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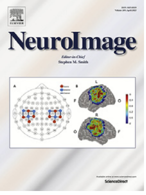

Home alone: A population neuroscience investigation of brain morphology substrates

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ABSTRACT

As a social species, ready exchange with peers is a pivotal asset - our "social capital". Yet, single-person households have come to pervade metropolitan cities worldwide, with unknown consequences in the long run. Here, we systematically explore the morphological manifestations associated with singular living in ~40,000 UK Biobank participants. The uncovered population-level signature spotlights the highly associative default mode network, in addition to findings such as in the amygdala central, cortical and corticoamygdaloid nuclei groups, as well as the hippocampal fimbria and dentate gyrus. Both positive effects, equating to greater gray matter volume associated with living alone, and negative effects, which can be interpreted as greater gray matter associations with not living alone, were found across the cortex and subcortical structures Sex-stratified analyses revealed male-specific neural substrates, including somatomotor, saliency and visual systems, while female-specific neural substrates centered on the dorsomedial prefrontal cortex. In line with our demographic profiling results, the discovered neural pattern of living alone is potentially linked to alcohol and tobacco consumption, anxiety, sleep quality as well as daily TV watching. The persistent trend for solitary living will require new answers from public-health decision makers.

Significance statement: Living alone has profound consequences for mental and physical health. Despite this, there has been a rapid increase in single-person households worldwide, with the long-term consequences yet unknown. In the largest study of its kind, we investigate how the objective lack of everyday social interaction, through living alone, manifests in the brain. Our population neuroscience approach uncovered a gray matter signature that converged on the 'default network', alongside targeted subcortical, sex and demographic profiling analyses. The human urge for social relationships is highlighted by the evolving COVID-19 pandemic. Better understanding of how social isolation relates to the brain will influence health and social policy decision-making of pandemic planning, as well as social interventions in light of global shifts in houseful structures.

1. Introduction

Some animals have evolved by adapting to the benefits of living in a social group. In the primate lineage, this mode of living and coordination has probably improved the identification of scarce resources, and may have refined cooperating and dealing with predators and prey as a cohesive group (Dunbar and Shultz 2017). As a result, various behavior, neuronal, hormonal, cellular and genetic mechanisms have likely co-evolved to support these advantageous social forms (Robinson et al., 2008; Adolphs 2009). For humans, the consequences of detachment from social group living can be expected to be pervasive due to the impoverished social environment. Indeed, social isolation is known to affect mental and physical well-being (Bzdok and Dunbar 2020). Such a state of deprived everyday stimulation is deemed so bad by society that it is used as an institutionalized form of punishment for individuals incarcerated in prisons (Cloud et al., 2015). Here we have investigated the relationship between brain structure and living alone in a large community cohort of participants recruited from across the United Kingdom. This recently emerged population resource opens a unique window to investigate the day-to-day social experience at the population scale in a naturalistic approach that goes beyond what traditional psychological and neuroscience experiments can do.

A wealth of neuroscience research now suggests that social abilities in humans and at least some non-human primates are realized by in-

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voking a cohesive set of brain regions referred to as the 'Social Brain'. Early support for the Social Brain idea came from evidence that, across species, the neocortex-to-brain volume ratio tracks the number of individuals per social group (Dunbar 1992; Dunbar and Shultz 2007a, 2007b). This insight has been argued to imply that brain circuits particularly tuned to serving social processes have expanded via selection pressures acting over evolutionary time. For example, numerous subregions within the medial-temporal limbic system and medial prefrontal cortex show high neural responses to social information processing (e.g. face, expression, gaze) and dynamic social interaction (Noonan et al., 2016). This includes information of faces (Kanwisher et al., 1997; Ku et al., 2011), facial expression and gaze direction (Morin et al., 2015), species-specific vocalizations (Joly et al., 2012) and biological motion (Perrett et al., 1992). These brain circuits linked to social interplay are therefore key candidates in which differences in solitary living would be expected to manifest.

As such, we confront the question whether these recently evolved brain circuits that may have enabled advanced coping with living in social groups may expose susceptibility when people undergo social scarcity in the environment. Clues to answer this question come from studies that have shown robust correlation of the size of individuals' social network with indexes of structural and functional brain organization. In humans, such studies have again typically implicated regions in the prefrontal cortex and the temporal lobe, particularly the amygdala (Bickart et al., 2011; Lewis et al., 2011; Von Der Heide, Vyas et al. 2014; Noonan et al., 2018). Further, there is evidence that this pattern of effects may not simply reflect the individual's predisposition towards seeking or avoiding social companionship. Instead, the brain may show plasticity effects in the face of recurring social experiences. In particular, Sallet and colleagues (Sallet et al., 2011) conducted controlled experiments with random allocation of monkeys to social housing for parallel laboratory studies (groups of 1–7 monkeys). This rare experimental feat demonstrated that the mid superior temporal sulcus (mSTS) and the medial prefrontal cortex both showed plasticity adaptations to daily living in a social group that has an experimentally imposed size. Later anatomical work has provided indicators that the temporal parietal junction (TPJ) is a strong candidate to be the human homologue of macaque mSTS (Mars et al., 2013), a region identified in humans as engaged in instantiating mental models of other people's thoughts (Frith and Frith 2006). These brain regions are also spatially contiguous with the default mode network (DNM) (Mars et al., 2012).

Collectively, these earlier studies bring to the surface how not only richness but also paucity of the social environment reverberates with specific brain systems. At its extreme, small-scale studies, in the context of arctic exploration or astronaut training and experience, have shown that enduring periods of social isolation is associated with increased stress hormone responses (Jacubowski et al., 2015; Weber et al., 2019). In the brain, these experiences of social isolation correlated with broad reductions in global cortical activity (Jacubowski et al., 2015; Weber et al., 2019) and specific reductions of the gray matter volume in prefrontal and hippocampal regions (Stahn et al., 2019). More generally, paucity of opportunity for social interaction in the real world has profound consequences for mental and physical health (Holt-Lunstad et al., 2010, 2017; Bzdok and Dunbar 2020). For example, social isolation is a major risk factor for age-related cognitive decline and Alzheimer's dementia (Heinrich and Gullone 2006).

Even the mere subjective perception of social disconnection from others, loneliness, takes a toll on mental health and cognition in all ages (reviewed by Cacioppo and Hawkley (2009)). The perception of social disconnection is also associated with reduced overall life expectancy, and increases vulnerability to Alzheimer's disease related dementias. Indeed, we recently identified brain signatures of loneliness in gray matter morphology, intrinsic functional coupling, and fiber tract microstructure and found that they converged on the DMN (Spreng et al., 2020). This study also identified brain signatures to be more pronounced in males than females. On its flipside, objective measures of social isolation have been linked to the limbic and salience networks (Schurz et al. 2021). Again, there are sex-specific effects in the amygdala of various measures of social connection including not only household size, but also subject loneliness as well as objective access to social support (Kiesow et al., 2020). Note, diverging from typical categorizations of objective and subjective connection in the literature (Holt-Lunstad et al., 2017), we refer to the frequency of access to social support in the present paper as an objective measure. This reflects the quantitative nature of this variable and not the subjective nature of how this variable is measured. This array of robust brain-behavior associations speak to the relevance of social isolation has on the individual and the potential underlying neural substrates. As one possible interpretation, quantifiable sex-related divergences in social experience may be reflected in distinct neural profiles associated with living alone. However, it is worth noting that a human being not sharing his or her household with others does by itself not equate with social isolation. Such an individual can draw on a tightly knit network of family, close friends and acquaintances, with frequent high-quality interactions. For example, such a person may spend a large fraction of their free time with social encounters in the local community, such as church, coffee places, bars, and sport clubs. Conversely, solitary living is just a demographic fact that does not inform about the feelings of the individual living in that single-person household. Indeed, loneliness is widely recognized to be a subjective perception or the felt experience of unmet social needs - this subjective feeling is not always a reflection of the actual richness of social capital of an individual; but reflects that person's mental model of it. For these reasons, solitary living is a phenotype that is not identical with one's objective frequency of regular social encounters or subjective feelings of loneliness.

Finally, there are now swelling numbers of single-person households in numerous metropolitan cities across the globe. Hence, solitary living is becoming an increasing burden on modern societies (Raymo 2015; Byron 2019, Tang et al., 2019, Statistics 2019). These compounding developments now warrant deeper understanding into the primary biology underlying lack of regular social interaction in the home environment. Decisive steps towards filling this knowledge gap may bring crucial insights into the associated mental and physical health consequences. In the present population neuroscience study, we take a naturalistic approach by utilizing the large UK Biobank population imaging cohort (n=~40,000 aged 40–69 years, mean age 54.9) to examine the gray matter correlates of living alone relative to living with other persons at home. We then explored putative sex-specific differences in the day-to-day experience of living alone, subsequently contextualized the results by their relation to perceived loneliness and regular social support, and conduct a careful demographic profiling analysis across key behavioral traits.

2. Materials and methods

2.1. Population data source

The UK Biobank is a prospective epidemiology resource that offers extensive behavioral and demographic assessments, medical and cognitive measures, as well as biological samples in a cohort of ~500,000 participants recruited from across Great Britain (https://www.ukbiobank.ac.uk/). This openly accessible population dataset aims to provide multimodal brain-imaging for ~100,000 individuals, planned for completion in 2022. The present study was based on the recent data release from February 2020 that augmented brain scanning information to ~40,000 participants. For demographic profiles of the UK Biobank sample and their relation to social-isolation-related measures please see elsewhere (Spreng et al., 2020; Schurz et al., 2021). The present analyses were conducted under UK Biobank application number 25,163. All participants provided informed consent. Further information on the consent procedure can be found elsewhere (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=200).

In an attempt to improve comparability and reproducibility, our study built on the uniform data preprocessing pipelines designed and carried out by FMRIB, Oxford University, UK (Alfaro-Almagro et al., 2018). Our study involved data from the ~40,000 participant release with brain-imaging measures of gray matter morphology (T1-weighted MRI [sMRI]) from 48% men and 52% women, aged 40–69 years when recruited (mean age 55, standard deviation [SD] 7.5 years). Our study focused on single-person household status as a measure of richness of the social environment (Hawkley et al., 2003; Luhmann and Hawkley 2016; Bzdok and Dunbar 2020). This self-reported item was based on the following question: "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, partners in the armed forces or professions such as pilots)" (https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=709). Our analyses distinguished between people living by themselves (encoded as ‘1′) or living with other people (encoded as ‘0′) at home.

Binary target outcomes are found in widely used assessments of social embeddedness (Hawkley et al., 2005; Cyranowski et al., 2013). As one example, beyond the biobank database that supports the use of binary measures, the Social Relationships scales of the NIH Toolbox (Cyranowski et al., 2013) feature the dimension of emotional social support. This dimension holds items such as "I have someone I trust to talk with about my problems", or "I can get helpful advice from others when dealing with a problem". A variety of studies showed such single-item measures of social traits to be reliable and valid (Mashek et al., 2007; Dollinger and Malmquist 2009). Our own previous research has used yes-no items to study individuals who live alone.

2.2. *Multimodal brain-imaging and preprocessing procedures*

Magnetic resonance imaging (MRI) scanners were matched at several dedicated imaging sites with the same acquisition protocols and standard Siemens 32-channel radiofrequency receiver head coils (3T Siemens Skyra). To protect the anonymity of the study participants, brain-imaging data were defaced and any sensitive meta-information was removed. Automated processing and quality control pipelines were deployed (Miller et al., 2016; Alfaro-Almagro et al., 2018). To improve homogeneity of the imaging data, noise was removed by means of 190 sensitivity features. This approach allowed for the reliable identification and exclusion of problematic brain scans, such as due to excessive head motion (Alfaro-Almagro et al., 2018). The comprehensive set of quality control features covered a variety of aspects, including signal-to-noise ratio, global brain asymmetry, discrepancy to MNI reference brain, and white matter hyperintensity volume.

Structural MRI: The sMRI data were acquired as high-resolution T1-weighted images of brain anatomy using a 3D MPRAGE sequence at 1 mm isotropic resolution. Preprocessing included gradient distortion correction (GDC), field of view reduction using the Brain Extraction Tool and FLIRT (Jenkinson and Smith 2001; Jenkinson et al., 2002), as well as non-linear registration to MNI152 standard space at 1 mm resolution using FNIRT (Andersson et al., 2007). To avoid unnecessary interpolation, all image transformations were estimated, combined and applied by a single interpolation step. Tissue-type segmentation into cerebrospinal fluid (CSF), gray matter (GM) and white matter (WM) was applied using FAST (FMRIB's Automated Segmentation Tool (Zhang et al., 2001)) to generate full bias-field-corrected images. SIENAX (Smith et al., 2002), in turn, was used to derive volumetric measures normalized for head sizes.

2.3. *Analysis of associations between living alone and gray matter variation*

Neurobiologically interpretable measures of gray matter volume were extracted in all participants by summarizing whole-brain sMRI maps in Montreal Neurological Institute (MNI) reference space. This feature generation step was guided by the topographical brain region definitions of the widely used Schaefer-Yeo atlas comprising 100 parcels (Schaefer et al., 2018), without additional modal Gaussian smoothing. The derived quantities of local gray matter morphology provided 100 average volume measures for each participant. The participant-level brain region volumes provided the input variables for our Bayesian hierarchical modeling approach (cf. below). As a data-cleaning step, interindividual variation in brain region volumes that could be explained by variables of no interest were regressed out: age, age^2, sex, sex*age, sex*age^2, body mass index, head size, head motion during task-related brain scans, head motion during task-unrelated brain scans, head position and receiver coil in the scanner (x, y, and z), position of scanner table, as well as the acquisition site of the MRI data.

To examine population variation of our atlas regions in the context of household status, we purpose-designed a Bayesian hierarchical model, a natural choice of method building on our previous research (Bzdok et al., 2017; Bzdok and Dunbar 2020; Kiesow et al., 2020, 2021; Schurz et al. 2021). In contrast, classical linear regression combined with statistical significance testing would simply have provided p-values against the null hypothesis of no difference between participants living in a single-person household or not in each brain region. Instead of limiting our results and conclusions to strict categorical statements, each region being either relevant for differences in household size, our analytical strategy aimed at full probability distributions that expose how brain region volumes converge or diverge in their relation to household size as evidenced in the UK Biobank population. In a mathematically rigorous way, our approach estimated coherent, continuous estimates of uncertainty for each model parameter at play for its relevance in household situations. Our study thus addressed the question "How certain are we that a regional brain volume is divergent between individuals living alone or not?". Our analysis did not ask "Is there a strict categorical difference in region volume between individuals living alone or not?".

The elected Bayesian hierarchical framework also enabled simultaneous modeling of multiple organizational principles in one coherent estimation: (i) *segregation* into separate brain regions and ii) *integration* of groups of brain regions in the form of spatially distributed brain networks. Two regions of the same atlas network are more likely to exhibit similar volume effects than two regions belonging to two separate brain networks. Each of the region definitions was pre-assigned to one of the seven large-scale network definitions in the Schaefer-Yeo atlas https://paperpile.com/c/5UCjVS/UUZU7 (Schaefer et al., 2018), providing a native multilevel structure to be modelled explicitly. Please note that the used Schaefer-Yeo atlas does not include subcortical region definition because the associated subcortical MRI signals differ in systematic ways from those in the cortical space. Concretely, that is, if we did find differences between cortical and subcortical regions, we would be at a miss to discern whether it is due to biology or due to technical differences rooted in MRI physics.

Setting up a hierarchical generative process enabled our analytical approach to borrow statistical strength between model parameters at the higher network level and those at the lower level of constituent brain regions. By virtue of exploiting such partial pooling of information, the brain region parameters were modelled themselves by the hyper-parameters of the hierarchical regression as a function of the network hierarchy to explain interindividual differences in solitary living. Assigning informative priors centered around zero provided an additional form of regularization by shrinking coefficients to zero in the absence of evidence to the contrary. We could thus provide fully probabilistic answers to questions about the morphological relevance of individual brain locations and distributed cortical networks by a joint varying-effects estimation that profited from several biologically meaningful sources of population variation.

Our model specification placed emphasis on careful inference of unique posterior distributions of parameters at the brain network level to discriminate individuals living with others (encoded as outcome 0) or those living alone (outcome 1) at their household:

$$y \sim Bernoulli(p)$$

$$logit(p) = x_1 * \beta_{region_1} + \ldots + x_p * \beta_{region_p} +$$

$$\alpha_{men[sex]} + \alpha_{women[sex]} + \alpha_{men\_age[sex]} * age_{men} + \alpha_{women\_age[sex]} * age_{women}$$

$$\beta_{region_{network\_Visual}} \sim MVNormal\left(\begin{bmatrix} 0 \\ \vdots \\ 0 \end{bmatrix}, \Sigma_{Visual}\right); \Sigma_{Visual} = \begin{bmatrix} \sigma_o^2 & \cdots & \\ \vdots & \ddots & \vdots \\ & \cdots & \sigma_o^2 \end{bmatrix}$$

$$\beta_{region_{netwok\_SomMot}} \sim MVNormal\left(\begin{bmatrix} 0 \\ \vdots \\ 0 \end{bmatrix}, \Sigma_{SomMot}\right); \Sigma_{SomMot} = \begin{bmatrix} \sigma_p^2 & \cdots & \\ \vdots & \ddots & \vdots \\ & \cdots & \sigma_p^2 \end{bmatrix}$$

$$\beta_{region_{network\_Limbic}} \sim MVNormal\left(\begin{bmatrix} 0 \\ \vdots \\ 0 \end{bmatrix}, \Sigma_{Limbic}\right); \Sigma_{Limbic} = \begin{bmatrix} \sigma_q^2 & \cdots & \\ \vdots & \ddots & \vdots \\ & \cdots & \sigma_q^2 \end{bmatrix}$$

$$\beta_{region_{network\_Salience}} \sim MVNormal\left(\begin{bmatrix} 0 \\ \vdots \\ 0 \end{bmatrix}, \Sigma_{Salience}\right); \Sigma_{Salience} = \begin{bmatrix} \sigma_r^2 & \cdots & \\ \vdots & \ddots & \vdots \\ & \cdots & \sigma_r^2 \end{bmatrix}$$

$$\beta_{region_{network\_Control}} \sim MVNormal\left(\begin{bmatrix} 0 \\ \vdots \\ 0 \end{bmatrix}, \Sigma_{Control}\right); \Sigma_{Control} = \begin{bmatrix} \sigma_s^2 & \cdots & \\ \vdots & \ddots & \vdots \\ & \cdots & \sigma_s^2 \end{bmatrix}$$

$$\beta_{region_{network\_DorsalAttn}} \sim MVNormal\left(\begin{bmatrix} 0 \\ \vdots \\ 0 \end{bmatrix}, \Sigma_{DorsalAttn}\right); \Sigma_{DorsalAttn} = \begin{bmatrix} \sigma_t^2 & \cdots & \\ \vdots & \ddots & \vdots \\ & \cdots & \sigma_t^2 \end{bmatrix}$$

$$\beta_{region_{network\_Default}} \sim MVNormal\left(\begin{bmatrix} 0 \\ \vdots \\ 0 \end{bmatrix}, \Sigma_{Default}\right); \Sigma_{Default} = \begin{bmatrix} \sigma_u^2 & \cdots & \\ \vdots & \ddots & \vdots \\ & \cdots & \sigma_u^2 \end{bmatrix}$$

$$\alpha_{men} \sim \mathcal{N}(0,\ 1)$$

$$\alpha_{women} \sim \mathcal{N}(0,\ 1)$$

$$\alpha_{men\_age} \sim \mathcal{N}(0,\ 1)$$

$$\alpha_{women\_age} \sim \mathcal{N}(0,\ 1)$$

where *sigma* parameters estimated the overall variance across the *p* brain regions that belong to a given atlas network, independent of whether the volume effects of the respective constituent brain regions had positive or negative direction. As such, the network variance parameters *sigma* directly quantified the magnitude of intra-network coefficients, and thus the overall relevance of a given network in explaining lack of social interaction at home based on the dependent region morphology measures. All regions belonging to the same brain network shared the same variance parameter in the diagonal of the covariance matrix, while off-diagonal covariance relationships were zero. In other words, this notation means that each of the canonical network has a higher-level variance parameter from which its constituent region Gaussian distributions' variance components sample; without imposing additional constraining assumptions on relationships between the lower-level region Gaussian distributions that are bundled by that overall network hyperparameter.

Please note that in this case age-related variation is removed in how the outcome (solitary living) depends on the input variables. Additionally, we have used a preliminary deconfounding analysis to remove variation in the brain region measures - not related to the outcome of social isolation status - to remove brain variation related to age (cf. above). As such, these two separate steps of the analysis account for different aspects of age-related variation: on behavior and on the brain

Full probabilistic posterior distributions for all model parameters were inferred for the hierarchical modeling solution. By espousing a Bayesian attitude, we could thus simultaneously appreciate gray matter variation in segregated brain regions as well as in integrative brain networks in a population cohort. The approximation of the posterior distributions was carried out by the NUTS sampler (Gelman et al., 2014), a type of Markov chain Monte Carlo (MCMC), using the PyMC3 software (Salvatier et al., 2016). After tuning the sampler for 4000 steps, we drew 1000 samples from the joint posterior distribution over the full set of parameters in the model for analysis. Proper convergence was assessed by ensuring Rhat measures (Gelman et al., 2014) stayed below 1.02. In terms of neuroscientific interpretation, a positive volume effect indicated higher gray matter volumes related to living alone, while a negative volume effect indicated higher gray matter volume related to living with others, within the context of the full Bayesian model (Kiesow et al., 2020; Bonkhoff et al., 2021).

The Bayesian analysis framework that we have applied here is an *estimation* regime, not a *statistical testing* regime. Bayesian analyses do not attempt to dichotomize effects into 'significant' and 'not significant', but consider continuous posterior distributions of effects instead (Gelman, 2014; Kruschke, 2014). Instead of considering Type 1 or Type 2 error rates, Bayesian analysis aims to lay out the full probabilistic landscape of the degree of effect. As Bayesian analysis does not involve testing of any null hypothesis, there is hence also no tradition of correcting for multiple null hypothesis tests. In short, the notion of 'multiple comparisons' originates from theoretical null hypothesis significance testing (NHST), which was not used in any part of our conducted quantitative analyses.

For illustration purposes, all brain images in MNI space were mapped onto a pial surface (Glasser et al., 2016) using the Connectome Workbench command-line tools.

2.3.1. Analysis extensions: subcortical structures

The Schaefer-Yeo atlas provides extraordinary delineation of anatomical parcellations in cortex. However, due to differences in signal quality of subcortical structures these deeper brain regions are not included in this atlas. Given that the medial-temporal limbic system is particularly important for social behavior (Perrett et al., 1992, Amodio and Frith 2006, Stanley and Adolphs 2013, Noonan et al., 2017), and within this the amygdala and hippocampus are particularly well studied, we therefore extended our investigations to examine the associations between subcortical gray matter and living alone in these two subcorticyal regions. Specifically, we applied the exact same analysis pipeline described above to the two independent subcortical parcellation atlases of the amygdala and hippocampus.

For the amygdala, 18 volume measures were extracted using the automatic Freesurfer sub-segmentation protocol (Saygin et al., 2017). Similarly, for the hippocampus, 38 volume measures were extracted using the automatic Freesurfer sub-segmentation tool (Iglesias et al., 2015). The allocortical volumetric segmentation draws on a probabilistic amygdala or hippocampus atlas with ultra-high resolution at ~0.1 mm isotropic. This tool from the Freesurfer 7.0 suite gives special attention to surrounding anatomical structures to refine the amygdala/hippocampus subregion segmentation in each participant. These methods offer biologically and microanatomically valid parcellations and allowed us to uniquely examine patterns of gray matter associations at nuclei resolution.

2.3.2. Post-hoc characterization of the brain substrates of solitary living regarding social isolation traits

Next, in our full UK Biobank participant sample, we sought to deepen insight into the set of relevant regions that was most robustly linked to residing in a single-person home. For this purpose, we quantified the strength of association of the volume measures from the six top brain regions identified in the previous analysis (IFG, mSTS, aSTS, MTG/ITG, dmPFC and pSTS; based on the 10/90% HPI), in individuals from single person households, with external measures of objective and subjective social isolation that were not invoked in any previous steps of the analysis workflow: the opportunity of daily social exchange with others to confide is a well-accepted indicator for regular social support (data field: 2110; "How often are you able to confide in someone close to you?") (Schurz et al. 2021), while the experience of loneliness is commonly viewed to capture especially the feeling or personal impression of being social disconnected from others (data field: 2020; Do you often feel lonely? (Spreng et al., 2020)). While both metrics are derived from subjective self-report questionnaires, here we distinguish between phenotypical objective experience and subject feelings that the questionnaires inform us of. While with both questions participants had an option not to say or that they did not know, for the loneliness question their two informative answer options formed a binary option of yes/no. The quantification of the social support frequency question, in turn, was captured as daily vs. less-than-daily. Here, we examined all four possible combinations of these two complementary traits of social isolation in our UK Biobank sample which resulted in four groups: 1. Lonely with poor social support, 2. Not lonely but poor social support, 3. Lonely with good social support, 4. Not lonely with good social support (for demographics and group sizes please refer to (Spreng et al., 2020; Schurz et al. 2021). Given the four-group distinction setting, linear discriminant analysis was a natural choice of method as it was able to consider the four groups at the same time. This classification machine learning algorithm (Bzdok 2017; Bzdok et al., 2017) afforded inferential statements about the effect sizes paired with the region-wise associations with each of the four disparate qualities of social isolation (i.e., each combination of subjective loneliness and objective frequency of access to social support). Please note that our encoding of the target variables for i) loneliness and ii) social support follows directly previous UK Biobank work on these phenotypes (Spreng et al., 2020; Schurz et al. 2021; Zajner et al., 2021; Zajner et al., 2022).

2.4. Demographic profiling analysis of the brain substrates of solitary living

We finally performed a profiling analysis of the brain regions that were most strongly associated with residing in a single-person home (IFG, mSTS, aSTS, MTG/ITG, dmPFC and pSTS; based on the 10/90% HPI). In all subjects (single and multi person households). We carried out a rigorous test for multivariate associations between our top region set and a diverse set of lifestyle indicators that exemplify the domains of a) basic demographics, b) personality features, c) substance-use behaviors, and d) social network properties (for details see https://www.ukbiobank.ac.uk/data-showcase/). Specifically, from the rich UK Biobank population dataset, we selected a wide range of behavioral variables that are focused on social isolation features based on literature and range across physical, mental, and cognitive dimensions. Our collection covered aspects of physical health, daily habits and lifestyle, substance-use, cognitive abilities, mental health and wellbeing, and complementary measures of social embeddedness. In essence this analysis determines which demographic or lifestyle variables best explain variance across regional GM of the brain correlates of solitary living across individuals from single-person and multi-person households.

Each of the behavioral variables and brain measures (i.e. brain region volume) was z-scored across participants to conform to a mean of zero and a standard deviation of one. Analogous to our previous work (Schurz et al. 2021; Zajner et al., 2021; Zajner et al., 2022), using the two separate variable sets, brain measurements and behavior measurements, we then carried out a bootstrap difference analysis of the collection of target traits in single-person versus multi-person households (Efron and Tibshirani 1994). In 1000 bootstrap iterations, resampling the original number of participants with replacement in each bootstrap sample, we randomly pulled equally sized participant samples to perform a canonical correlation analysis (CCA), in parallel, according to household status (Miller et al., 2016; Wang et al., 2018). In each resampling iteration, this approach estimated the doubly multivariate correspondence between the brain and behavior indicators in each of the two groups (one model fit in 32,504 non-solitary participants, and one model fit in 5788 solitary participants). Based on several thousand data points, each CCA model was fitted on ~50 phenotype features on the one hand (Supplementary Table S7) and 6 relevant brain region volumes on the other hand. The ensuing canonical vectors of the leading CCA mode indicated the most explanatory demographic associations in a given pull of participants. To directly estimate the certainty of the brain-behavior cross-associations in the face of resample-to-resample variation, these canonical vectors of behavioral rankings, from CCA applications to single-person vs. multi-person households, were subtracted elementwise, recording the difference between each entry of the two vectors, and ultimately aggregated across the 1000 bootstrap datasets to plot absolute deviation effects for each target phenotype.

Using the two separate variable sets, brain measurements and behavior measurements, we then carried out a bootstrap difference analysis of the collection of target traits in single-person versus multi-person households (Efron and Tibshirani 1994). In 1000 bootstrap iterations, we randomly pulled equally sized participant samples to perform a canonical correlation analysis (CCA), in parallel, according to household status (Miller et al., 2016; Wang et al., 2018). In each resampling iteration, this approach estimated the doubly multivariate correspondence between the brain and behavior indicators in each of the two groups. The ensuing canonical vectors of the leading CCA mode indicated the most explanatory demographic associations in a given pull of participants. To directly estimate the certainty of the brain-behavior cross-associations in the face of resample-to-resample variation, these canonical vectors of behavioral rankings, from CCA applications to single-person vs. multi-person households, were subtracted elementwise, recorded, and ultimately aggregated across the 1000 bootstrap datasets. The advantage of this approach is that it brings project-specific covariates and their relation to the core brain effects out into the open instead of sweeping potential relationships under the rug as their removal via confounds in a regression would effectively do.

We thus propagated the noise due to participant sampling variation into the computed uncertainty estimates of group differences in the UK Biobank population cohort. Statistically relevant behavioral dimensions were determined by whether the (two-sided) bootstrap confidence interval included zero or not in the 5/95% bootstrap interval. In a fully multivariate setting, our non-parametric modeling tactic directly quantified the statistical uncertainty of how a UK Biobank trait is differentially linked to brain-behavior correspondence as a function of household size.

2.5. Data and code availability

All researchers in good standing can ask for access to the UK Biobank at https://www.ukbiobank.ac.uk/. The Python code is available for reproducibility and reuse at https://github.com/dblabs-mcgill-mila/.

3. Results

3.1. Network-level results whole population

By deploying an integrative Bayesian hierarchical modeling framework to the UK Biobank data, we associated the objective experience of living alone with volume variation across the 100 brain regions that belong to the 7 spatially distributed brain networks that populate the human cerebral cortex, according to the Schaefer-Yeo reference atlas (Schaefer et al., 2018). The key feature of the elected Bayesian analysis paradigm is that the fitted posterior parameter distributions yields a point estimate indicating the size of an effect (the mean of the distribution) as well as an uncertainty quantification that indicates confidence in an effect (width of the distribution). Critically, the Bayesian approach thus allowed us to carefully estimate the continuous degree of divergence between effects as opposed to only categorizing network effects as relevant or not (Bzdok and Yeo 2017; Bzdok et al., 2020). At the network level, volume variation was most prominently associated with living alone in the default network, with the largest share of explained variance (posterior sigma=0.065; 10–90% highest posterior density [HPD]=0.044/0.083; Fig. 1). The highest explanatory relevance of the collection of default network regions in living alone was followed by overall effects of the limbic network (sigma=0.054, HPD=0.001/0.081), somatomotor network (sigma=0.051, HPD=0.019/0.076), visual network (sigma=0.050, HPD=0.021/0.074), as well as salience (sigma=0.037, HPD=0.002/0.055), dorsal attention (sigma=0.025, HPD=0.001/0.038) and fronto-parietal (sigma=0.021, HPD=0.001/0.031) networks. As such, our quantitative findings indicate the deepest layers of the neural processing hierarchy – the DMN regions – to play the strongest role in the brain manifestations of solitary living.

Next, we investigated whether the relationship between living alone and gray matter volume at the network-level differed by biological sex. We found no salient differences in the degree of gray matter (GM) volume variation associated with living alone between the two sexes. Indeed, within the two groups the pattern of network effects were mostly similar to those of the whole population. For example, the top three networks that collectively explained most variance in women - limbic (posterior sigma=0.072; 10–90% highest posterior density [HPD]=0.002/0.106; Fig. S1), somatomotor (sigma=0.058; HPD=0.015/0.093) and default (sigma=0.057; HPD=0.032/0.08) - were those that also collectively explained the most GM variation at the whole population, albeit in a different ranked order. Similarly, men showed significant GM variation within the DMN (sigma=0.066; HPD=0.037/0.092) and limbic network (sigma=0.063; HPD=0.002/0.096), but contrary to the whole population, the salience network (Ventral Attention; sigma=0.061; HPD=0.003/0.087) explained the third most variance.

Region-level whole population:

We next inspected the inferred associations between living alone and regional brain structure. Using the previously described Bayesian hierarchical approach we focused on variation in GM volume in the 100 individual atlas regions (Fig. 1, Supplementary Table S1). Positive volume effects associated with living alone emerged in the right middle temporal gyrus/ inferior temporal gyrus (posterior mean=0.089, 10–90% HPD=0.033/0.147), right anterior superior temporal sulcus (mean=0.086, HPD=0.031/0.145), right middle superior temporal sulcus (mean=0.080, HPD=0.019/0.136) and right inferior frontal gyrus (mean=0.062, HPD=0.015/0.113). By contrast, negative volume effects became apparent in the left posterior superior temporal sulcus (mean=−0.076, HPD=−0.125/−0.021) and right dorsomedial prefrontal cortex (mean=−0.097, HPD=−0.144/−0.047). Lateral temporal subregions thus tended to explain the greatest amount of inter-individual variance in living alone.

3.2. Region-level sex differences

When we turned to examine regional sex differences in the relationship between living alone and GM volume, we reported relevant effects in a range of association cortical regions broadly linked to action and perception. Please note that many sex effects can be subtle and more brittle than other brain-behavior associations. As such report sex-differences sub-analyses at a more lenient threshold (25–75% HPI) given that this parameter contrast constitute a difference in a difference, rather than in a difference (as the main effects of solitary living above). Our Bayesian hierarchical inference revealed a relatively right lateralized set of positive GM volume effects (Fig. 2, Supplementary Table S2), indexing greater GM volume effects in men than women. These regions included the insula (mean=0.076, 25–75% HPD=0.013/0.103), cuneus (mean=0.075, HPD=0.016/0.099), precuneus/posterior cingulate cortex (mean=0.059, HPD=0.008/0.099), motor/dorsal supplementary motor cortex (mean=0.055, HPD=0.006/0.083) and posterior cingulate sulcus (mean=0.052, HPD=0.004/0.079). Only motor/dorsal supplementary motor cortex showed positive volume effects in the left hemisphere (mean=0.05, HPD=0.003/0.075). By contrast negative volume effects, indexing greater GM volume associations with living alone in women than men, were lateralized to the left hemisphere. The only significant effects evident were in the PFC; frontal polar cortex (mean=−0.093, HPD=−0.127/−0.05) and dorsal premotor cortex (mean=−0.07, HPD=−0.109/−0.02). These two frontal regions, both belonging to the DMN.

3.3. Key regional effects are distinctly related to loneliness and social support

The results from our main analysis suggested that one set of brain regions were larger in individuals who live alone (positive volume effects in IFG, mSTS, aSTS and MTG/ITG), while another set of brain regions were larger in individuals who live together with others in the home (negative volume effects in dmPFC and pSTS). One potentially co-occurring psychological state for those living alone is the subjective feeling of loneliness, while another is the objective (as phenotyped by the UK Biobank questionnaires) loss of easy access to good social support. These two factors are likely to co-occur in some participants who were living alone (see Fig. 4 and description below). Focusing explicitly on individuals in single person households, the aim of this analysis was to tease apart these two unique contributions in order to further annotate our GM effects associated with living alone. We divided individuals in single person households into four discrete groups; 1. Lonely with poor social support, 2. Not lonely but poor social support, 3. Lonely with good social support, 4. Not lonely with good social support.

One simple hypothesis is that the positive GM effects we observed in individuals living alone would correspond to a similar pattern of gray

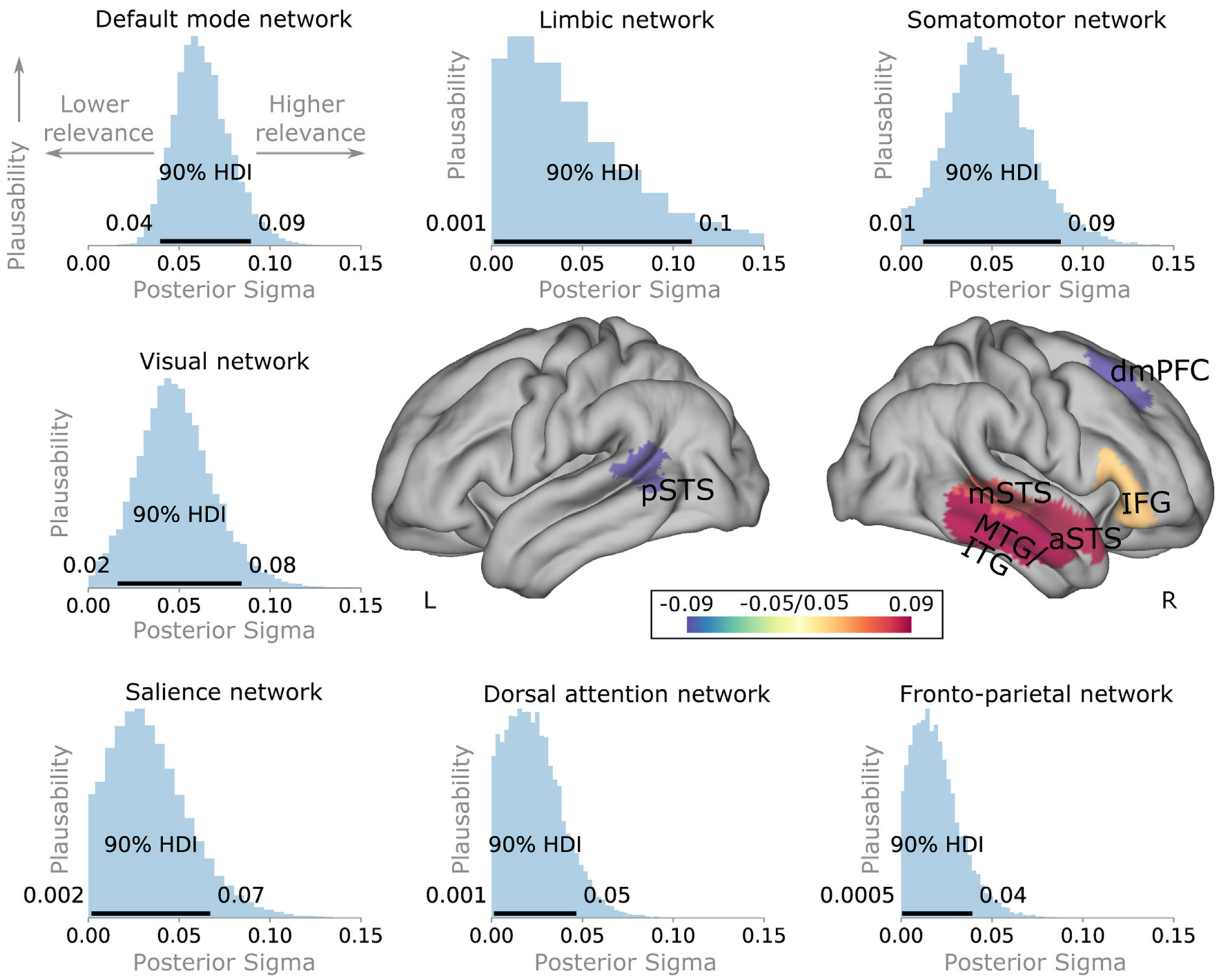

Fig. 1. Solitary living is associated with default mode structure at the network and region level. Our Bayesian hierarchical modeling framework estimated the gray matter effects jointly of single regions and distributed networks of brain regions in explaining living alone. The x axis denotes the magnitude of each variance parameter value, while the y axis denotes the relative plausibility of these possible parameter values (i.e., higher histogram bar means higher certainty), given the model posterior parameter distributions inferred from the brain data. Roughly analogous to ANOVA, the network definitions could be viewed as factors and the region definitions could be viewed as continuous factor levels. In this model specification, a network-level effect can be individually relevant, while a region-level effect could also be individually relevant. Our framework allowed to begin quantifying the degree to which volume variation in each canonical network of regions reliably relates to living alone, as well as each separate region from those brain networks. Histograms show the inferred marginal posterior parameter distributions of the overall explanatory variance (sigma parameter) for each major brain network (volume measures in standard units). Horizontal black bars indicate the highest posterior density interval (HPI) of the model's network variance parameters, ranging from 10 to 90% probability. Posterior distributions for the variance parameter (sigma) of each brain network are ordered from strongest (DMN; top left) to weakest (fronto-parietal; bottom right). The two brain renderings show the individual brain regions which were found to have the most robust relationship with living alone with their posterior parameter distributions (mean parameter). The brain regions that emerged as the most explanatory were in the lateral temporal lobe (pSTS [LH_Default_Par_1], mSTS [RH_Default_Temp_3], aSTS [RH_Default_Temp_2], MTG/ITG [RH_Default_Temp_1]), and frontal cortex (IFG [RH_Default_PFCv_2], and dmPFC [RH_Default_PFCdPFCm_3]). These were the only six regions where the 10/90% HPI excluded zero. a/m/pSTS = anterior/middle/posterior superior temporal sulcus, IFG = inferior frontal gyrus, dmPFC = dorsomedial prefrontal cortex, MTG = middle temporal gyrus, ITG = inferior temporal gyrus. *L*/*R*=left/right. Overall, the DMN and the limbic system showed the most convincing effects in explaining inter-individual variation in living alone, with both networks having the strongest explanatory effects, visible as the posterior parameter distribution's mean, and the DMN additionally having the highest effect certainty, indexed by the narrowness of the associated posterior parameter distribution.

matter effects in people who report loneliness or poor social support. Some brain region effects are in line with such a view, but others are not (Fig. 3). For example, the MTG/ITG showed positive associations with GM in individuals who live alone, and also showed larger GM effects when people reported being lonely (regardless of social support frequency, i.e. groups 1 and 3; Lonely with poor social support and Lonely with good social support). Similarly, the aSTS showed positive GM effects in individuals who live alone, but also positive effects in people who have poor access to social support (regardless of how lonely they report feeling, i.e. groups 1 and 2; Lonely with poor social support, Not lonely but poor social support). However, these brain-behavior associations painted a more complex picture in the other examined brain regions. First, while living alone was associated with larger GM effects in the IFG, this region was also larger in individuals who reported they are not lonely (regardless of the frequency of social support, i.e. groups 2 and 4; Not lonely but poor social support and Not lonely with good social support). By contrast, the mSTS showed positive effects in individuals who live alone, but also appeared larger in individuals who have access to a good social support network (regardless of how lonely they report feeling, i.e. groups 2 and 3; Not lonely but poor social support, Lonely with good social support). Nevertheless, it is important to bear in mind that this in-depth annotation departed from the originally obtained set of solitary living substrates in the brain and follows a dedicated statistical model.

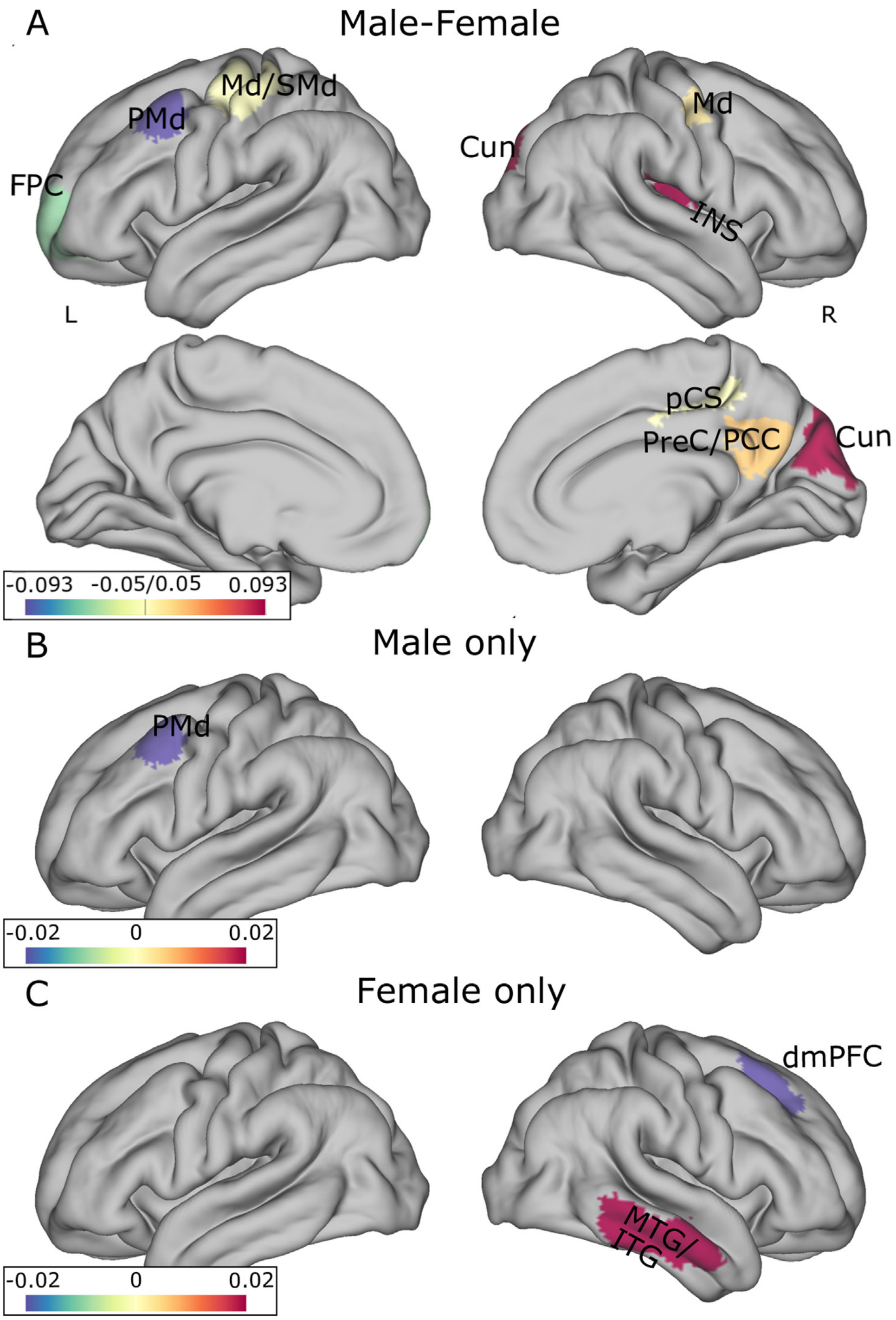

Fig. 2. Degrees of sex bias characterize the gray matter substrates associated with living alone. Results highlight the brain regions that show different relationships to the experience of living alone in men and women. A. Sex contrast effects (male minus female) in the left (left column) and right (right column) hemispheres on lateral (upper rendering) and medial (lower rendering) at the region level (subtracting women's posterior parameter distribution for a given effect from that inferred from males). For example, means of the posterior parameter distribution above zero can indicate a relatively male-biased effect with a positive volume effect associated with living alone (towards red color). Accordingly, in this case, for means below zero there would be a relatively female-biased volume effect for such brain-behavior association (towards blue color). B-C. Repetition of the Bayesian hierarchical analysis separately in (B) only males and (C) only females from our UK Biobank cohort: relevant gray matter effects (means of the marginal posterior parameter distributions). The neurostructural concomitants of living alone in men and women are notably different in a disparate assortment of brain regions. In men but not women, the dorsal premotor region emerges as robustly explanatory of living alone. Conversely the middle temporal gyrus/inferior temporal gyrus and dmPFC emerges in women but not men. FPC = frontal polar cortex, PMd = premotor dorsal, Md/SMd = dorsal motor/dorsal supplementary motor cortex, Cun = Cuneus, INS = insular cortex, pCS = posterior cingulate sulcus, PreC/PCC = PreCuneus/posterior cingulate cortex, MTG = middle temporal gyrus, ITG = inferior temporal gyrus, dmPFC = dorsomedial prefrontal cortex. L/*R* = left/right.

There were also elements that did not support our hypotheses seen in the two brain regions reported with negative GM effects in individuals living alone. The dmPFC was larger in individuals who live with others and it was also larger in people who reported not feeling lonely (regardless of access to social support, i.e. groups 2 and 4; Not lonely but poor social support and Not lonely with good social support). By contrast, the pSTS, despite being larger in individuals who live with others, was also larger in individuals who reported being lonely (regardless of access to social support, i.e. groups 1 and 3; Lonely with poor social support and Lonely with good social support).

Our results add weight to the idea that the three social dimensions i) solitary living, ii) loneliness and iii) social support contribute in largely distinct ways to the neurobiological profile. However, to confirm this at the level of the phenotype we conducted a more in-depth analysis of the overlap of these three features in our UK Biobank sample (Fig. 4). Importantly, among the participants living alone, only 8.8% have indicated to experience *both* feelings of loneliness and to have low frequency of interactions with close ones (poor social support). Participant residents in single-person households exclusively expressed feeling lonely in only 17.1% of the cases. Participants living alone exclusively expressed lacking social support in 40.6% of the cases. Again, this summary statistic goes to show that solitary living is not equivalent with the examined dimensions of subjective and objective social isolation.

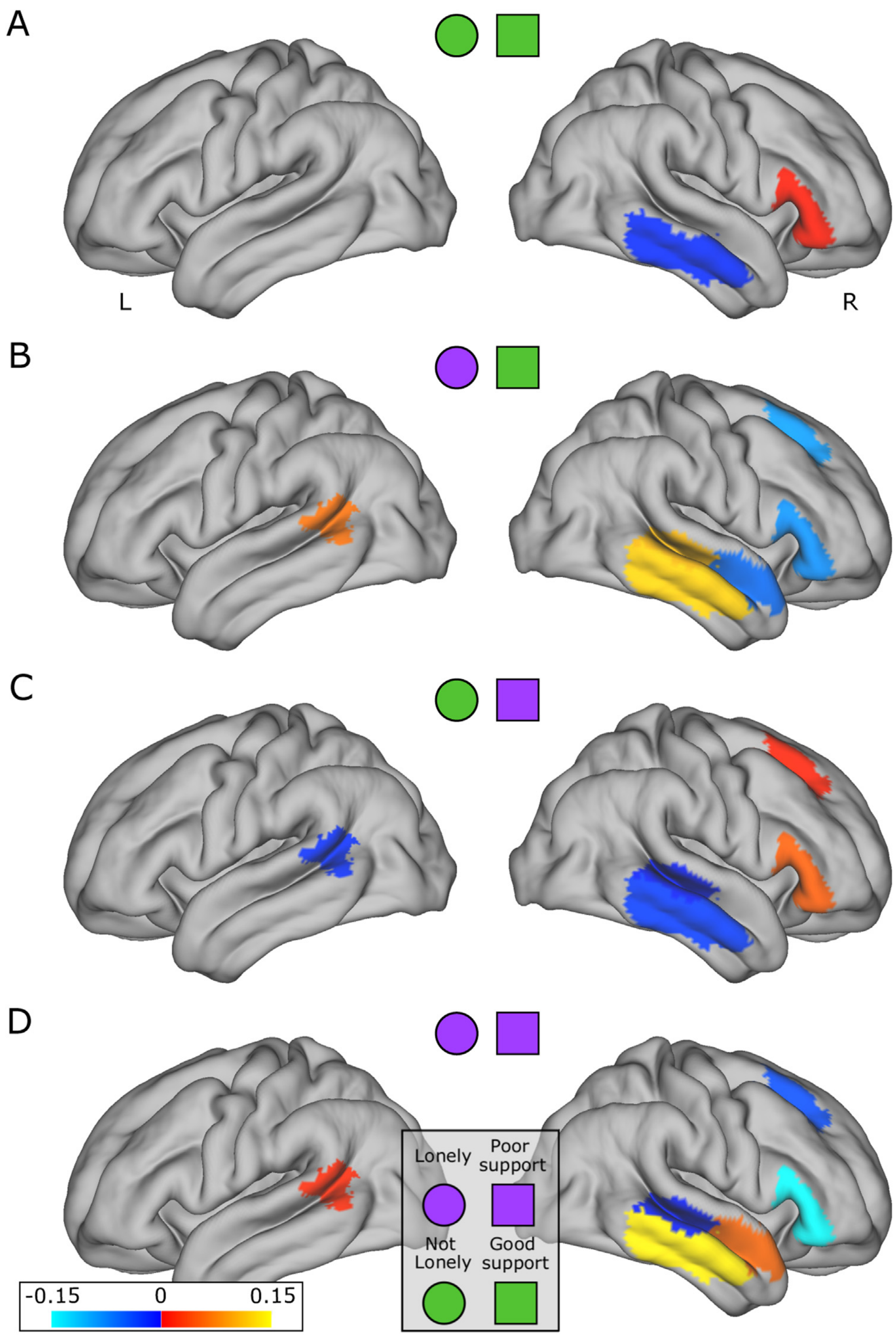

Fig. 3. Top brain substrates of solitary living show differential links with objective and subjective isolation. As a means to further functionally annotate the brain correlates that we identified as relevant for solitary living (cf. Fig. 1; Bayesian hierarchical model), we conducted a post-hoc analysis to examine the interindividual differences in volume variation in the identified relevant brain regions. This descriptive approach estimated how the participants of our UK Biobank sample can be distinguished based on their self-report measures of subjective and/or objective social isolation, that is, probing against all combinations of loneliness and frequency of social support. We thus aimed to map out which solitary-living correlates are preferentially linked to facets of social isolation that were external to the upstream analysis steps. Gray matter volume variation associated with individuals who do not feel lonely and indicate good social support (A). We show effects in individuals who report loneliness despite good social support (B), individuals who are not lonely despite poor social support (C), individuals who are lonely and have poor social support (D). Effects were thresholded at 0.01 before surface mapping to the Connectome brain. Overall, the brain correlates of solitary living show especially strong volumetric relationships with loneliness. In particular, the MTG/ITG, IFG, and dmPFC are highlighted in loneliness.

3.4. Amygdala nuclei gray matter relationships with living alone

We next turned to a fine-scale assessment of a closely associated subcortical structure with our identified whole-brain correlates of solitary living - the amygdala. To this end, we examined the relationship between amygdala nuclei GM and living alone using Bayesian inference (Fig. 5, Supplementary Table S3). Notably, there was a strong lateralisation in the amygdala volume effects. Further, all but one amygdala subregion with a relevant effect showed a negative association between GM volume and living alone (ie. larger GM in those living with others). Negative volume effects associated with living alone emerged in the right central (posterior mean=−0.048, 10–90% HPD=−0.078/−0.017), right cortical (mean=−0.057, HPD=−0.095/−0.019), right cortico-amygdaloid-transition (mean=0.08, HPD=0.019/0.136), and left accessory basal nucleus (mean=−0.109, HPD=−0.196/−0.018). The left accessory basal nucleus was the only robust effect we observed in the left amygdala. Conversely, we observed a positive effect in the right accessory basal nucleus (i.e. larger GM in those living alone, mean=0.224, HPD=0.136/0.319). In sum, the majority of the salient relationships between amygdala nuclei GM volume and solitary living were on the

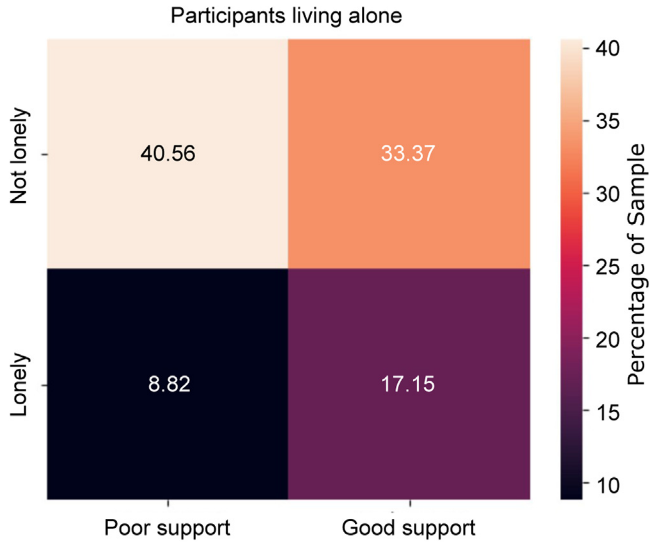

Fig. 4. Demographics show that solitary living, loneliness and lacking social support track distinct phenotypes. In our UK Biobank cohort, we chart the extent to which our target phenotypes are distinct from one another, as reflected by how they overlap in the participants. Only very few participants in a single household feel lonely and lack social support (8.8%, lower left) or only lonely (17.2%, lower right). As such, living alone at home is a phenotype that is not identical with these two other dimensions of social isolation. Numbers are percentages.

right hemisphere. Most of these effects were also negative amygdala-household-living associations.

3.5. Sex differentiation in amygdala nuclei relationships with solitary living

Given identified sex deviation in the association of cortical regions with living alone, we then sought to examine possible sex differences in amygdala nuclei (male – female, Supplementary Table S4). For example, male-biased positive volume effects can be indexed by greater volume contributions in men than women with less regular social interaction at home. Positive volume effects (that can be indicative of larger GM volume effect in men than women) were identified in the right paralaminar (mean=0.084, 25–75% highest posterior density [HPD]=0.040/0.139), and right central nuclei (mean=0.039, HPD=0.002/0.068), as well as the left lateral nucleus (mean=0.091, HPD=0.037/0.125), and left anterior amygdaloid area (mean=0.051, HPD=0.021/0.085). Negative sex-biased volume effects (that can be indicative of larger GM volume effect in women than men) were evident in right cortical (mean=−0.09, HPD=−0.124/−0.045) and right lateral nuclei (mean=−0.140, HPD=−0.181/−0.087), in addition to the left central nucleus (mean=−0.067, HPD=−0.096/−0.034). We thus found various amygdala nuclei which showed diverging sex effects with respect to living alone. The sex effects also showed opposite patterns for the left and right amygdala for some nuclei. For example, the right central nucleus and left lateral nucleus showed a relationship of greater volume in men than women, while their opposite hemisphere counterparts, the left central nucleus and right lateral nucleus, showed greater volume effects in women than men.

3.6. Hippocampus subregion volumetric relationships with living alone

Next, we examined the variation in volume amongst hippocampal subregions that explain the trait of living alone (Fig. 6, Supplementary Table S5). Several anatomical subregions in the hippocampus head showed relevant volume effects for the target phenotype. For example, our fine-resolution mapping approach identified positive volume effects (i.e. larger GM in individuals living alone) in the head of the hippocampus in left CA1 (mean=0.048, 10–90% highest posterior density [HPD]=0.003/0.094), right molecular layer (mean=0.040, HPD=0.008/0.071), bilateral presubiculum (right mean=0.043, 10–90% HPD=0.002/0.084, and left mean=0.054, HPD=0.014/0.096), right CA2/3 (mean=−0.09, HPD=−0.127/−0.054), and right dentate gyrus (mean=0.099 HPD=0/0.203). Additionally, we identified salient negative volume effects (i.e. larger GM in individuals living with others) in the head in the left dentate gyrus (mean=−0.034, HPD=−0.064/−0.003) and left molecular layer (mean=−0.034, HPD=−0.064/−0.003). We also found relevant volume effects in the body of the hippocampus, including the bilateral presubiculum (right mean=0.046, HPD=0.013/0.08, and left mean=−0.044, HPD=−0.079/−0.01), right dentate gyrus (mean=−0.113, HPD=−0.192/−0.038), and left CA4 (mean=0.094, HPD=0.018/0.175). Overall, our model pinpointed various robust relationships between the hippocampus at a subregion resolution and living alone, many of which were located towards the anterior (head) portion of the hippocampus.

In addition to the general trend of stronger structural associations of living with features of the head of the hippocampus than the body, we observed varying patterns of bilateral and lateralized volume effects. For example, the right and left presubiculum head both showed strong positive effects. However, the other laterality patterns show the opposite direction of effects comparing the two hemispheres. For example, the presubiculum body showed positive volume effects on the right and negative effects on the left. A similar pattern is found in the hippocampal tail (right mean=0.046, 10–90% highest posterior density [HPD]=0.016/0.079, left mean=−0.046, HPD=−0.079/−0.015), dentate gyrus head, and molecular layer head. Unilateral positive volume effects were additionally found in the left CA4 body and left CA1 head. In the right hemisphere, unilateral negative volume effects were found in the fimbria (mean=−0.036, HPD=−0.059/−0.014), CA2/3 head, as well as the dentate gyrus body. As such, there were generally diverging relationships between right and left hippocampal subregion volumes and solitary living.

3.7. Sex differentiation in hippocampus subregion relationships with solitary living

Sex-specific analyses of hippocampal subregions (male – female, Supplementary Table S6) revealed positive volume effects in the right GC-ML-DG-head (mean=0.137, 25–75% highest posterior density [HPD]=0.029/0.241), right CA4 body (mean=0.133, HPD=0.036/0.215), right parasubiculum (mean=0.01, HPD=0.076/0.128), and the right hippocampal fissure (mean=0.063, HPD=0.032/0.092). We also identified two subregions in the left hemisphere with greater GM volume effects in men than women: molecular layer body (mean=0.113, HPD=0.08/0.14) and the fimbria (mean=0.043, HPD=0.017/0.069). By contrast, negative volume effects (which can indicate greater GM effects in women compared to men) were found in the right molecular layer body (mean=−0.047, HPD=−0.076/−0.017), right hippocampal tail (mean=−0.066, HPD=−0.098/−0.034), right subiculum body (mean=−0.086, HPD=−0.127/−0.048), and right CA2/3 head (mean=−0.117, HPD=−0.157/−0.08). There were also a number of subregions in the left hemisphere with greater GM volume effects in women than men: parasubiculum (mean=−0.027, HPD=−0.055/−0.003), presubiculum body (mean=−0.054, HPD=−0.095/−0.022), and CA4 head (mean=−0.12, HPD=−0.23/−0.018). Overall, we isolated a collection of hippocampal subregions that featured robust incongruencies of structural relationships with living alone depending on sex. Right and left hippocampal subregions which also showed differential associations based on sex included the parasubiculum and molecular layer body. For example, the right parasubiculum and left molecular layer body showed greater volume in men than women, while the left parasubiculum and right molecular layer body showed greater volume in women than men.

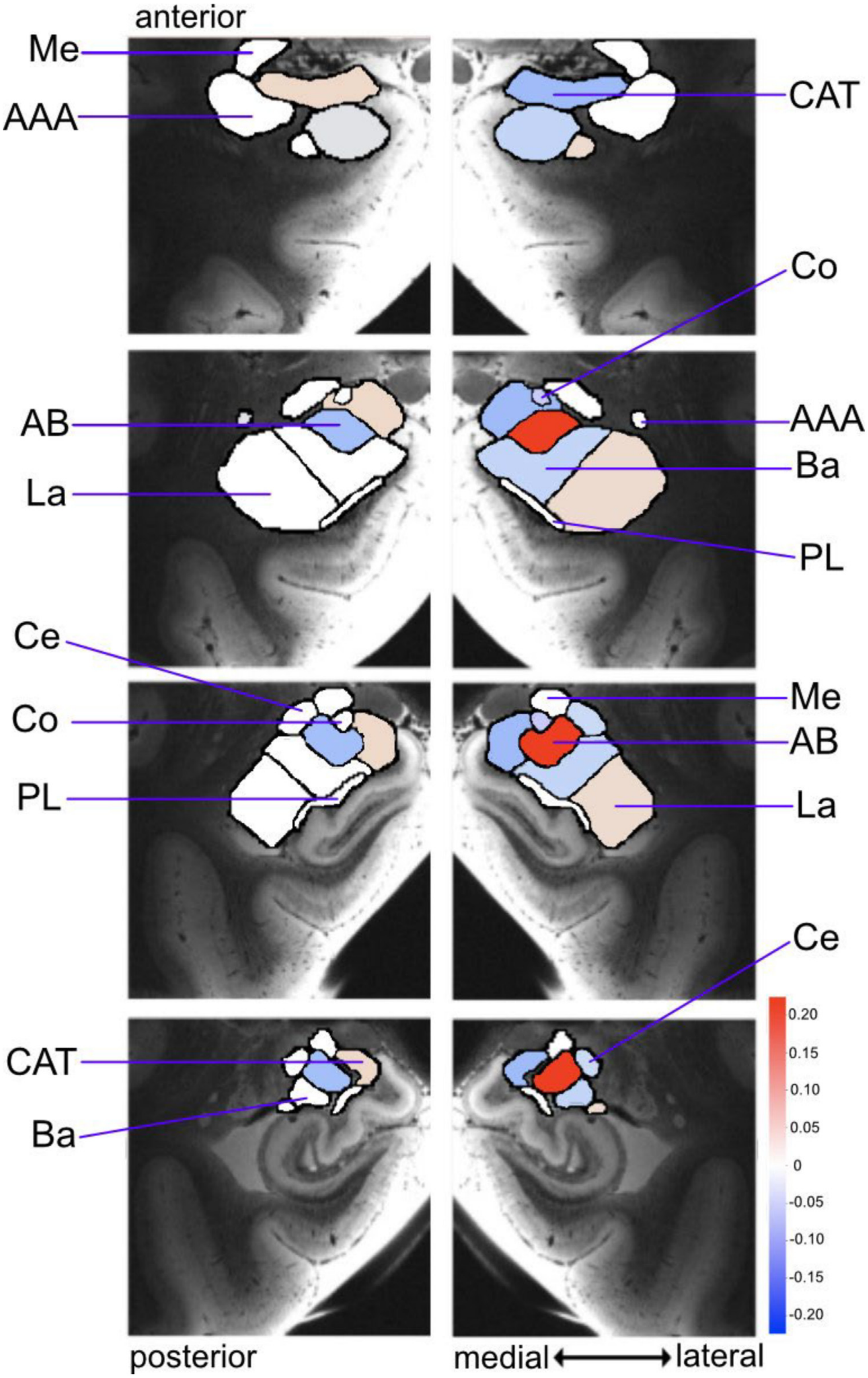

Fig. 5. Specific amygdala nuclei groups are differentially affected in solitary living. Shows the results from Bayesian modeling applied to the amygdala based on the 9 cytoarchitectonically distinguishable nuclei groups from an automatically derived amygdala segmentation protocol (Saygin, Klienmann et al. 2017). The inferred Bayesian posterior parameter distributions indicate where volume variation can explain single person households. Shown as means of the marginal posterior parameter distributions, the results are mapped to 4 consecutive coronal sections of the left and right amygdala from anterior (top) to posterior (bottom) (hot/cold colors = positive/negative volume associations). The left and right accessory basal nucleus show particularly strong, but opposing volumetric relationships. ME = Medial, AAA = Anterior Amygdala Area, CAT = Cortico-amygdaloid Transition Area, Co = Cortical, AB = Accessory Basal, La = Lateral Nucleus, Ba = Basal Nucleus, Ce = Central, PL = Paralaminar Nucleus. Overall, the amygdala nuclei with strong relationships to solitary living were primarily in the right hemisphere.

3.8. *Self-medicative and protective factors linked to living alone are pinpointed by demographic profiling*

Finally, we performed a demographic profiling analysis that set out from the brain regions that were most strongly associated with living alone (Fig. 1). We tested for multivariate cross-associations between these regions (see methods) and a diverse set of factors that covered the domains of (a) basic demographics, (b) personality features, (c) substance-use behaviors, and (d) social network properties. The resulting associations revealed that the largest real-world explanatory factors (but most variance) that accounted for the GM volume effects were linked to interindividual differences in everyday behavior (Fig. 7). These lifestyle indicators included self-medicative behaviours such as time spent watching television, past smoking frequency, alcohol intake on a typical day drinking day, alcohol intake frequency. Notably, potentially protective social factors also showed a strong association with the

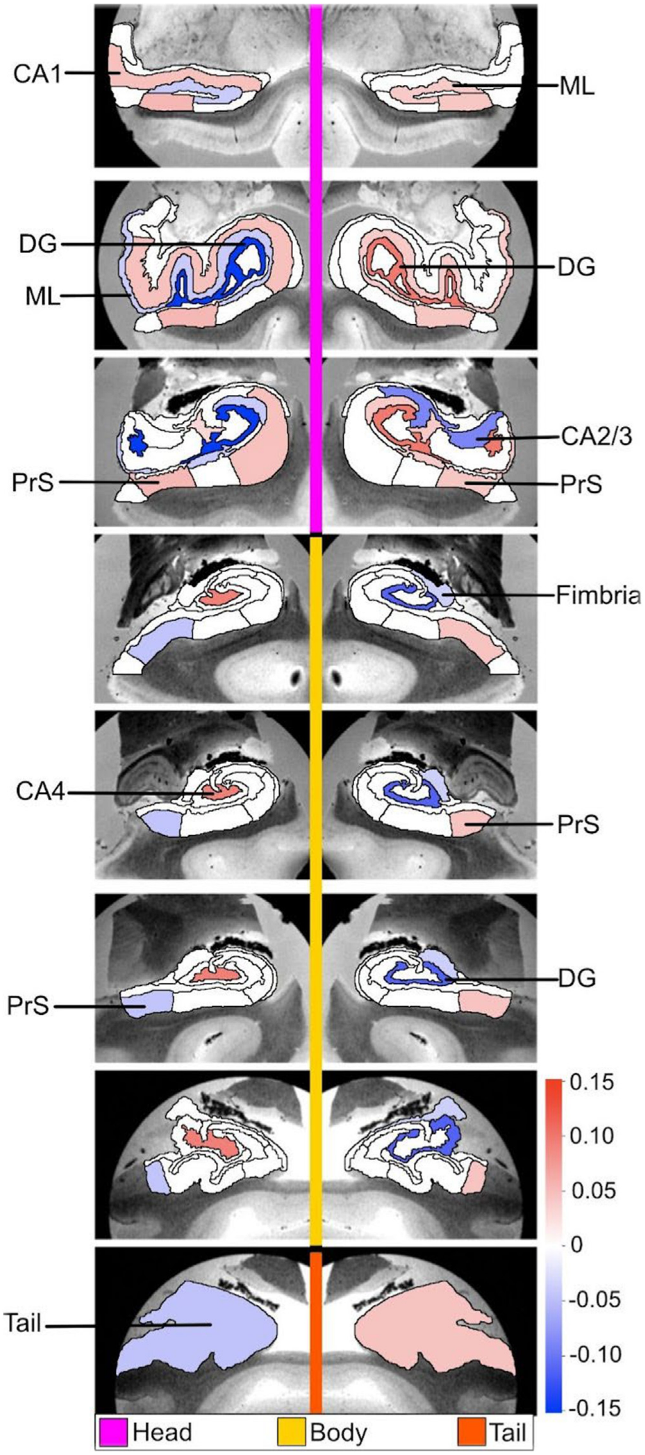

Fig. 6. Specific hippocampus subfields are differentially affected by solitary living. The hippocampus subregions have robust links to living alone, indicated by our Bayesian model inference based on 38 subregions from an automatically derived hippocampus MRI image segmentation protocol (Iglesias et al., 2015). Shown as means of the marginal posterior parameter distributions, volume variation that can be explained by single person households by each specific hippocampus subregion mapped onto 8 consecutive coronal sections of the left and right hippocampus from anterior (top) to posterior (bottom) direction (hot/cold colors = positive/negative volume associations). The majority of subregions with robust effects were additionally located towards the head portion of the hippocampus. CA = cornu ammonis, PrS = presubiculum, GC = granule cell layer of dentate gyrus, DG = dentate gyrus, ML = molecular layer. Together, the subregions which explain inter-individual variation in living alone tend to have opposite effects in the left and right hippocampi.

identified top brain regions, specifically the number of sisters and the number of brothers, suggesting family structure plays an important role in the social support system of individuals in a single-person household.

4. Discussion

Single-person households are becoming more common around the world, especially in many metropolitan cities (Nations, 2019). This unprecedented circumstance reduces the amount of daily social exchange for many people, with measurable sequelae for brain and behavior. Despite the known mental and physical health costs of solitary living, there is a knowledge gap in our understanding of the relationship between living alone and the brain at the population level. To begin addressing this need, the present population neuroscience study set out to systematically trace out brain manifestations linked to living alone in the ~40,000 UK Biobank cohort. We uncover a population-level signature that highlights structural alterations in the highly associative DMN, in addition to subregion-specific effects in particular hippocampus subfields and amygdala nuclei. Sex-specific effects emerged in the highest association circuits in medial prefrontal cortex of women. Instead, males showed these effects at the intermediate (salience network) and lower (visual and somatomotor cortex) layers of the neural processing hierarchy.

Our study showed the DMN yielded broad network-wide associations with living alone. Additionally, at the region-level, our analysis uncovered that all regional GM effects that distinguish single-household individuals from those living with one or more persons at home coalesce to parts of the DMN. Specifically, we identified robust GM volume effects in individuals living alone in the pSTS and dmPFC. Additionally, we identified consistent gray matter volume effects in a number of superior and middle temporal lobe regions in individuals living alone. Based on several decades of social neuroscience research, the DMN is well known to typically show neural activity responses during tasks in the social domain including perspective taking capacities (Theory of Mind) as well as certain forms of empathy (Frith and Frith 2006) and the acute experience of social exclusion as measured through the virtual ball-throwing game, Cyberball (Mwilambwe-Tshilobo and Spreng 2021). Furthermore, DMN aberration is at the cross-roads of a number of neurological and psychiatric conditions with aspects of disordered social cognition, such as Alzheimer's disease (Hafkemeijer et al., 2012) and autism (Anderson et al., 2011). It is therefore intriguing that, while our analysis approach was not specifically tuned to a particular brain system, the DMN emerged as a central point of convergence in solitary living across analyzes.

Our collective findings not only highlight the DMN in understanding the sociocognitive factors associated with living alone, but replicate key findings from experimental studies in macaque monkeys. Sallet and colleagues (2011) showed associations of the GM volume with the size of an individual monkeys' social group size, defined as the number of animals the individual shared their home cage with, ranging from single-housed to seven-socially housed animals. In the present study in humans, we report a negative relationship between GM and living alone in the dmPFC and the posterior STS. Our human dmPFC atlas region overlaps with the likely human homologue of the monkey area 9/46D, identified by Sallet et al. as larger in monkeys living in larger social groups. In humans, this region is associated with neural activity responses when predictions are made and updated about the intentions of others (Behrens et al., 2008; Seo and Lee 2008). By contrast, the pSTS atlas region, like the dmPFC, is believed to be involved in theory of mind. This part of the temporal lobe is dorsally adjacent to a possible candidate of the human homologue of the mSTS identified in the macaque as larger in animals living in larger social groups; the posterior temporal parietal junction (Mars et al., 2013). Given evidence that dmPFC activity correlates with predicting another social agent's choice (Seo et al., 2014), as well as actively maintaining and manipulating social information in memory (Krol et al., 2018), one possible interpretation of the collective present and previous findings in macaques and humans is that these kinds of

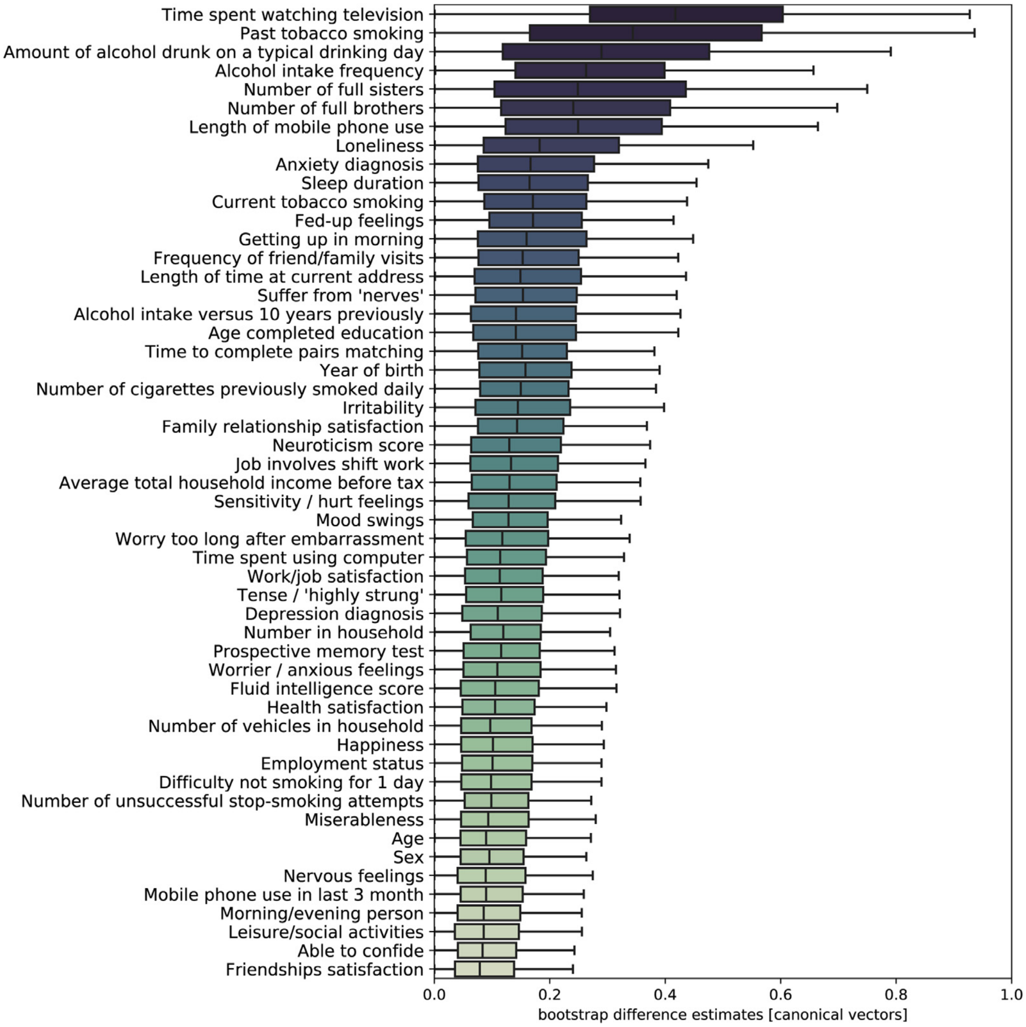

Fig. 7. Demographic profiling analysis ranks lifestyle factors by relation to solitary living substrates in the brain. Multivariate pattern-learning (cf. Methods) was used to explore how the top brain regions (see Fig. 1) are linked to a portfolio of behavioral indicators in individuals living alone or with others. Behavioral markers covered domains of mental and physical well-being, lifestyle choices, and social embeddedness. In 1000 bootstrap resampling iterations, our entire pattern-learning pipeline was repeated separately in the two participant groups: UK Biobank participants who live alone vs. with others. The computed differences in modelled brain-behavior associations between both groups (i.e., diverging canonical vector entries) were gathered across the 1000 perturbed re-draws of our original sample to obtain faithful bootstrap intervals. The derived estimates of uncertainty directly quantified how group-related deviations vary in the wider population. The boxplot whiskers show the interquartile range (i.e., 25/75% interquartile distance derived from bootstrap resampling distributions). The boxplot is a common tool to summarize aspects of the spread of obtained group differences in brain-phenotype associations (e.g., the 25/75% interquartile distance, the box, shows the distribution of the middle 50% of the points from the bootstrap resampling distributions). The highlighted divergences (sorted from most relevant [top] to least relevant [bottom]) in individuals living in a single-person household reveal characteristics of these population strata that implicate indicators of media consumption, health and smoking behavior, as well as alcohol consumption at the population level.

social predictions occur less frequently in the absence of social interactions and result in reduced gray matter in individuals who live alone. However, given the limitations of the analysis framework used in the present study it is not possible to rule out the alternative interpretation that individuals with certain brain structures, or more proximally, their phenotypic outcomes, become more likely to live alone because of their social skills, motivation to be with others, or, for example, socioeconomic status. These explanations are not mutually exclusive with both likely to contribute to the observed difference. Nor are they exhaustive of all plausible causal relationships among these variables, with other possible intermediary social or medial modulatory factors such as social status, cardiovascular health or epigenetic changes.

Living alone is associated with detrimental physical and emotional consequences (Holt-Lunstad et al., 2010; Holt-Lunstad et al., 2017; Bzdok and Dunbar 2020). But many people know from their own experience that one does not need to physically be alone to succumb to the subjective feeling of loneliness. Indeed, subjective isolation sometimes appears more predictive of cognitive and emotional well-being than objective social isolation (Holwerda et al., 2014; Lee and Ko 2017). The results from the present study reveal the neurobiological commonalities between the emotional states of loneliness and living alone in the UK Biobank cohort. We find that many of the regions associated with single-person households also bear some relation with loneliness. First, our findings speak to previous work showing positive association between MTG/ITG and pSTS and the experience of loneliness (Spreng et al., 2020) but now observe this relationship is linked to the access to social support. For example, there is a main effect of loneliness in MTG/ITG GM effects, regardless of the availability of social support, with the predicted positive GM effects between MTG/ITG and loneliness in individuals who report good and poor social support systems. By contrast, we found interactions between loneliness and social support in pSTS GM effects. GM effects are positive when loneliness is reported, regardless of social support, but negative when individuals who are not lonely have a poor social support system. Further, we did not always observe a corresponding association between living alone and the states of loneliness/access to social support, that was seen in the MTG/ITG (i.e., positive GM effects in living alone, positive GM effects in lonely states, positive GM effects in individuals with poor social support). For example, the IFG showed the counterintuitive pattern; positive effects in individuals living alone, but negative GM effects in lonely individuals and positive GM effects in not-lonely individuals. Given the IFG's role in inhibitory control and affect regulation (Aron et al., 2004; Ochsner et al., 2004; Lieberman et al., 2007), and recent finding that IFG activity correlates with lower self-reported social distress during social exclusion (Eisenberger et al., 2007), one interpretation of the IFG's role in the present context may be to moderate the emotional experience of living alone. Future research should examine the interaction between these three social factors and link neural relationships with behavior to further identify adaptive and maladaptive effects. This could then improve our understanding of the neural mechanisms that support adaptive coping strategies of objectively isolated individuals that appear to protect them from the detrimental emotional and cognitive effects of subjective loneliness (Holwerda et al., 2014; Lee and Ko 2017). Future research should also seek to replicate these results using more detailed outcome measures. Despite the Biobank's power in numbers and breadth of demographic information, our understanding of the relationship between loneliness and brain structure is limited by the relative lack of depth of database questions along the dimensions of interest; loneliness, social support and living alone.

An important source of interindividual variability in living alone turned out to be sex in our present study. In the UK, more men live alone before the age of 65 years, but notably this pattern reverses after that age (Esteve et al., 2020). Given known sex bias in primate behavioural and social development (Baron-Cohen et al., 1999; Key and Ross 1999; Silk et al., 2003; Bhattacharya et al., 2016; Amici et al., 2019; Amici and Widdig 2019), and various sex-dependent neuroanatomical differences reported in the amygdala, hippocampus, and various cortical regions (Lenroot and Giedd 2010; Ritchie et al., 2018; Kiesow et al., 2020), we examined sex differences in neurobiological variability to solitary living. The sex-focused analyses corroborated the findings from the full sample, but notable patterns of differences became apparent between the sexes. Living alone in men was associated with a stronger negative volume effect than women in the frontal cortex and especially its medial portion, a region associated with tracking the significance of multiple goals in parallel, as well as switching between them (Boorman et al., 2009). By contrast, living alone in women was associated with more negative GM relationships, compared to men, in a number of visual, sensory motor and attentional regions, as well as relatively posterior subregions within the DMN including precuneus and cingulate gyrus. In fact, the reported effects did not localize to the higher-order association areas but to regions known to be involved in perception, memory and action, which may reflect evidence of sex differences in cognitive abilities (Asperholm et al., 2019). For example, sex differences in face processing, such as women judging faces as more positive and arousing than men, may translate to fundamental differences in lower-level perceptual experiences of men and women who live alone (Lewin and Herlitz 2002; Proverbio 2017; Mishra et al., 2019; Olderbak et al., 2019). Future research will be needed to directly link biological and cognitive differences to the sex-specific differences in behavioural strategies adopted when living alone. For example, women tend to entertain larger social networks and maintain more close friendships than men, especially later in life (Dunbar 2018). This observation may act to protect women from the negative elements of living alone. By contrast, solitary living men, in this cohort, may be particularly adversely affected after retirement age if their social circles are grounded in their working environment. Finally, while we controlled for participants' age, it will be critical for future research to also examine and control for menopausal status in women when examining sex differences in older samples. It is becoming increasingly clear that the progression of menopause is related to gray matter differences across the brain (Mosconi et al., 2021; Than et al., 2021), with further evidence that loneliness is negatively related to menopausal symptoms (Ozcan et al., 2022). Further studies in this population will allow us to understand the important interactions between changes in ovarian hormone levels and neural mechanisms associated with social isolation.

In our pattern analyses dedicated to the amygdala at subregion resolution, living alone was associated with distinct anatomically defined nuclei groups. Besides bilateral effects in the accessory-basal nuclei group, the central nuclei group, cortical nuclei group and corticoamygdaloid transition all showed effects preferentially in the right hemisphere. The laterobasal nuclei group is commonly conceptualized as a likely integrator of preprocessed visual, auditory, gustatory, somatosensory, and, in part, olfactory environmental information (Aggleton et al., 1980; Iwai and Yukie 1987; Stefanacci and Amaral 2002; Yukie 2002). As such, living alone may relate to stimulus-value associations subserved by the human laterobasal nuclei group that are believed to be implicated in associative processing of environmental information and the integration with self-relevant cognition in a way that is biased to the right brain hemisphere. Instead, the centromedial nulcei group, the amygdala's putative major output center, has been related to integration of information originating from various intra-amygdala circuits to mediate behavioral and autonomic responses (Pessoa and Adolphs 2010), including motor behavior and response preparation in humans. These amygdala subregion deviations may in part reflect the previous observation that socially deprived individuals show worse aptitude at significance detection, such as in detecting social cues from other's faces or gestures to be overly negative and allocating attentional resources accordingly (Cacioppo et al., 2009). Such individuals are also known to react differently towards others, such as part of approach-vs-avoidance decisions and facial motor responses (Cacioppo et al., 2009). A right-hemispheric bias in such stimulus-response cycles could be related to the previous neuroimaging observation that the right hemisphere shows attention- and stress-related differences in socially deprived individuals (Cacioppo and Hawkley 2009). Indeed, it has been proposed that social disconnection may trigger an evolutionary alarm signal and effects appear to lateralise to the right hemisphere as it could reflect increased attention towards threat and may link to the right ventral attention stream (Eisenberger et al., 2003; Cacioppo and Hawkley 2009); flagging survival-relevant information in the environment.

Indeed, both the amygdala *and* hippocampus are known to be affected by social stress. This includes long-term changes in gross morphology, dendritic remodeling (retraction in CA1 and CA3 in the hippocampus and expansion in amygdala), functional connectivity and changes in neurogenesis (Woolley et al., 1990; Watanabe et al., 1992; Magarin and McEwen 1995; Magariños et al., 1996, 1997; Vyas et al., 2002; Vyas et al., 2006; Anacker et al., 2018; Biggio et al., 2019). Here we show robust associations between living alone and GM structure at hippocampal subfield scale). This resolution goes far beyond previous studies, which were often limited to a crude posterior/anterior division in the primate brain (Fanselow and Dong 2010). We report numerous bilaterally coherent effects in the molecular layer head, presubiculum, para-subiculum and hippocampus tail, many of which have been modulated by social experience and stress. Social isolation is an extreme stress trigger and when induced by long term confinement is associated with broad reductions in global cortical activity and increased cortisol levels (Jacubowski et al., 2015; Weber et al., 2019). While inherently methodologically and ethically challenging to manipulate, findings from a number of studies in this area align with the current results. For example, experimentally induced social isolation during adolescence in monkeys chronically alters functional connectivity between the hippocampus and amygdala, and frontal cortical structures (Yuan et al., 2021). Similarly, in humans, the relative social isolation induced by a 14 month expedition of the Antarctic was exploited by researchers to reveal decreased GM volume in the DG hippocampal subfield, and decreased markers of neurogenesis at the end of the expedition (Stahn et al., 2019). Our observed effects in the DG (including the left CA4 body, right GC-DG-ML body, and bilateral GC-DG-ML head) fit with these and other studies of the neurostructural concomitants of living in limited social environments (Gould et al., 1998; Kempermann et al., 1998; Stranahan et al., 2006; Ibi et al., 2008; Dranovsky and Leonardo 2012; Li et al., 2013; Anacker et al., 2018; Biggio et al., 2019). The anterior portion of the DG/hippocampus has also been found to be particularly associated with stress susceptibility (Anacker et al., 2018). The chronically stressful experience of solitary living may thus manifest in the form of altered DG structure and function, but also in cooperating anterior (head) structures. For example, we found robust effects in the molecular layer head in both the right and left molecular layer - a region which has been well-described as being particularly sensitive to chronic stress (Gould et al., 1990; Woolley et al., 1990; Watanabe et al., 1992; Magariños et al., 1997). Finally, we also identified bilaterally both presubiculum subfields (head, body) in the context of solitary living. The presubiculum is composed of grid cells (Boccara et al., 2010) and recent work has suggested the hippocampus tracks social relationships in the form of a social cognitive map that relies on a hexagonal coding structure (Tavares et al., 2015). A strong relationship between the presubiculum and living alone may therefore indicate an alteration of the neural underpinnings of a robust cognitive map of social spaces.

Finally, we charted brain-behavior associations between explanatory real-world factors and variation in the set of brain regions associated with living alone. At population level, this test for robust cross-associations suggest that one set of factors, such as smoking and frequent alcohol intake, may reflect compensatory or self-medicating associative behaviors that run parallel to living alone. By contrast, family structure, indexed by numbers of brothers and sisters may speak to a protective role linked to the discovered brain-behavior cross-associations. This insight may reflect the stable nature of a sibling relationship, compared to friendship circles which may be periodically disconnected. Further, small but significant variance in GM effects were also explained by individual differences in loneliness and the ability to confide a social support structure, which fits well with the analysis that explored the interactions between these three factors. Indeed we can see evidence that many of these behavioural factors have changed at the population level during this period of social restrictions during the pandemic, with increased total video viewing time (including TV and online streaming (OfCom 2020)), increased intake of alcohol in UK samples, particularly women (Sallie et al., 2020; Jackson et al., 2021), and increased smoking, mostly in younger age groups (Jackson et al., 2021). Collectively, these behavioural factors, including the likely positive effect of siblings, should be studied carefully alongside future investigations into the neural mechanisms associated with living alone as they could provide targets to support individuals in such social environments. One factor missing from the UK Biobank database is the length of time each individual has experienced social isolation. As a result, we are unable to include and account for its variance in our analyses. If this data had been available and was shown to correlate with gray matter volume in the structures we identified we would have been better placed to propose a causal relationship between brain structure and social experience. Brain plasticity in other functional domains can occur very rapidly in humans and non-human animals (Zatorre et al., 2012; Sampaio-Baptista et al., 2013; Sallet et al., 2020). Indeed, in macaques changes in social group size correlated with prefrontal and temporal gray matter within an average of one year later (Sallet et al., 2011).

For millennia, primates have socially cohabited. However, it is only over the last 10–20 years that we have seen a significant trend for more people to live alone and to reside at a greater geographically distant from their immediate families. The parallel increase in the frequency of global crises also acts to accelerate and aggravate the progressive dislocation and alienation of normal social forms of living. At the extreme, and as a result of the coronavirus pandemic, there was more than 50% of the world's entire population under stay and home orders in April 2020 Sandford (2020). These unusual global circumstances and other extraordinary events, such as natural catastrophes or abrupt economic change, are likely to disproportionately jeopardize the well-being of people who live alone, increasing demands on both individual resilience but also financially on government and charity resources in the future. While online social networks can partially recapitulate real-world networks (Kanai et al., 2012; Dunbar 2016) they cannot replace them. Consequently, a growing appreciation of cognitive, psychological and neural implications of solitary living and loneliness could directly inform social and health policies.

Data and code availability

All researchers in good standing can ask for access to the UK Biobank at https://www.ukbiobank.ac.uk/. The Python code is available for reproducibility and reuse at https://github.com/dblabs-mcgill-mila/.

Declaration of Competing Interest

None.

Credit authorship contribution statement

MaryAnn Noonan: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Chris Zajner:** Methodology, Investigation, Writing – original draft, Visualization. **Danilo Bzdok:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization, Supervision, Funding acquisition.

Data Availability

The authors do not have permission to share data.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2023.119936.

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