiology and symptomology.