DUNEDIN STUDY CONCEPT PAPER FORM

Provisional Paper Title: Social isolation from childhood to mid-adulthood: is there an association with brain age, a biomarker of dementia?

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Objective of the study:

Introduction

This study will investigate the relationship between trajectories of social isolation and brain age, a biomarker of cognitive function. It draws on both life-course and psycho-social determinants of health perspectives.

Social isolation

An acute indicator of social connectedness is the degree to which an individual is isolated, i.e., lacking contact with others (Cacioppo et al., 2011; de Jong Gierveld et al., 2016). There has been growing recognition of social isolation as a significant threat to public health and well-being that requires intervention at a societal level (Holt-Lunstad et al., 2017; Leigh-Hunt et al., 2017). Social isolation can affect individuals at any age, may have an earlier or later onset during the life course, and may be transient or persistent. We have recently identified four distinct trajectory groups of social isolation (low, increasing, decreasing, and high), and have demonstrated that these have different risk factor profiles (Lay-Yee et al., 2021). Longitudinal investigations of social isolation from childhood to adulthood (Caspi et al., 2006) are important to understand the development of social isolation, and its relationship to harmful outcomes. Social isolation has been shown to have negative consequences for the child's social and emotional functioning (Bukowski & Adams, 2005; Coplan et al., 2018; Laursen et al., 2007; Marryat et al., 2014). Social isolation occurring in childhood may have continuing wide-ranging adverse effects into adulthood, for example, resulting in worse mental and physical health (e.g., cardiovascular disease (Caspi et al., 2006), depression (Danese et al., 2009), hospitalization (Almquist, 2011), inflammation (Lacey et al., 2014), and suicide (Rojas, 2018)).

Social isolation and dementia

Dementia is a syndrome affecting mainly older people that is the result of abnormal neurodegenerative changes leading to progressive cognitive impairment. Globally, dementia is a major cause of disability, dependency, and death among older people (WHO, 2017). With societies - including New Zealand – ageing demographically across the world, dementia among older people is becoming a significant social and health issue that needs to be addressed. *The Lancet* Commission on dementia prevention, intervention, and care identified social isolation as one of 12 modifiable risk factors for dementia (Livingston et al., 2020). Recent systematic reviews have concluded that a lack of social contact is associated with elevated dementia risk (Desai et al., 2020; Kuiper et al., 2015). Longitudinal studies have shown that social isolation is related to cognitive decline in older adults (Lara et al., 2019; Luo & LI, 2021; Shankar et al., 2013).

Dementia and brain age

Greater risk of dementia is associated with changes in brain structure due to the process of human ageing. Magnetic resonance imaging (MRI) measures of brain structure can be extracted and analysed to estimate biological brain age (Franke & Gaser, 2019; MacDonald & Pike, 2021). The difference between brain age and chronological age can then indicate whether an individual's brain has aged more or less compared to a population benchmark, reflecting overall brain health and the degree of any underlying neuroanatomical abnormalities present (Smith et al., 2019). Relatively greater brain age has been shown to predict accelerated cognitive decline and dementia risk (Franke & Gaser, 2012). In particular, higher brain age at midlife is associated with cognitive impairment in later life (Elliott et al., 2021; Zheng et al., 2022). Brain age has been applied as a diagnostic tool for assessing the transition from cognitive deficit to dementia as well as assessing extant dementia and prognosis (Gaser et al., 2013).

Social isolation and brain age

Neurophysiological mechanisms have been implicated in the relationship between social ties and health (Eisenberger & Cole, 2012). Social isolation can be considered as an extreme case of the lack of social ties. There is evidence that socially isolated individuals show higher brain age relative to controls in a large population-based study (de Lange et al., 2021).

Research Question

Given social isolation is associated with dementia in older adults, are trajectories of social isolation from childhood to midlife related to brain age, a known biomarker of cognitive decline and dementia? If so, then the relationship found between social isolation and the development of dementia may – at least in part - be mediated by deleterious changes in brain structure that accelerate brain ageing. For instance, child-onset social isolation may have long-term negative effects on adult brain structure and thus on dementia risk.

We hypothesize that membership of trajectory groups affects adult brain structure and therefore brain age. We expect that outcomes will be worse in 'child-onset' versus 'adult-onset' groups, and even worser in the group with persistent social isolation.

Specifically, we will investigate:

1. How does the course of social isolation (child onset, adult onset, persistence) impact brain age?

2. Can the associations between social isolation and brain age (uncovered in a) be explained by risk factors associated with social isolation also being associated with brain age?

Data analysis methods:

Data source

The Dunedin Study has conducted a brain imaging study of participants at age 45 (Poulton et al., 2015). As part of this MRI study, structural neuroimaging measures were used to estimate brain age (Elliott et al., 2021).

Analysis

Social isolation in the Dunedin Study was assessed in childhood at ages 5-11 (Caspi et al., 2006; Danese et al., 2009), and again in adulthood at ages 26, 32, and 38. We previously employed trajectory modelling (Nagin, 2005) to derive trajectory groups based on the presence of social isolation (Lay-Yee et al., 2021). We will now use regression modelling to understand whether adult brain age is predicted by persistent versus transient social isolation with respect to different trajectory group membership, while controlling for childhood factors.

<u>Variables needed at which ages:</u>

Social isolation

- *Child isolation* was assessed by a collection of measures from ages 5 to 11. When a study member was 5, 7, 9, and 11 years old, their parent and teacher completed the Rutter Child Scale, reporting on two items that measure peer problems: 'tends to do things on his/her own; is rather solitary' and 'not much liked by other children'. At each age, scores on these two scale items will be averaged across the two reporting sources (i.e., parent and teacher).

- *Adult isolation* was assessed using *informant report* at ages 26, 32 and 38. At each of these ages, up to three informants whom the study member nominated as 'knowing them well' was mailed a questionnaire. At each age, scores on the item 'seems lonely' (0 = not a problem, 1 = bit of a problem, 2 = yes, a problem) will be averaged across informants.

MRI measures (at age 45)

Measures were taken on four brain hubs: the amygdala, the ventral striatum; the hippocampus; and the dorsolateral prefrontal cortex. Brain age was then estimated using these structural measures.

Confounders (childhood)

A complex interplay of factors may be involved in the relationship between social isolation and brain age (de Lange et al., 2021; Richmond-Rakerd et al., 2021). We have found a number of factors to be associated with social isolation trajectory group membership (Lay-Yee et al., 2021), and these may potentially confound associations between social isolation and brain age. We will include sex and the following as potential confounders:

- Sex
- Socio-economic status, measures at ages 0-15 using the Elley-Irving scale
- Teenage mother
- Experience of single parenting up to age 11

- Changes of residence up to age 11
- Maltreatment in childhood
- Self-control in childhood
- Worry/fearfulness from the Rutter problem behaviour scale (ages 5-11)

Significance of the Study (for theory, research methods or clinical practice):

Firstly, the theoretical significance of this study lies in its focus on the development of social isolation longitudinally, and adult outcomes (de Jong Gierveld et al., 2016), brain age in this case. The study will elucidate the contribution of social isolation (while controlling for confounders located in childhood), and add novel evidence, as to its negative effect on brain ageing. More broadly, if we can show an association (and assume it is likely to be causal), then it supports the importance of our social life, and the social conditions which allow it to flourish, in - at least partially - determining health outcomes via neurophysiological mechanisms impacting brain structure.

Secondly, with respect to the methods employed, this is a novel use of trajectory modelling to examine the development of social isolation in relation to a mid-life outcome, i.e., brain age.

Thirdly, in terms of policy and practice, understanding the influence of life-course differences in onset and the persistence of social isolation on an adult outcome, i.e., brain age, assists the design and implementation of interventions that may reduce risk and prevent or delay deleterious changes in brain structure. This study goes further in enabling the specification of interventions to suit sub-populations or individuals at different life stages and in identifying vulnerable groups that might benefit from public services. The impact of the duration and timing of social isolation may indicate points for intervention. For example, if childhood social isolation has negative impacts regardless of whether it persists into adulthood, this would argue for prevention strategies focused on childhood; otherwise, if only persistent social isolation is associated with negative consequences, then this would argue for prevention strategies which involve either identifying children with profiles suggestive of persistent social isolation or waiting until adolescence to see which individuals have persistent social isolation (e.g., see Lay-Yee et al., 2021).

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