ALL THE LONELY PEOPLE: THE RELATIONSHIP OF LONELINESS AND SOCIAL ISOLATION TO AGE-RELATED CHANGES IN BRAIN STRUCTURE

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ABSTRACT

In this study, we sought to test whether interactions with loneliness and social isolation with age were significant predictors of age-related changes in brain structure. Loneliness, or the subjective lack of satisfying social connections, poses a growing public health problem. Both loneliness and objective social isolation are risk factors for adverse physical and mental health outcomes, as well as age-related cognitive decline. However, few studies have characterized the relationship of loneliness or isolation to differences in brain structure and function across the mid- to late adult lifespan. Mapping of the structural correlates of loneliness and isolation in the human brain would lend insight into the associations of loneliness and isolation with cognitive decline. We used a data-driven, whole-brain approach to analyze structural imaging data from a UK-based sample (n = 14,666) and identify 70 statistically independent sources of variability across measures of cortical thickness, curvature, and surface area. Of these modes of variation, 50 correlated significantly with age, but interactions of loneliness/isolation with age did not explain the age-related structural changes. These results indicate that loneliness and isolation may not be associated with any more or less severe age-related reductions in cortical thickness, curvature, and surface area. However, the study affirms the importance of loneliness and isolation as critical factors associated with multiple measures of health and wellbeing, and informs future directions for studies investigating the relationship of loneliness/isolation to cognitive decline.

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INTRODUCTION

In 2017, former U.S. Surgeon General Vivek Murthy warned of a "loneliness epidemic" among modern Americans. According to him, "we live in the most technologically connected age in the history of civilization, yet rates of loneliness have doubled since the 1980s" (Murthy, 2017). While prevalence estimates vary depending on the measure of loneliness used and the age, demographic, and size of the population studied, the rate of loneliness among adults in developed countries nevertheless warrants concern. In support of Murthy's statement, the prevalence of loneliness has been estimated to have increased from 11-17% in the 1970s to over 40% of middle aged and older adults in the current decade (Edmondson, 2010; Peplau, Russell, & Heim, 1979; Perissinotto, Cenzer, & Covinsky, 2012). Estimates of loneliness rates among studies of U.S. adults aged 70 years and older have ranged from 25 to 29% (Edmondson, 2010; Hughes, Waite, Hawkley, & Cacioppo, 2004; Perissinotto et al., 2012; Theeke, 2009).

Outside of the U.S., other developed countries face similar concerns. Recent data show that the prevalence of loneliness in Europe ranges from 10% in countries in the West and North to 35% in countries in the East (Stickley et al., 2013; Victor & Bowling, 2012; Victor, Scambler, Bowling, & Bond, 2005). In the U.K., a 2010 online survey reported rates of loneliness as high as 45% among adults (Griffin, 2010). In China as well, rates of loneliness reach up to 29.6% among adults aged 60 years and older (Yang & Victor, 2008). Loneliness thus seems to represent a widespread, common phenomenon among industrialized countries.

Loneliness/Isolation and Health

Defined as an individual's subjective experience of the generalized lack of satisfying human relationships, loneliness differs from measures of objective social isolation (Andersson,

1998). Though related to the number and frequency of one's contact with others, loneliness involves a subjective perception of the quality of one's relationships. An individual can feel lonely in the midst of a marriage, a group of friends, family, or other social groups. One can also feel happy and fulfilled despite having few contacts (Tillich, 1959). Depending on perception, the same objective relationship can feel protective or threatening. However, the experience of loneliness cannot be attributed solely to personality qualities like introversion, but rather describes the distinct feeling that one's social relationships do not match up to one's preferences for social engagement (Cacioppo, Cacioppo, & Boomsma, 2014; Cacioppo, Hawkley, et al., 2006). It would make sense then that chronic loneliness has often been associated with increased depressive symptomatology (Booth, 2000; Cacioppo et al, 2010; Cacioppo et al., 2006; Vanderweele et al., 2011) and lower subjective wellbeing (Kong & You, 2013; Vanderweele et al., 2012). Despite this close association, cross-sectional and longitudinal studies have shown that loneliness and depression are related but separable measures (Booth, 2000; Cacioppo, Hawkley, & Thisted, 2010; VanderWeele, Hawkley, Thisted, & Cacioppo, 2011). Research has demonstrated that loneliness has effects on health outcomes independent of depressive symptoms (Cacioppo, Hughes, Waite, Hawkley, & Thisted, 2006; Heinrich & Gullone, 2006).

In addition to its relationship to poor mental health, loneliness poses serious implications for a myriad of adverse health outcomes. Numerous meta-analyses have reported loneliness as a risk factor for all-cause mortality, with hazard ratios between 1.22 and 1.44 and odds ratios for loneliness double that for obesity and quadruple that for air pollution (Cacioppo & Cacioppo, 2018; Holt-Lunstad, Smith, & Layton, 2010; Rico-Uribe et al., 2018). Longitudinal studies have also shown loneliness at baseline to be associated with increased mortality risk over several years (Luo, Hawkley, Waite, & Cacioppo, 2012; Patterson & Veenstra, 2010). Moreover, loneliness has been implicated in a host of health issues, including immune dysfunction (Pressman et al., 2005), metabolic syndrome (Whisman, 2010), increased inflammation (Hackett, Hamer, Endrighi, Brydon, & Steptoe, 2012), sleep difficulties (Cacioppo, Hawkley, Crawford, et al., 2002), alcoholism (Åkerlind & Hörnquist, 1992), Alzheimer's disease (AD) (Gow, Pattie, Whiteman, Whalley, & Deary, 2007; Tilvis et al., 2004; Wilson et al., 2007), cardiovascular problems (Holt-Lunstad & Smith, 2016), stroke (Hakulinen et al., 2018), and poor overall health (Rico-Uribe et al., 2016).

To explain the health effects of social isolation, many researchers have proposed the social control hypothesis, which stipulates that interactions with others encourage better health behavior (Umberson, 1987, 1992; Pettee et al., 2006; Satariano et al., 2002; Schmitz et al., 1997). The hypothesis suggests that other people exert a form of social control over one's behaviors, and this control theoretically promotes healthy behaviors like physical activity, nutritious diets, and more sleep, while discouraging unhealthy behaviors, like alcohol consumption or smoking. For example, married status has been associated with greater engagement with healthy behaviors like physical activity (Pettee et al., 2006; Satariano, Haight, & Tager, 2002; Schmitz, French, & Jeffery, 1997; Umberson, 1992). A similar study among women found that reminders from friends or family to protect one's health were associated with increases in physical activity three years later (Umberson, 1987). The healthy behaviors encouraged by social interactions decrease risks for premature mortality and other adverse health outcomes.

While greater social isolation indeed contributes to worse health outcomes, the social control model has been found insufficient for explaining loneliness' effects (Holt-Lunstad et al., 2010; House, Landis, & Umberson, 1988). A longitudinal study showed that neither health behaviors nor objective features of social relationships accounted for loneliness' association with

increased mortality risk over a six-year period (Luo et al., 2012). Another longitudinal study showed that loneliness predicted declines in physical activity over time, but the effects of loneliness on executive functioning, rather than social control, mediated this association (Hawkley, Thisted, & Cacioppo, 2009).

Unlike the social control hypothesis, a social neuroscience model of loneliness centers the brain as a social organ and highlights its role in influencing neurobiological mechanisms of health. The social neuroscience model posits that living in social communities has made the establishing, monitoring, and maintenance of social connections a key requisite of individual and species survival. Over time, various neural, hormonal, and genetic mechanisms evolved to support sociality (Cacioppo et al., 2014; Cacioppo, Hawkley, et al., 2006). Since the brain plays a large role in forming and cultivating these social connections, evolution has wired the brain to preferentially process social information. For example, newborns prefer to look at faces or facelike patterns over non-face-like stimuli (Valenza, Simion, Macchi Cassia, & Umiltà, 1996). Further, a large area of the temporal cortex, known as the fusiform face area, is dedicated to the preferential processing of faces (Adolphs, 2008). Even among rodents, a study has also found that dopamine neurons in the dorsal raphe nucleus display increased activation in response to social contact after periods of social isolation. This study demonstrates that for many animals, the brain has mechanisms in place to reward social contact and discourage isolation (Matthews et al., 2016). Given the brain's central role in processing and prioritizing social information, it would make logical sense for us to look for neural correlates of unsatisfactory social connections.

The structures and behaviors that have evolved to support sociality may manifest in the brain and the body in ways that are meant to be adaptive. According to the social neuroscience model, social relationships serve as protective mechanisms—people in a community watch out for and help out other members of the community. Without this mutual protection, or the perception of such protection, an individual consciously or subconsciously believes that they must devote greater resources to looking out for themselves. As such, the brain launches into a temporary self-preservation mode. Many studies have associated loneliness and isolation with a sustained fight-or-flight response that includes increased sleep fragmentation (Cacioppo et al., 2002; Hawkley et al., 2010; Jacobs et al., 2006; Kurina et al., 2011), increased hypothalamicpituitary-adrenal activity (Adam et al., 2006; Cacioppo et al., 2000; Doane & Adam, 2010; Glaser et al., 1985; Kiecolt-Glaser et al., 1984; Steptoe et al., 2004), decreased inflammatory control (Cole et al., 2011), increased glucocorticoid insensitivity (Cole et al., 2007), elevated blood pressure (Cacioppo et al., 2002; Hawkley et al., 2010), lowered immunity (Dixon et al., 2001; Glaser et al., 2005; Pressman et al, 2005; Straits-Tröster et al., 1994), and impaired executive functioning (Cacioppo et al., 2000; Hawkley et al., 2009; Baumeister & DeWall, 2005. This short-term survival mechanism allows the brain to adapt to constantly changing social environments, but it carries long-term costs when the experience or perception of isolation becomes chronic. Studies have shown long-term activation of this stress response to contribute to insulin resistance, cardiovascular problems, and negative psychosocial symptoms (Curtis & O'Keefe, 2002). While this model could serve as a potential mechanism by which loneliness or isolation affects health outcomes, the causal relationship between these factors should not be overstated. With major bidirectional interactions between the brain and the body, it is possible that people struggling with poor health experience loneliness or isolation as a function of their physical condition, just as loneliness or isolation could influence physical health outcomes.

Loneliness/Isolation and Social Cognition

In addition to changes in mental and physical health, the brain's adaptive response to chronic loneliness or isolation could alter one's perception of social situations. Accustomed to feeling like they must watch out for themselves, a lonely individual could perceive others as more hostile or unpleasant, and interpret social situations in more negative ways. In turn, these negative social interactions could then motivate an individual to seek further isolation or cause them to feel a greater sense of alienation. As such, the experience of loneliness or isolation could constitute a mutually reinforcing cycle, perpetuating a state of social dissatisfaction. While originally an adaptive response to the lack of social support, the brain's response to perceived isolation could in fact prove to be self-destructive rather than self-preservational (Duck et al., 1994; Rotenberg, 1994; Rotenberg et al., 2002; Cacioppo et al., 2014; Lau & Gruen, 1992; Rotenberg & Kmill, 1992; Petersen et al., 2015).

Research into the cognitive effects of loneliness supports the social neuroscience model. Several task-related functional magnetic resonance imaging (fMRI) studies have demonstrated that loneliness is associated with increased attention to negative social stimuli (Cacioppo, Norris, Decety, Monteleone, & Nusbaum, 2009; Powers, Wagner, Norris, & Heatherton, 2011; Shintel, Nusbaum, & Cacioppo, 2006; Yamada & Decety, 2009). Compared to non-lonely participants, lonely participants demonstrated greater Stroop interference for negative social words than for negative nonsocial words. Since Stroop interference is a measure of how difficult it is to inhibit reactions to certain stimuli, this result indicates that lonely individuals harbored a heightened sensitivity to negative social information (Shintel et al., 2006). Similarly, in a study on subliminal priming, lonely participants detected painful facial expressions in dislikable faces more readily than did non-lonely participants, reinforcing the notion that lonely individuals are more attentive to negative social cues (Yamada & Decety, 2009).

Other studies have identified differences in activation of certain brain regions among lonely and non-lonely individuals in response to social stimuli. These brain regions tend to be associated with perception and social cognition. For example, an fMRI study related the loneliness of the participant to activation of the visual cortex during exposure to unpleasant social, as opposed to nonsocial, images. By contrast, during the unpleasant social condition, loneliness was inversely related to activation in the temporo-parietal junction (TPJ), which is involved in imagining others' perspectives and mental states (Cacioppo et al., 2009). This result suggests that while lonely individuals may devote greater attention to negative social stimuli, they also may not relate to others as well during unpleasant social situations. In line with this finding, another fMRI study found that part of the dorsomedial prefrontal cortex (DMPFC) showed less activation during negative situations among participants who had just experienced an instance of social exclusion. Like the TPJ, the DMPFC has been implicated in thinking about the mental states of others, and the decreased activation of this area in response to social exclusion implies that the experience of exclusion suppresses attempts to relate to others (Powers et al., 2013). Conversely, loneliness or isolation can also reduce the reward gained from pleasant social stimuli. One study investigated differences in activation of the ventral striatum, which responds to primary and secondary rewards, in lonely versus non-lonely participants. Lonely participants showed less activation of the ventral striatum in response to positive social stimuli than non-lonely participants (Cacioppo et al., 2009). In sum, these neuroimaging findings link loneliness with altered processing across a distributed set of brain regions important for social perception and cognition. However, it remains unclear from these studies whether differences in

social perception reflect state-dependent changes or indicate trait-like biases associated with lifetime measures of social connection and satisfaction.

Loneliness/Isolation and Brain Structure

While numerous studies have noted variation in task-related brain activation based on loneliness, relatively few studies have investigated differences in brain structure associated with loneliness or isolation. The studies that have looked into these relationships have observed regional changes in brain size that correspond with a social brain hypothesis. This hypothesis posits that growing sociality promoted the evolutionary growth of neocortex in primates (Dunbar, 1998, 2003; Dunbar, 2009; Dunbar R.I.M & Shultz Susanne, 2007; Lihoreau et al., 2012; Semendeferi et al., 2011). Outside of evolutionary effects, social information can also influence individual structural changes in the adult brain. The social brain hypothesis also theorizes that, because the brain is energetically expensive, certain regions will enlarge or shrink as a result of functional demands (Alexander, 1974; Niven & Laughlin, 2008). For example, differences in hippocampus size between taxi drivers and non-taxi drivers support this notion of experience-driven plasticity. The posterior hippocampus, responsible for encoding spatial information, was significantly larger for taxi drivers than for non-taxi drivers, while the anterior hippocampus was significantly larger for non-taxi drivers, suggesting a redistribution of brain volume based on experience (Maguire et al., 2000). Likewise, loneliness and social isolation should lead to reductions in the size of brain regions involved in social functions (Alexander, 1974).

The results of experimental animal studies support this model of social isolationdependent brain plasticity. While animal models can only measure isolation and not the subjective experience of loneliness, experiments with animals allow for greater manipulation of the social environment and more invasive investigation of biological targets. Studies in rodents have found that, relative to controls, socially isolated rodents exhibit loss of gray matter volume in areas like the prefrontal cortex, the occipital cortex, and the hippocampus, which are involved in memory, sensorimotor integration, and the processing of social and spatial information (Diordievic et al., 2010; Diamond et al., 1975, 1976; Moser et al., 1997). Similar experimental studies have shown that compared to rodents housed in groups, rodents housed alone developed a smaller cerebral cortex, smaller cell bodies, shorter synapses, and fewer glial cells in regions of the brain involved in sensorimotor integration and social functioning (Bhide & Bedi, 1984; Biørnebekk et al., 2007; Garrido et al., 2013), Rosenzweig et al., 1968). For example, socially isolated rats displayed lighter and shorter forebrains and less cortical depth in one section of the left occipital cortex (Bhide & Bedi, 1984; Diamond et al., 1972, 1975, 1976, 2001). For socially isolated songbirds as well, studies have found fewer neurons in brain areas involved in vocal communication, such as the neostriatum caudale, as well as those involved in memory and spatial information processing in the hippocampal complex (Lipkind et al., 2002; Barnea et al., 2006). Overall, in line with the social brain hypothesis, these animal studies demonstrate reductions in gray matter in brain areas related to social functioning.

By comparison, a limited number of studies has examined structural brain features related to loneliness or isolation in humans (Uylings & de Brabander, 2002). Kanai et al. (2012) found that among 108 healthy adults, loneliness correlated negatively with gray matter density in the left posterior superior temporal sulcus (pSTS), which is involved in biological motion and social perception. A more recent study that sought to identify the neural correlates of loneliness found lonely individuals to have greater gray matter volume in the left dorsolateral prefrontal cortex (DLPFC). Since the DLPFC is one of the brain regions implicated in down-regulating negative emotions, the researchers interpreted the increased gray matter volume as a sign of lonely individuals having less emotional self-control, particularly over negative emotions (Kong et al., 2015). While this conclusion may seem counterintuitive, it counters the assumption that increases in gray matter enhance the function of that region. The increased volume of the DLPFC could reflect neuronal immaturity, or inefficient synaptic pruning processes (Kanai & Rees, 2011; Takeuchi et al., 2014). While most studies of loneliness in animals and humans have focused on gray matter, one study investigated white matter structures related to loneliness. It found that loneliness scores correlated negatively with regional white matter density in areas related to self- and social cognition, empathy, and self-efficacy. In support of a social neuroscience model, the decreased white matter in these regions suggests that lonely people experience dysfunction in feeling empathy for others and in maintaining the mental states necessary to establish close relationships (Nakagawa et al., 2015). As in studies with animal models, studies of brain structure in humans also seem to support distributed increases or reductions in gray or white matter volume depending on the function of the brain region. These studies support an extension of the social brain hypothesis that posits that loneliness and isolation contribute to structural adaptations in the brain that reflect the degree of sociality of one's lifestyle.

Loneliness/Isolation and Age-Related Brain Changes

Since loneliness and isolation are also highly related to cognitive decline with aging, it follows that structural brain changes associated with loneliness would have some relationship with structural changes related to age. Several studies have demonstrated that loneliness is a risk factor for age-related cognitive decline and dementia (Gow et al., 2007; Tilvis et al., 2004; Wilson et al., 2007). For example, a study exploring mental ability correlates in 488 individuals found that only loneliness was significantly associated with changes in IQ, after controlling for age, sex, education, and socioeconomic status (Gow et al., 2007). Other longitudinal studies have addressed the possibility that loneliness could be a predictor of cognitive decline. In a cohort of 800 elderly adults over a period of four years, lonely participants were over twice as likely to develop AD-like dementia as non-lonely participants, even after controlling for social isolation (Wilson et al., 2007). These results are consistent with a previous longitudinal study that showed an association between loneliness and increased risk of cognitive decline over ten years among a sample of adults aged 75 to 85 years (Tilvis et al., 2004). Further, studies investigating the biological markers of Alzheimer's disease (AD) have associated loneliness with increased amyloid- β deposition and tau pathology. A cross-sectional study among healthy older adults found loneliness to be associated with higher brain amyloid burden independent of depressive symptoms and social network. Loneliness could thus be indicative of early brain changes in preclinical AD (Donovan et al., 2016). Using positron emission tomography (PET), another study linked greater loneliness with greater tau pathology in the right entorhinal cortex, a region of early plaque accumulation in aging adults (Uquillas et al., 2018). Loneliness has thus been related not only to increased risk for cognitive decline but also to the greater burden of biological markers that precede this decline.

Loneliness could act as an early sign or result of dementia pathology, or it could somehow compromise neural systems for cognition and memory in a way that makes these systems more vulnerable to the effects of age. Since most of the studies analyzing loneliness and AD pathology have used cross-sectional methods, loneliness could be a behavioral reaction to experienced cognitive decline or a direct effect of dementia pathology, even before the onset of clinical AD. Based on findings of structural changes in animal models however, possible changes in neural systems underlying social behavior could also make lonely individuals less able to compensate for changes to those or other neural systems that occur with age.

Structural changes that occur with age include global reductions in gray matter volume as a result of neuronal shrinkage, reductions of synaptic spines, lower numbers of synapses, and reduced length of myelinated axons (Reisberg et al., 2002; McGinnis et al., 2011; Raz et al., 2000; Peters, 2006; Fjell & Walhovd, 2010). Research has associated reduced gray matter volume with worse performance on a wide range of domain-general and language-specific cognitive tests (Ramanoël et al., 2018). Other studies have shown that subjects with AD or mild cognitive impairment experience greater global gray matter loss than subjects undergoing healthy aging, reinforcing the notion that global gray matter reductions are associated with cognitive decline (Karas et al., 2004). On the other hand, other studies have found age-related reductions in gray matter volume specific to certain regions, particularly the association cortices and less so the primary visual and somatosensory cortices (Uylings & de Brabander, 2002). Similar studies have located age-related gray matter reductions in the fronto-parietal neocortex, insula, and cerebellum, but not so much in the limbic and paralimbic structures and primary visual cortices (Terribilli et al., 2011; Williamson et al., 2005). Relative rates of change also vary by brain region (Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010). In addition, while both cortical thickness and surface area are used to calculate gray matter volume, studies have found some brain regions to experience only thickness or surface area reductions with age, and not reductions in both measures (Lemaitre et al., 2012). The shape, or curvature, of the cortical

surface has also been found to change significantly with age, with the sulci flattening and the gyri becoming more steeply curved (Heckel et al., 1999; Resnick et al., 2005). Independent variation of cortical thickness, surface area, and curvature with age suggests that these measures reflect distinct age-related changes and warrants studying them separately (Panizzon et al., 2009; Hofman, 1989; Kaas, 2000; Laughlin & Sejnowski, 2003; Zhang & Sejnowski, 2000; Lee et al., 2008; Pakkenberg & Gundersen, 1997).

Despite loneliness' relationship to cognitive decline, few studies have investigated whether loneliness is associated with age-related changes in brain structure. Such research could help to better illuminate the biological basis of loneliness/isolation's relationship to age-related decline, as well as add to the emerging scientific literature on the neural correlates of loneliness and isolation.

Therefore, we aimed to determine the relationship of loneliness and social isolation to age-related structural changes in the human brain. Since aging has been shown to affect the whole brain, and there is little conclusive evidence on specific regions or aspects of brain anatomy associated with loneliness, we used a data-driven, whole-brain approach and a large sample size to identify age-related changes in brain structure. We hypothesized that interactions of loneliness/isolation with age would predict age-related reductions in cortical thickness, surface area, and curvature.

METHODS

Data

Behavioral and imaging data were downloaded from the UK Biobank, an epidemiological dataset that includes extensive questionnaires, physical and cognitive indicators, genotyping, and

biological samples from a cohort of over 500,000 participants (Matthews et al., 2016). At the time of baseline recruitment, which occurred between April 2006 and December 2010, participants were between the ages of 40 and 69 years. Follow-up assessments were conducted in 2012 and 2017 and are projected to continue every five years until 2027. The study used UK National Health Service registers to send invitations to individuals who were within the above age range and lived a reasonable distance from the 22 assessment centers across the UK. Of the eligible population, 5.5% participated. Participants completed a touch-screen questionnaire focused on their health and lifestyle characteristics, and trained data nurses took physical measurements, such as height, weight, and blood pressure (Sudlow et al., 2015; Palmer, 2007). Neuroimaging scans have been collected on a subset of participants (N=21,262; Target N=100,000). The brain imaging data includes six modalities: three structural modalities (T1-weighted, T2-weighted, and susceptibility-weighted), diffusion MRI (dMRI), task MRI (tfMRI), and resting-state fMRI (rfMRI) (Miller et al., 2016). Of the imaging data, only T1 structural scans were used for this project.

Pre-processing of structural data

Anatomical data (T1 structural images) for 21,262 subjects were downloaded from the UK Biobank. Anatomical scans were collected over four minutes and 54 seconds, with a voxel size of 1.0x1.0x1.0 mm and a field of view (FOV) of 256 mm. The data underwent minimal pre-processing that included blurring subjects' faces to preserve anonymity and normalizing signal intensity across voxels (Miller et al., 2016). Additional pre-processing of T1 data was conducted through Freesurfer v6.0. Since face blurring can lead to biases in cortical thickness estimates, we reconstructed data from raw DICOM files, which store and group imaging information in data

sets (Holmes et al., 2015). We then implemented the UK Biobank structural processing pipeline, which included gradient unwarping to correct for biases in scanner magnetic fields and FOV reduction to minimize non-brain voxel space (C. F. Beckmann & S. M. Smith, 2004; Jenkinson, Bannister, Brady, & Smith, 2002; Miller et al., 2016). Importantly, we omitted facial censoring as a preprocessing step to avoid biasing Freesurfer anatomical estimates.

Our primary measures of brain structure were cortical thickness, surface area, and curvature. Cortical thickness is defined as the length of the shortest possible path from each point on the outer cortical surface (i.e. pial/gray matter boundary) to a point on the inner cortical surface (i.e. white matter/gray matter boundary; Lohmann, Preul, & Hund-Georgiadis, 2003). Thickness measurements are obtained at each vertex of a cortical surface mesh, which represents the cortex as a geometric net of triangles (Van Essen, Drury, Joshi, & Miller, 1998). This surface-based visualization preserves the topology and geometry of the original cortex and allows for comparison between subjects (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000). Cortical surface area represents an overall degree of folding and is calculated from the areas of the triangles making up the surface mesh (Luders et al., 2006; Wiegand et al., 2005). Cortical curvature is defined as the average of the maximum and minimum curving degrees of the surface and represents the shape of gyri and sulci (Resnick, Rettmann, Kraut, & Prince, 2005; Tosun, Rettmann, & Prince, 2004).

We then transformed surface parcellations for each individual to a common template, known as fsaverage space, with approximately 140,000 vertices per hemisphere. Data values were downsampled to an fsaverage6 space with 40,000 vertices per hemisphere, and smoothed to 10 mm full-width/half-max (FWHM). Alignment to this common space allows for cross-subject comparison, as each subject now has the same number of vertices in approximately the same locations across the surface mesh. Data files were concatenated in Freesurfer with the command mri_concat to form a single file each for thickness, curvature, and surface area by hemisphere.

Variables and exclusions

Loneliness was quantified on a scale of 0 to 2 based on responses to two questions in the UK Biobank's survey: 1) "Do you often feel lonely?" (1 point for yes) and 2) "How often are you able to confide in someone close to you?" (1 point for never or almost never). Social isolation was quantified on a scale of 0 to 3 according to responses to the following three questions: 1) "Including yourself, how many people are living together in your household? Include those who usually live in the house such as students living away from home during term time, partners in the armed forces or professions such as pilots" (one point for living alone); 2) "How often do you visit friends of family or have them visit you?" (one point for friends and family visiting less than once a month); and 3) "Which of the following [leisure/social activities] do you engage in once a week or more often?" (one point for no participation in social activities at least weekly). Since only 67 individuals, or 0.4% of the total population, scored a three on the isolation scale, these individuals were combined with those who scored a two on the scale.

Covariates used in regression analyses included age at imaging visit, sex, height, weight, body mass index (BMI), diastolic and systolic blood pressure, T1 volume of ventricular cerebrospinal fluid (CSF), T1 volume of gray matter and white matter normalized for head size, T1 inverted signal-to-noise ratio (SNR), and inverted SNR and head motion in rfMRI.

Because neurodegenerative disorders may be prevalent in older adult populations, brain lesion volume was normalized as a function of brain size, and brains with lesion volumes that were 1.5 standard deviations (SD) above the norm were excluded from the dataset. Brain size was normalized by gender, and brains that deviated by more than three SDs from the average were excluded. Missing values for head motion and SNR were excluded. Missing values for BMI were calculated by hand from height and weight variables and were found to be consistent with estimates provided by UK Biobank. The "last value carried forward" method was used to impute missing diastolic and systolic blood pressure values at the time of the imaging visit from measurements taken at previous visits (Salkind, 2019). For variables used to calculate loneliness and isolation, missing values or answers of "Prefer not to answer" or "Do not know" were excluded. The final sample consisted of 14,666 subjects.

Statistical analysis

A linked independent component analysis (FLICA), developed by Groves et al. (2011), was used to identify independent modes of variation across subjects. An unsupervised, datadriven approach, independent component analysis (ICA) is a method of separating out statistically independent sources of variation that have been linearly mixed together, similar to distinguishing separate voices at a noisy cocktail party (Amari, Cichocki, & Yang, 1995). The independent components represent biophysically plausible sources of variation in brain structure across participants. While several studies have used ICA to identify changes in the brain in separate modalities (for example, diffusion tensor imaging or T1 imaging), the differences in units, voxel counts, signal-to-noise ratios, and other features across modalities often prevent meaningful comparison across modalities (Calhoun, Adali, Pearlson, & Pekar, 2001; Hutchison, Mirsattari, Jones, Gati, & Leung, 2010; T. -. Jung et al., 2001; Xu, Groth, Pearlson, Schretlen, & Calhoun, 2009). However, FLICA uses a modular Bayesian framework to adaptively combine multimodal data according to each modality's signal properties, and to extract common patterns of change across these modalities (Groves, Beckmann, Smith, & Woolrich, 2011).

FLICA was run on measures of cortical thickness, curvature, and surface area, based on the findings of a previous paper that used the method to identify independent components related to age (Douaud et al., 2014). To make the analysis comparable with previous studies, FLICA was run with 70 components, such that it identified 70 independent modes of variation across subjects' cortical thickness, surface area, and curvature measures (Douaud et al., 2014; Smith et al., 2004). From these 70 components, age-related components were identified using linear and quadratic fits. We ran linear regressions of the age-related components with age, loneliness or isolation score, interactions of age with loneliness or isolation score, and the full list of covariates as predictors.

All analyses were conducted with FreeSurfer v6.0, RStudio v1.1.463, R v3.4.4, Python Anaconda3, and MATLAB 2016b.

RESULTS

Loneliness and Isolation Associated with Poor Health and Low Life Satisfaction

Before beginning statistical analyses, we wanted to explore whether our data on loneliness and isolation were consistent with previous studies. Table 1.1 and 1.2 show the subjects' sociodemographic characteristics, health-impacting behaviors, health outcomes, life satisfaction characteristics, and mean head motion by their loneliness and isolation scores. Out of 14666 participants, 11286 people (77% of the sample population) had a loneliness score of 0, 2832 people (19%) had a loneliness score of 1, and 548 people (4%) had a loneliness score of 2. For isolation, 8506 people (58%) had a score of 0, 5129 people (35%) had a score 1, and 1031 people (7%) had a score of 2. The mean age of the sample population was 62.9 ± 7.3 years, and there were significant differences in age by loneliness and isolation scores, with lonelier and more isolated people tending to be younger (F(1, 14664) = 27.1, p < 0.001 for loneliness; F(1, 14664) = 27.1, p < 0.001 for loneliness; F(1, 14664) = 27.1, p < 0.001 for loneliness; F(1, 14664) = 27.1, p < 0.001 for loneliness; F(1, 14664) = 27.1, p < 0.001 for loneliness; F(1, 14664) = 27.1, p < 0.001 for loneliness; F(1, 14664) = 27.1, p < 0.001 for loneliness; F(1, 14664) = 27.1, p < 0.001 for loneliness; F(1, 14664) = 27.1, p < 0.001 for loneliness; F(1, 14664) = 27.1, p < 0.001 for loneliness; F(1, 14664) = 27.1, p < 0.001 for loneliness; F(1, 14664) = 27.1, p < 0.001 for loneliness; F(1, 14664) = 27.1, p < 0.001 for loneliness; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) = 27.1, p < 0.001 for lonelines; F(1, 14664) =14664) = 20.0, p < 0.001 for isolation). Lonelier and more isolated people were also more likely to have less than a college or university degree (F(1, 14664) = 45.0, p < 0.001 for loneliness; F(1, 14664) = 14.3, p < 0.001 for isolation), have an annual household income below \$31,000 (F(1, 14664) = 258.4, p < 0.001 for loneliness; F(1, 14664) = 19.42, p < 0.001 for isolation), and to be currently employed (F(1, 14664) = 21.4, p < 0.001 for loneliness; F(1, 14664) = 20, p < 0.0010.001 for isolation). The greater proportion of lonely and isolated people who were employed may be due to the fact that the questions that comprised the isolation measure asked about visits with friends or family, which working people may not be able to do as often. Lonelier, but not more isolated, people were more likely to be male (F(1, 14664) = 7.0, p < 0.01 for loneliness; F(1, 14664) = 1.26, p = 0.26 for isolation). These results are consistent with previous studies that have identified differences in rates of loneliness based on sex, age, and household income (Edmondson, 2010; Rico-Uribe et al., 2018).

	All	Loneliness Score				
		0	1	2	ANOVA F(1,14664)	Correlation (r)
Sample size, N (%)	14,666	(77)	2,832 (19)	548 (4)		
Sociodemographic characteristics						
Age, years	62.9 ± 7.3	63.0 ± 7.3	62.6 ± 7.5	61.6 ± 7.2	27.1***	-0.04***
Sex, percent female Education, percent with college or	53.3 ± 0.8	53.9 ± 0.9	51.3 ± 1.8	50.7 ± 4.2	7.0**	-0.04***
university degree Household income.	45.9 ± 0.8	47.5 ± 1.1	40.8 ± 1.8	38.7 ± 4.1	45.0***	-0.08***
percent > 31,000 Employment status	54.1 ± 0.8	55.9 ± 0.9	48.3 ± 1.8	46.6 ± 4.2	31.9***	-0.09***
percent employed	43.0 ± 0.8	41.9 ± 0.9	45.9 ± 1.8	46.4 ± 4.2	21.4***	0.06***
frequency, percent > 2x/wk	45.8 ± 0.8	46.9 ± 0.9	43.0 ± 1.8	37.4 ± 4.1	30.0***	-0.06***
Sleep duration, hours	7.14 ± 1.1	7.2 ± 1.1	7.1 ± 1.2	6.8 ± 1.4	58.1***	-0.07***
Health characteristics						
Mean BMI (kg/m ²)	26.5 ± 4.3	26.3 ± 4.2	27.0 ± 4.6	27.9 ± 5.4	106.8***	0.07***
Longtime illness, yes	25.8 ± 0.7	24.5 ± 0.8	30.7 ± 1.7	35.3 ± 4.0	339.6***	0.12***
Overall health, yes Moderate or severe	1.9 ± 0.2	1.3 ± 0.2	3.1 ± 0.6	7.9 ± 2.3	137.9***	0.24***
depression, yes	14.8 ± 0.6	13.1 ± 0.6	20.0 ± 1.5	25.7 ± 3.7	37.0***	0.16***
yes	4.3 ± 0.3	3.4 ± 0.3	6.9 ± 0.9	9.9 ± 2.5	108.3***	0.23***
characteristics						
Happiness, unhappy Financial satisfaction.	3.6 ± 0.3	1.2 ± 0.2	8.8 ± 1.1	25.7 ± 3.7	945.7***	0.59***
unhappy Friendship	5.7 ± 0.4	4.0 ± 0.4	10.8 ± 1.1	13.1 ± 2.8	224.5***	0.28***
satisfaction, unhappy	2.9 ± 0.3	1.0 ± 0.2	6.6 ± 0.9	21.4 ± 3.4	597***	0.51***
unhappy Relationship	7.9 ± 0.4	6.1 ± 0.4	12.3 ± 1.2	20.4 ± 3.4	244.3***	0.24***
satisfaction, unhappy	5.5 ± 0.4	3.0 ± 0.3	10.7 ± 1.1	28.8 ± 3.8	730.5***	0.53***
MRI characteristics						
Head motion	0.12 ± 0.06	0.12 ± 0.05	0.12 ± 0.06	0.13 ± 0.07	63.8***	0.06***

Table 1.1. Sociodemographic characteristics, health-impacting behaviors, health outcomes, life satisfaction characteristics, and mean head motion by their loneliness scores among 14,666 adults in the UK Biobank. There were significant differences in all variables by loneliness score. Loneliness was quantified on a scale of 0 to 2 based on responses to two questions in the UK Biobank's survey: 1) "Do you often feel lonely?" (1 point for yes) and 2) "How often are you able to confide in someone close to you?" (1 point for never or almost never). Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' 1

	All	Isolation Score				
		0	1	2	ANOVA F (1,14664)	Correlation (<i>r</i>)
Sample size, N (%)	14,666	8,506 (58)	5,129 (35)	1,031 (7)		
Sociodemographic characteristics						
Age, years	62.9 ± 7.3	63.0 ± 7.3	62.8 ± 7.4	61.8 ± 7.4	20***	-0.03***
Sex, percent female Education, percent with college or university	53.3 ± 0.8	53.2 ± 1.1	54.4 ± 1.4	48.4 ± 3.1	1.26	-0.01***
degree Household income.	45.9 ± 0.8	47.5 ± 1.1	43.8 ± 1.4	43.3 ± 3.0	14.3***	-0.06***
percent > 31,000 Employment status.	54.1 ± 0.8	60.6 ± 1.0	46.9 ± 1.4	35.9 ± 2.9	258.4***	-0.21***
percent employed	43.0 ± 0.8	40.1 ± 1.1	45.0 ± 1.4	53.2 ± 3.0	19.42***	0.09***
Alcohol consumption						
frequency, percent >	158+08	196+11	121+11	225+20	1/6 2***	_0 12***
Sleep duration, hours	40.0 ± 0.0 7.1 ± 1.1	49.0 ± 1.1 7.2 ± 1.0	7.1 ± 1.1	7.1 ± 1.3	16.68***	-0.03***
Health characteristics						
Mean BMI (kg/m²)	26.5 ± 4.3	26.3 ± 4.1	26.7 ± 4.5	27.2 ± 5.1	61.89***	0.05***
Longtime illness, yes	25.8 ± 0.7	24.4 ± 0.9	27.6 ± 1.2	33.0 ± 2.9	52.08***	0.09***
Overall health, yes Moderate or severe	1.9 ± 0.2	1.2 ± 0.2	2.5 ± 0.4	4.8 ± 1.3	189.2***	0.23***
depression, yes	14.8 ± 0.6	13.7 ± 0.2	16.4 ± 1.0	17.0 ± 2.3	20.58***	0.07***
Severe depression, yes	4.3 ± 0.3	3.9 ± 0.4	4.8 ± 0.6	5.6 ± 1.4	10.89***	0.07***
Satisfaction characteristics						
Happiness, unhappy	3.6 ± 0.3	2.3 ± 0.3	4.4 ± 0.6	10.2 ± 1.8	166.1***	0.27***
unhappy	5.7 ± 0.4	4.0 ± 0.4	7.0 ± 0.7	13.1 ± 2.1	159.8***	0.23***
unhappy	2.9 ± 0.3	1.9 ± 0.3	3.4 ± 0.5	7.9 ± 1.6	204.2***	0.28***
nealth satisfaction, unhappy Balatianabia	7.9 ± 0.4	6.0 ± 0.5	9.7 ± 0.8	13.9 ± 2.1	122.4***	0.17***
satisfaction, unhappy	5.5 ± 0.4	3.9 ± 0.4	6.6 ± 0.7	12.3 ± 2.0	314.8***	0.27***
MRI characteristics						
Head motion	0.12 ± 0.06	0.12 ± 0.05	0.12 ± 0.06	0.13 ± 0.06	52.08***	0.05***

Table 1.2. Sociodemographic characteristics, health-impacting behaviors, health outcomes, life satisfaction characteristics, and mean head motion by their isolation scores among 14,666 adults in the UK Biobank. There were significant differences in all variables except sex by isolation score. Social isolation was quantified on a scale of 0 to 3 according to responses to the following three questions: 1) "Including yourself, how many people are living together in your household?; 2) "How often do you visit friends of family or have them visit you?"; and 3) "Which of the following [leisure/social activities] do you engage in once a week or more often?". Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

While our data demonstrate significantly different health-related behaviors among people with varying degrees of loneliness or isolation, lonelier and more isolated people do not necessarily exhibit worse health-related behaviors. Lonelier and more isolated people slept significantly less, though not by much (F(1, 14664) = 58.1, p < 0.001 for loneliness; F(1, 14664)= 16.68, p < 0.001 for isolation). The overall population slept on average 7.1 ± 1.1 hours per night, while people with a loneliness score of 2 slept on average 6.8 ± 1.4 hours per night, and people with an isolation score of 2 slept on average 7.1 ± 1.3 hours per night. Lonelier and more isolated people had significantly higher BMIs, which can also be indicative of physical activity and diet. The overall population had an average BMI of $26.5 \pm 4.3 \text{ kg/m}^2$ while people with a loneliness score of 2 had an average BMI of $27.9 \pm 5.4 \text{ kg/m}^2$ and people with an isolation score of 2 had an average BMI of $27.2 \pm 5.1 \text{ kg/m}^2$. However, lonelier and more isolated people consumed alcohol significantly less frequently, as $45.8 \pm 0.8\%$ of the average population consumed alcohol more than twice per week, compared to $37.4 \pm 4.1\%$ of people with a loneliness score of 2 and $32.5 \pm 2.9\%$ of people with an isolation score of 2 (F(1, 14664) = 30.0, p < 0.001 for loneliness; F(1, 14664) = 146.3, p < 0.001 for isolation). The decreased alcohol consumption in lonelier and more isolated people may be due to the fact that alcohol consumption often occurs at social activities. These results support the notion that social supports are associated with some healthy behaviors, such as greater physical activity and longer sleep duration, but also some unhealthy behaviors, such as more frequent alcohol consumption (Luo et al., 2012; Hawkley et al., 2009; Holt-Lunstad et al., 2010; House et al., 1988).

The greatest effect sizes were found for measures of health outcomes, happiness, and life satisfaction. Lonelier and more isolated people were more likely to experience poor overall and mental health (Fig. 1). While $25.8 \pm 0.7\%$ of the overall population had a longtime illness, $35.3 \pm$

4.0% of people with a loneliness score of 2 and $33.0 \pm 2.9\%$ of people with an isolation score of 2 had a longtime illness (F(1, 14664) = 339.6, p < 0.001 for loneliness; F(1, 14664) = 52.08, p < 0.0010.001 for isolation). Compared to the $1.9 \pm 0.2\%$ of the overall population with poor overall health, the loneliest people were almost four times more likely to have poor overall health at 7.9 $\pm 2.3\%$ and the most isolated people were over twice as likely at $4.8 \pm 1.3\%$ (F(1, 14664) = 137.9, p < 0.001 for loneliness; F(1, 14664) = 189.2, p < 0.001 for isolation). While both lonelier and more isolated people were more likely to have moderate or severe depression, the effect sizes were greater with loneliness (F(1, 14664) = 37.0, p < 0.001 for loneliness and moderate depression; F(1, 14664) = 20.58, p < 0.001 for isolation and moderate depression; F(1, 14664) =108.3, p < 0.001 for loneliness and severe depression; F(1, 14664) = 10.89, p < 0.001 for isolation and severe depression). In addition, in regards to happiness and life satisfaction variables, including financial, friendship, health, and relationship satisfaction, the loneliest people were between three to 21 times more unhappy or dissatisfied with their life situation than the least lonely people, while the most isolated people were between two to four times more unhappy or dissatisfied than the least isolated people (Table 1.1, Table 1.2). Happiness and life satisfaction variables were also most highly correlated with loneliness and isolation scores, with correlation values up to r = 0.59, p < 0.001 for loneliness and r = 0.28, p < 0.001 for isolation. The greater discrepancy in happiness and life satisfaction based on loneliness than isolation supports the idea that loneliness is a more proximal measure to subjective wellbeing. These results are also consistent with previous studies that associate loneliness and isolation with increases in adverse health effects and decreases in subjective wellbeing ().



Fig. 1. Loneliness and isolation scores by poor overall health, moderate or severe depression, and severe depression. Lonelier and more isolated people were more likely to experience poor overall and mental health. Compared to the $1.9 \pm 0.2\%$ of the overall population with poor overall health, the loneliest people were almost four times more likely to have poor overall health at $7.9 \pm 2.3\%$ and the most isolated people were over twice as likely at $4.8 \pm 1.3\%$ (*F*(1, 14664) = 137.9, *p* < 0.001 for loneliness; *F*(1, 14664) = 189.2, *p* < 0.001 for isolation). While both lonelier and more isolated people were more likely to have moderate or severe depression, the effect sizes were greater with loneliness (*F*(1, 14664) = 37.0, *p* < 0.001 for loneliness and moderate depression; *F*(1, 14664) = 20.58, *p* < 0.001 for isolation and moderate depression; *F*(1, 14664) = 10.89, *p* < 0.001 for isolation and severe depression).

No Significant Interactions between Loneliness/Isolation and Age-Related Gray Matter Changes

Although lonelier and more isolated people tended to be younger in age, lack of social connection may still be tied to changes in brain morphology and anatomy, as not everyone uniformly becomes less lonely with age. Given the lack of conclusive empirical work in this area, we did not have explicit hypotheses about which aspects of brain anatomy might track with loneliness. Thus we opted for a multi-dimensional approach, integrating data on cortical thickness, surface area, and curvature. FLICA, an unsupervised method of identifying statistically independent sources of variability across imaging modalities, produced 70 independent components. Of these components, 50 were found through post-hoc linear and quadratic regression to be correlated significantly with age. Table 2.1 includes the linear and quadratic fits of the nine age-related components with an \mathbb{R}^2 value greater than or equal to 0.01, meaning that age explained at least 1% of the variance of each of these components. The component with the strongest correlation with age had a correlation value of r = -0.46, p < 0.001 and 21% of its variance was explained by age ($\mathbb{R}^2 = 0.21$, p < 0.001). Figure 2 shows the four components with strongest correlations with age.

Independent component numbers	Correlation (<i>r</i>)	Quadratic fit (<i>R</i> ²)	p	Quadratic coefficient (<i>q)</i>
2	-0.46	0.21	0	2.10E-09
57	0.28	0.08	5.80E-268	3.70E-13
23	-0.14	0.02	6.10E-63	0.26
52	-0.13	0.02	1.70E-56	0.93
19	-0.11	0.01	6.90E-43	0.93
62	0.11	0.01	1.60E-39	0.01
9	-0.11	0.01	2.00E-38	0.00018
33	0.09	0.01	6.50E-28	0.28
47	0.08	0.01	9.00E-24	0.29

Table 2.1. Linear and quadratic fits of the nine age-related components with an R^2 value greater than or equal to 0.01, meaning that age explained at least 1% of the variance of each of these components. FLICA, an unsupervised method of identifying statistically independent sources of variability across imaging modalities, produced 70 independent components. Of these components, 50 were found through post-hoc linear and quadratic regression to be correlated significantly with age and nine had an R^2 value greater than or equal to 0.01.

Based on a similar study by Douaud et al. (2014), we expected to find an overall decrease in gray matter volume with age. Five of the nine practically significant components showed decreases in cortical thickness, curvature, and surface area with increased age. Four of the nine components demonstrated positive correlations of thickness, curvature, and area with age. These positive correlations could describe actual trends in brain structure (it is unclear from previous research how cortical curvature varies with age), and could also represent scanning artifacts. Since age explained 8% or less of the variance in these components, the positive correlations may also reflect increases in thickness, area, and curvature as a function of factors other than age. Douaud et al. (2014) also found a U-shaped component with age that represented regions that matured later in adolescence and declined faster in later life. The lack of this U-shaped component can be explained by the fact that Douaud et al.'s sample had an age range of 8 to 85 years, while this sample population had an age range of 46 to 80 years, which would not capture changes in gray matter related to childhood or young adult development.



Fig. 2. The four independent age-related components, identified by FLICA and post-hoc correlation analyses, that had the strongest correlations with age. FLICA, an unsupervised method of identifying statistically independent sources of variability across imaging modalities, produced 70 independent components. Of these components, 50 were found through post-hoc linear and quadratic regression to be correlated significantly with age. Nine of the age-related components had an R^2 value greater than or equal to 0.01, meaning that age explained at least 1% of the variance of each of these components. These four components had the strongest correlations with age at *r* = -0.46, *p* < 0.001 for Component 2; *r* = 0.28, *p* < 0.001 for Component 57; *r* = -0.14, *p* < 0.001 for Component 23; and *r* = -0.13, *p* < 0.001 for Component 52.

Given these age-related components, we wanted to see whether loneliness or isolation interacted with age to account for the variance in thickness, curvature, and area. We found that interactions of age with loneliness or isolation scores were not significant predictors of linear regressions of each component with age, loneliness, isolation, and the full set of anatomical and behavioral covariates (*Methods*). While one of the nine practically significant age-related components showed an interaction between loneliness and age (t = -2.22, p = 0.03), and one component showed an interaction between isolation and age (t = 2.67, p = 0.01), these interactions did not survive correction for multiple comparisons. Table 2.2 and Table 2.3 show the results of the linear regressions for the nine practically significant age-related components.

			Interaction of loneliness with age as predictor		
Independent component numbers	F(1,14642)	Adjusted <i>R</i> ²	t	p	
2	468.3	0.31	-0.28	0.78	
57	388	0.27	1.4	0.16	
23	129.4	0.11	-0.28	0.78	
52	28.01	0.03	1.11	0.27	
19	51.24	0.05	-2.22*	0.03	
62	21.66	0.02	-1.86	0.06	
9	19.25	0.02	0.47	0.64	
33	20.92	0.02	-0.66	0.51	
47	38.53	0.03	-0.04	0.97	

Table 2.2. Results of the linear regressions for the nine practically significant age-related components, with interaction of loneliness with age as a predictor. While Component 19 showed an interaction between loneliness and age (t = -2.22, p = 0.03), this interaction did not survive correction for multiple comparisons.

			Interaction of isolation with age as predictor		
Independent					
numbers	F(1,14642)	Adjusted R ²	t	p	
2	468.3	0.31	1.76	0.08	
57	388	0.27	1.17	0.24	
23	129.4	0.11	-0.36	0.72	
52	28.01	0.03	0.47	0.64	
19	51.24	0.05	-1.5	0.13	
62	21.66	0.02	-1.47	0.14	
9	19.25	0.02	1.34	0.18	
33	20.92	0.02	2.67**	0.01	
47	38.53	0.03	0.22	0.83	

Table 2.2. Results of the linear regressions for the nine practically significant age-related components, with interaction of isolation with age as a predictor. While Component 33 showed an interaction between loneliness and age (t = 2.67, p = 0.01), this interaction did not survive correction for multiple comparisons.

DISCUSSION

In this study, we sought to test whether interactions with loneliness and social isolation with age were significant predictors of age-related structural changes in the brain. Consistent with previous studies, loneliness and isolation are associated with worse health outcomes and less life satisfaction, and some worse health-related behaviors (Rico-Uribe et al., 2016; Cacioppo et al., 2006; Cacioppo & Hawkley, 2010; Booth, 2000; Cacioppo et al, 2010; Cacioppo et al., 2006; Vanderweele et al., 2011; Kong & You, 2013; Vanderweele et al., 2012). These results would support a social neuroscience model of loneliness/isolation slightly more strongly than a social control model. Analyses of age-related changes in gray matter produced fifty modes of variation across multiple modalities that correlated significantly with age, but interactions of loneliness/isolation with age did not explain the identified age-related structural changes. These results indicate that loneliness and isolation may not be associated with any more or less severe

age-related reductions in cortical thickness, curvature, and surface area.

Several methodological and statistical reasons may account for the lack of observed interaction between age and loneliness/isolation in age-related structural changes. The age range of the dataset between 46 and 80 years may have limited detection of age-related structural effects. Individual variability among participants may have also been too great to identify significant interactions of age with loneliness/isolation. In addition, the definitions of loneliness and isolation using self-reported questions, ordinal measures, and a compressed three-point scale may have also decreased the predictive value of these variables. While single-item questions about loneliness (such as "Do you often feel lonely?") serve as widely used and suitable measures for population-based studies, the directness of such questions could also produce anxiety around the stigma of being seen as lonely and lead to underreporting. Other assessment methods like the UCLA Loneliness Scale consist of multidimensional scales that measure subjective feelings of loneliness without directly referencing loneliness (Russell, Peplau, & Cutrona, 1980). The greater multidimensionality of such constructs could make up for some of the bias that comes with self-reported measures.

In addition, a previous paper has commented on the fact that very little population variance can be explained by pairwise associations between a single brain measure and a single behavioral variable in a dataset as large as the UK Biobank. By contrast, multivariate approaches are preferred because they can account for a greater amount of variance (Smith & Nichols, 2018). While we took a multimodal brain approach by using the FLICA method, we only looked at single behavioral measures (either loneliness or isolation). Investigating a larger constellation of behaviors that are tied to loneliness or isolation could increase the signal-to-noise ratio in our analysis. Further studies into loneliness with the UK Biobank dataset can consider incorporating the questions on happiness and life satisfaction that were shown to be significantly correlated with loneliness and isolation (*r* values range from 0.17 to 0.59, p < 0.001). The questions asking about satisfaction with one's friendships and relationships seem particularly relevant to a characterization of loneliness.

Other methodologies may also be more effective for revealing interactions of loneliness/isolation with age as predictors of structural changes. Since most studies examining the structural effects of loneliness and isolation have used animal models with different methods of characterizing structural changes in the brain, it is possible that human structural MRI is a less robust method for detecting gray matter changes related to loneliness and isolation (Diordievic et al., 2010; Diamond et al., 1975, 1976; Moser et al., 1997; Bhide & Bedi, 1984; Biørnebekk et al., 2007; Garrido et al., 2013, Rosenzweig et al., 1968; Bhide & Bedi, 1984; Diamond et al., 1972, 1975, 1976, 2001; Lipkind et al., 2002; Barnea et al., 2006). Other studies can look into conducting the same analyses with multiple imaging modalities, such as in the study by Groves et al., which combined two different types of structural MRI data: morphological data and diffusion data (2011). Such a study may detect common age-related variations across a wider range of imaging modalities and potentially reveal interactions with loneliness/isolation that would not otherwise be apparent. Other imaging modalities that have revealed age-related structural changes and could be examined in relation to loneliness/isolation include diffusion weighted imaging and white matter lesions, as well as positron emission tomography (PET) of beta amyloid plaques and tau pathology. For example, a previous study on the neural correlates of loneliness identified reductions in white matter density, which would not have been captured by this analysis (Nakagawa et al., 2015).

Alternatively, it is possible that there indeed is no clear relationship of

loneliness/isolation to age-related gray matter changes in the whole brain. Rather, according to the social brain hypothesis, loneliness/isolation should be related to gray matter decreases in brain areas related to social perception and cognition (Alexander, 1974; Niven & Laughlin, 2008; Kong et al., 2014; Kanai et al., 2012). Perhaps the relationship of loneliness/isolation to age-related changes would become more apparent through a focused investigation of these brain regions rather than from a whole-brain approach. Based on previous studies that found associations of loneliness with gray matter changes in the DLPFC and pSTS, future studies could begin by characterizing age-related changes in these regions and testing for interactions of loneliness/isolation with age as predictors of such changes (Kong et al., 2014; Kanai et al., 2012). In addition, since a previous study has associated loneliness with regional increases in gray matter volume, it is possible that structural changes related to loneliness may not be similar to patterns observed in age-related decline, which involves global and regional reductions in cortical volume (Kong et al., 2015).

In addition to targeting specific brain regions related to social functioning, future studies could consider investigating the relationship of loneliness/isolation to age-related changes in task-evoked brain activation. In relation to task-evoked function, we would expect to see associations of loneliness/isolation with greater age-related declines in task-relevant activation, particularly in areas related to social perception and cognition. Previous studies have compared activation of brain regions of lonely and non-lonely people during social and emotional tasks, but none have analyzed the relationships of these differing activations to age (Shintel et al., 2006; Yamada & Decety, 2009; Cacioppo et al., 2009; Powers et al., 2013).

Overall, a greater number of longitudinal studies is needed to better delineate a causal relationship of loneliness/isolation to age-related changes. The current study is limited by its cross-sectional design and thus cannot differentiate between whether age-related gray matter reductions affect experiences of loneliness/isolation or whether loneliness and isolation have effects on age-related structural changes. As the causal relationship of loneliness to cognitive decline is still debated and inconclusive, longitudinal studies investigating the structural changes behind this relationship could help address this issue (Gow et al., 2007; Tilvis et al., 2004; Wilson et al., 2007; Shankar et al., 2013; Helmer et al., 1958; Ho et al., 2001; Seeman et al., 2001; Fratiglioni et al., 2000; Helmer et al., 1958). Analyses of loneliness and isolation using data from the Adolescent Brain Cognitive Development Study, a longitudinal developmental brain study with a younger sample (nine to ten years of age at recruitment), could form a possible future direction. Since social relationships are at once most critical and most volatile during adolescence, studies using this dataset could capture more developmentally relevant age-related components and possibly show greater interactions between loneliness/isolation and age in brain development (Casey et al., 2018).

Despite the limitations of the study, the strengths of this study lie in its application of a data-driven, whole-brain approach to investigating the relationship of loneliness and isolation to age-related structural changes. The effect of subjective and objective states of social connectedness on gray matter reductions with age has not been extensively explored, and this study will form the foundation for further data-driven investigations into the structural effects of loneliness/isolation or factors contributing to cognitive decline. While this study did not find significant interactions between loneliness/isolation and age in explaining age-related structural changes, it affirms the importance of loneliness and isolation as critical factors associated with

multiple measures of health and wellbeing and informs future directions for studies investigating the relationship of loneliness/isolation to cognitive decline.

AUTHOR CONTRIBUTIONS

With the guidance of Dr. Avram Holmes, Dr. Steve Chang, and Ph.D. candidate Kevin Anderson, Kacey Fang conducted the literature search and identified the research questions for this paper. The research approach was designed in collaboration with Anderson. Anderson provided practical assistance, as well as reconstructed T1 data that underwent the UK Biobank structural pre-processing pipeline. Fang analyzed and interpreted the data with theoretical guidance from Anderson, Dr. Holmes, and Dr. Chang. Fang wrote and revised the paper, with feedback from all authors.

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