Project Details	
Project Code	MRC23NMHEx Brent
Title	Social Modifiers of Molecular Ageing across the Brain
Research Theme	Neuroscience and Mental Health
Summary	Social isolation increases the risk of dementia and cognitive decline in older individuals. But how social isolation alters the pace of ageing in the brain remains elusive. This project will quantify the social contributions to molecular ageing across brain regions in a unique model system. In doing so, we will generate insights into the multifaceted process of ageing in the brain, and the social contributions to ageing in areas linked to human cognitive health.
Description	With a rapidly growing ageing population comes a rapid increase in the incidence of ageing-related diseases. A major medical challenge is to extend the period of good health. Meeting this challenge depends on understanding the biological mechanisms that drive senescence, and how these mechanisms can be manipulated. The social environment has been revealed as a key factor driving the pace at which individuals age. People who are socially isolated have impaired immune function, greater risk of cardiovascular disease, and die younger than people with strong social connections. These effects extend to the brain, where social isolation is associated with a two-fold increase in risk of late-life dementia as well as cognitive decline. But how social isolation "gets under the skin" to alter the pace at which individuals age, resulting in declines that begin prior to clinical diagnosis of neurodegeneration, remains elusive. Progress lags because comprehensive portraits of realized biological age are required across the lifespan of currently healthy individuals, a feat largely unfeasible in humans. A suitable animal model is needed with natural variation in social isolation and ageing that is homologous to humans and can be tracked across the lifespan in relevant tissues. This DTP project will develop a model of the social contributions to molecular ageing in a naturalistic population of nonhuman primates. We will leverage our long-term study of free-living rhesus macaques at the Cayo Santiago field station in Puerto Rico. Rhesus macaques are a popular biomedical model, with an ever-growing suite of molecular tools designed for this system. However, a major limitation of captive research is the absence of a naturalistic social environment, where animals freely form social groups and inter-individual relationships as they would in the wild. The free-living Cayo Santiago macaques afford researchers the ability to ask fundamental questions about the impact of the social environment on the ageing process. Our preliminary studies on this population show that social isolation varies across individuals; that more socially integrated animals live longer, and that the physiological changes associated with ageing are similar to those in humans. Here, we propose to: 1) quantify the heterogeneity of molecular aging in the brain to identify modifiable sources of ageing variation across the lifespan; and 2) to test the hypothesis that social adversity accelerates (and that social advantage slows) the pace of ageing in the brain. 1) Quantify the heterogeneity of molecular ageing across the brain. The student will characterize molecular ageing across the brain using known hallmarks of aging, including transcriptomic, epigenomic (e.g., DNA methylation), and

	genetic (e.g., somatic mutation, telomere attrition) changes. This will allow them to identify synchrony (or asynchrony) in the rates different brain regions age. Flash-frozen right hemispheres are available for 200 adult male and female macaques ranging from 6-25 years old (median lifespan is 18 years). We obtained this unique resource opportunistically from the field station following their humane removal of animals as an extraordinary population control measure. The student will be able to take ownership on areas including, but not limited to, determining the regions of the brain to examine and the molecular ageing markers to explore. 2) Test if social isolation accelerates the pace of ageing in the brain. The student will use previously collected observational data on social interactions for individual animals. The student will extract quantitative measures of social isolation and will test how they relate to the pace of molecular ageing in the brain. They will model covariates, such as sex and social status, and will be able to test the impact age by environment interactions on molecular markers.
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