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Frontoinsular cortical microstructure is linked to life satisfaction in young adulthood

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Abstract Life satisfaction is a component of subjective well-being that reflects a global judgement of the quality of life according to an individual's own needs and expectations. As a psychological construct, it has attracted attention due to its relationship to mental health, resilience to stress, and other factors. Neuroimaging studies have identified neurobiological correlates of life satisfaction; however, they are limited to functional connectivity and gray matter morphometry. We explored features of gray matter microstructure obtained through compartmental modeling of multi-shell diffusion MRI data, and we examined cortical microstructure in frontoinsular cortex in a cohort of 807 typical young adults scanned as part of the Human Connectome Project. Our experiments identified the orientation dispersion index (ODI), and analogously fractional anisotropy (FA), of frontoinsular cortex as a robust set of anatomically-specific lateralized diffusion MRI microstructure features that are linked to life satisfaction, independent of other demographic, socioeconomic, and behavioral factors. We further validated our findings in a secondary test-retest dataset and found high reliability of our imaging metrics and reproducibility of outcomes. In our analysis of twin and non-twin siblings, we found basic microstructure in frontoinsular cortex to be strongly genetically determined. We also found a more moderate but still very significant genetic role in determining microstructure as it relates to life satisfaction in frontoinsular cortex. Our findings suggest a potential linkage between well-being and microscopic features of frontoinsular cortex, which may reflect cellular morphology and architecture and may more broadly implicate the integrity of the homeostatic processing performed by frontoinsular cortex as an important component of an individual's judgements of life satisfaction.

Keywords subjective well-being · diffusion microstructure · frontoinsular cortex · young adulthood · von Economo neurons

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Introduction

Subjective well-being is a concept that encompasses the many facets of an individual's psychological state concerning whether life is desirable, pleasant, and good (Diener, 2009). As a topic of research, subjective well-being has been approached theoretically to differentiate it from happiness (Shin and Johnson, 1978) and to subdivide it into hedonic and eudaimonic components (Ryan and Deci, 2001; Ryff et al., 2004). Life satisfaction is an element of subjective well-being that is a judgement of the global quality of life, as assessed by an individual's own chosen criteria regarding their needs and expectations (Shin and Johnson, 1978). Viewed as a psychological construct, life satisfaction has raised substantial interest, as it reflects personal orientations such as meaning, pleasure, and engagement (Peterson et al., 2005), and it is a factor in mental health and response to stress, anxiety, and depression (Mahmoud et al., 2012; Pavot and Diener, 2009); furthermore, it may provide a beneficial target for guiding public policy beyond economic measures of wealth (Diener and Seligman, 2004). Several multi-item questionnaires have been developed to provide a life satisfaction measurement scale representing "a cognitive and global evaluation of the quality of one's life as a whole"

(Pavot and Diener, 2009), and these scales have been widely applied and shown to be highly reliable (Diener et al., 1985; Samman, 2007; Salsman et al., 2014, 2013). The genetic heritability of life satisfaction has also been measured in 10 separate studies in monozygotic twins (total N=44,450). A meta-analysis of these studies found an average heritability index of 0.32 with a 95% confidence range between 0.29 and 0.35 (Bartels, 2015).

An emerging goal of well-being research is to understand its underlying neural substrate, and in particular, to characterize how brain structure and function relates to the psychological construct of life satisfaction. Magnetic resonance imaging (MRI) has been the primary tool for investigating such brain factors related to subjective well-being, with studies looking at both functional connectivity and gray matter morphometry (Machado and Cantilino, 2017). Functional MRI studies have employed resting-state approaches to identify low frequency oscillatory features associated with well-being, including effects in temporal, insular, and subcortical regions (Kong et al., 2015b,c). More targeted seed-based functional MRI has shown associations between insular connectivity and subjective well-being (Li et al., 2020). Furthermore, functional MRI work has looked more specifically at life satisfaction and mediation effects, finding the insula and dorsal anterior cingulate cortices to be activated with mediation by resilience (Kong et al., 2015d), insular and dorsolateral prefrontal cortex connectivity conditional on a valenced face-word task (Kim et al., 2016), and activation of ventrolateral prefrontal and posterior cingulate cortices mediated by self-respect and self-criticism (Kyeong et al., 2020). The meta-analysis by Tanzer and Weyandt (2019) provides a quantitative summary of functional MRI findings, which include meaningful activation clusters identified in the claustrum, insula, basal ganglia, and thalamus. In particular, in our review of Tanzer and Weyandt (2019), we found that functional activity related to happiness based on meaning, which is closest to eudiamonia, was localized to frontoinsular cortex in both the right and left hemispheres, as based on a comparison of their reported coordinates and our own manually delineated frontoinsular region. Beyond functional imaging, structural MRI studies have employed voxel-based morphometry to estimate local changes in gray matter volume, finding insular gray matter volume related to eudaimonia (Lewis et al., 2014), differences with subjective well-being in the precunus (Sato et al., 2015), and a relationship between measures of quality-of-life and anterior insula volume in older adults Ourry et al. (2021). Some works have further identified hippocampal volumetric differences with subjective well-being (Van't Ent et al., 2017), and a combination of subcortical and cortical changes to be mediated by self-esteem (Kong et al., 2015a). Cortical thickness has also been investigated, finding frontal cortex thickness associated with life satisfaction with mediation by relationship status (Zhu et al., 2018).

Together, these findings show widespread associations between well-being scales and brain structure and function, with some convergence in frontal, insular, and posterior cingulate areas; however, they do not tell the whole story, as structural imaging metrics derived from voxel-based morphometry and cortical thickness analysis are somewhat non-specific to underlying cellular changes. Diffusion MRI is a well-established technique that has yet to be applied to study subjective well-being, and it offers a unique probe into the microstructural features of brain tissue, which may reflect changes in cellular morphology and organization (Alexander et al., 2019). While typically applied in white matter imaging, computational modeling techniques are making it possible to characterize the microstructure of the cortex (Fukutomi et al., 2018). Such analyses have previously proven challenging due to limited image resolution, geometric distortion, and partial volume effects of diffusion MRI scans. However, these issues are more recently mitigated by higher resolution imaging sequences, multi-shell gradient protocols for separating tissue compartments, and by sophisticated artifact correction tools to reduce susceptibility-induced geometric distortion. This has led the way to work showing how cortical microstructure reflects aspects of environmental exposure, genetics, and neurodegeneration (Genç et al., 2018; Schmitz et al., 2019; Cabeen et al., 2020; Baxi et al., 2020; Torso et al.; Caron et al., 2020). In contrast to white matter imaging, microstructure modeling of gray matter may potentially reveal aggregate features of soma density, myelination, dendritic complexity, and laminar architectural features of cortex (Nazeri et al., 2020). This provides a valuable direction for investigating well-being and understanding how it relates to the integrity of cortical homeostatic processes beyond what is available through volumetric analysis.

Our present study investigates how such cortical microstructural features are related to life satisfaction, as a part of ongoing research characterizing features of frontoinsular cortex and other subcortical brain regions related to decision making and emotion regulation. Our motivation for focusing on frontoinsular cortex is due to its central role in homeostatic processing (Craig, 2009), emotional awareness (Gu et al., 2013), salience processing (Seeley et al., 2007), and its distinct cytoarchitectonic features (Allman et al., 2010). We focused on neurite orientation dispersion and density imaging (NODDI), as its component measures depict distinct cytoarchitectural features, i.e. separating features of cellular density and myelination from dendritic complexity and cell morphology (Fukutomi et al., 2018). After identifying a relationship with life satisfaction in frontoinsular cortex, we broadened our analysis to assess lateralization, the anatomical specificity of our findings across the cortex, and the relationship of frontoinsular microstructure to other demo-

graphic and behavioral variables. We further expanded our analysis with a validation experiment conducted with a secondary test-retest dataset to establish the reliability of our microstructural metrics and to examine replicability of our specific outcomes across cohorts and scanning sessions. We further examined a cohort of twin and non-twin siblings to determine the heritability of frontoinsular microstructure parameters and to examine inter-sibling differences in microstructure and life satisfaction. Our data was obtained from the Human Connectome Project, which provides a large cohort of typical young adults scanned with a high quality diffusion MRI sequence suitable for multi-modal analysis with cortical surface modeling. We next describe the design and procedures of our experiments, present our findings, and subsequently discuss our results, their interpretation and implications, and potential limitations.

Materials and Methods

Participants and Datasets

Data for our experiments were acquired from participants as part of the Human Connectome Project (HCP). We performed a multi-modal analysis that included both T_1-weighted (T1wMRI) and diffusion-weighted MRI (dwMRI) data, and in total, we included 807 participants with scans that pass quality control and completed image processing. With approval from the University of Southern California Institutional Review Board, we accessed and analyzed demographic and behavioral data from the restricted data release. We collected scores from the Emotion Battery of the *NIH Toolbox General Life Satisfaction Survey* (Salsman et al., 2013, 2014) [1]. According to the toolbox technical manual, the questionnaire is designed to measure "one's cognitive evaluation of life experiences and is concerned with whether people like their lives or not." We also collected other behavioral variables to determine the specificity of our effect. This included two other NIH Toolbox well-being measures: positive affect and a combined variable for meaning and purpose. From the set of instruments from the Achenbach System of Empirically Based Assessment (ASEBA) (Achenbach and Rescorla, 2003), we also retained the adult self-report thought problems scale (Abdellaoui et al., 2012). We used this scale to operationalize a summary measure of negative intrusive thinking, as the questionnaire includes self-reported measures of hallucinations, self-destructive thoughts, repetitive behavior, and other factors that negatively impact daily life. To provide general summaries of cognitive performance, the overall accuracy in working memory and the cognitive function composite score were extracted from the NIH Toolbox measures. We also retained the following demographic variables from the semi-structured assessment for the genetics of alcoholism (SSAGA) that are possibly relevant to life satisfaction: income, relationship status, employment status, level of education, and body mass index.

[1] `https://www.healthmeasures.net/explore-measurement-systems/nih-toolbox/intro-to-nih-toolbox/emotion`

Image Acquisition and Preprocessing

The data were collected using the imaging protocol designed for the Human Connectome Project, which we briefly summarize here. The T1wMRI and dwMRI data from the HCP was collected on a Connectome Siemens 3 Tesla Skyra scanner using a 32-channel head coil (Glasser et al., 2013; Van Essen et al., 2013). The T1wMRIs were acquired using a 3D MPRAGE sequence with 0.7 mm isotropic resolution (FOV = 224 mm, matrix = 320, 256 sagittal slices in a single slab), repetition time (TR) = 2400 ms, echo time (TE) = 2.14 ms, inversion time (TI) = 1000 ms, flip angle = 8°, bandwidth = 210 Hz per pixel, echo spacing = 7.6 ms, and phase encoding undersampling factor GRAPPA = 2.10%. dwMRIs were collected with a single-shot 2D spin-echo EPI acquisition with a multi-band factor of 3, 1.25 mm isotropic voxels with FOV PE by Readout = 210 x 180; matrix size PE by Readout = 144 x 168; 111 interleaved slices without gap; left-right and right-left phase encoding; flip angles = 78° and 160°. For each phase encoding direction, the diffusion sampling scheme consisted of 18 baseline scans and 270 diffusion-weighted scans acquired using single diffusion encoding across 3 shells with b = 1000, 2000, and 3000 s/mm^2; all dwMRI scans had TE = 89 ms and TR = 5.5 s. Each shell included 192 data points representing 90 diffusion gradient directions and six b = 0 shells acquired twice resulting in 270 non-collinear directions for each PE. Total acquisition time was approximately 54 min (6 segments of 9 min each). dwMRI data were preprocessed with the HCP workflow (Sotiropoulos et al., 2013). This included the sophisticated approach for correction of artifact due to motion and eddy-current and susceptibility induced geometric distortion in FSL EDDY. Using an additional set of diffusion MRI scans collected with reversed phase encoding, this scheme estimates and corrects for the off-resonance field and subject head motion using a Gaussian process framework for robust non-parametric interpolation of the dwMRI signal. This is a crucial step for mapping cortical microstructure, as surface-based mapping of microstructure parameters requires accurate alignment between T1wMRI and dwMRI data, which can be otherwise disturbed by susceptibility-induced geometric distortion.

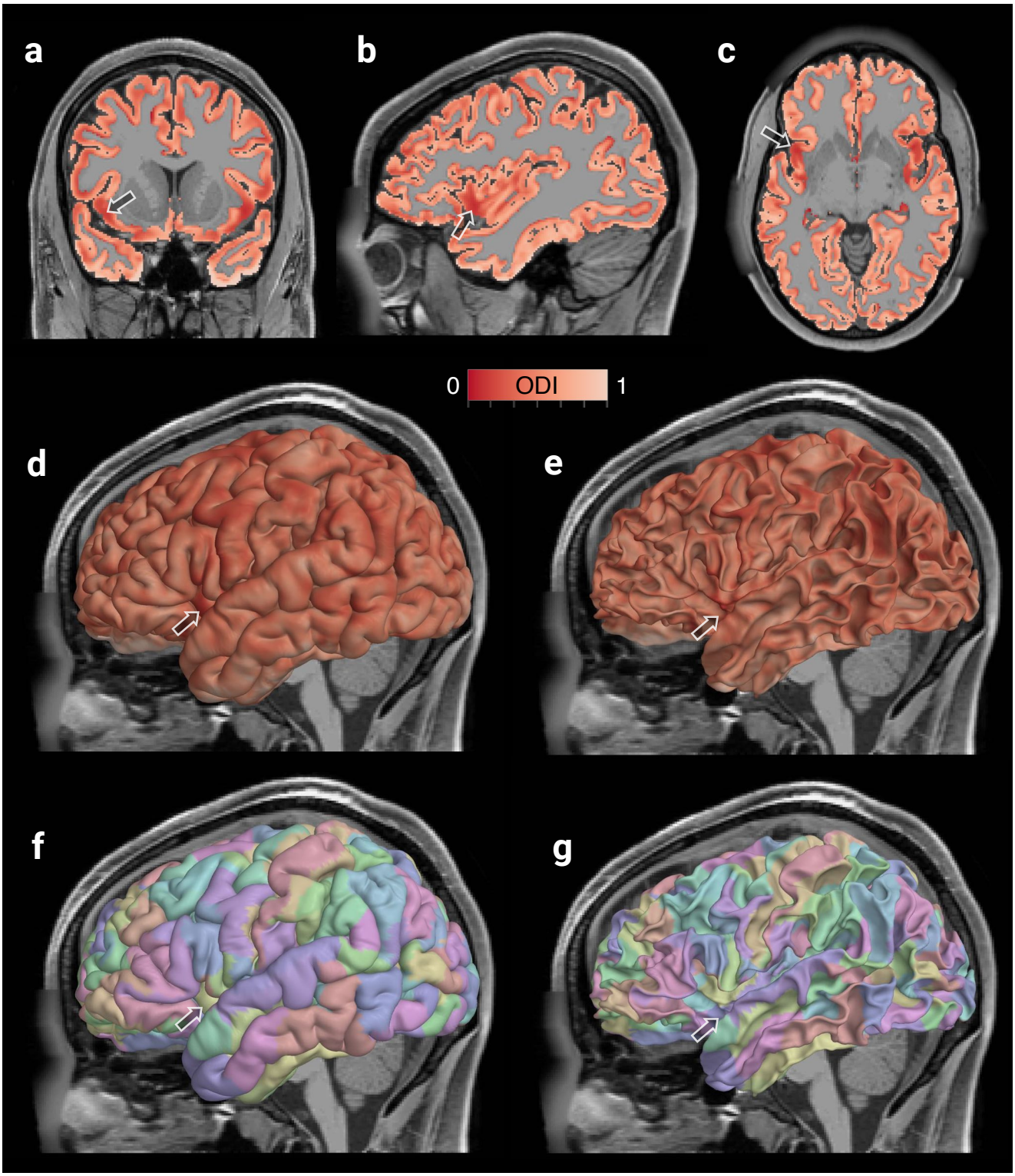

Fig. 1 An overview of the imaging results illustrated using data from a randomly selected individual. The top row shows an overlay of the orientation dispersion index on the structural T1 image in coronal (a), sagittal (b), and axial (c) planes. Frontoinsular cortex is identified by an arrow, which lies in an area with lower dispersion than other parts of cortex. The middle row shows an overlay of orientation dispersion on a cortical surface models, which are produced using a statistical mapping procedure that samples microstructure parameters between the pial (d) and white matter (e) boundary surfaces. The bottom row shows the HCP multi-modal parcellation used in our analysis, where the pial (f) and white matter (g) boundary surfaces are randomly colored to distinguish separate parcels. The agranular anterior insular cortex (AAIC) parcel is identified by an arrow, which also coincides with frontoinsular cortex.

Image Analysis

Our image analysis took a multi-modal approach that uses intra-subject registration to accurately segment cortical structures in dwMRI data using gray-white tissue contrast of T1wMRI. Our initial experiment performed a simple region-of-interest based approach to investigate microstructure in frontoinsular cortex and several other regions. We subsequently expanded this analysis to the entire cortex and performed further validation experiments. Our analysis is similar to our previous work (Cabeen et al., 2020), with several algorithmic refinements in an effort to make our pipeline into a tool that can be applied by other researchers. The data were analyzed using the LONI Pipeline (Dinov et al., 2009) with components including the Quantitative Imaging Toolkit (QIT) (Cabeen et al., 2018), Freesurfer (Fischl, 2012), FSL (Jenkinson et al., 2012), ANTs (Avants et al., 2008), and DTI-TK (Zhang et al., 2006). The specific steps of our analysis are described in detail as follows.

The dwMRI data were denoised using a non-local means filter and microstructure parameters were obtained using two multi-shell modeling approaches. First, we performed neurite orientation dispersion and density imaging (NODDI) (Zhang et al., 2012) and estimated its parameters using a non-linear fitting approach accelerated using the spherical mean technique (Cabeen et al., 2019), resulting in volumetric maps of the orientation dispersion index (ODI) and neurite density index (NDI). Because our experiments look specifically at gray matter, we used a parallel diffusivity of 1.1 x 10^{-3} mm^2/s, which is an optimized value obtained from previous work (Fukutomi et al., 2018). NDI is meant to depict the proportion of neurite volume relative to the total cellular volume, while ODI is meant to separately depict neurite orientational heterogeneity. We also estimated diffusion tensor imaging (DTI) (Basser and Jones, 2002) parameters using weighted linear least squares fitting with free-water elimination with a fixed diffusivity of 3.0 x 10^{-3} mm$^2/s$ in the isotropic compartment using the non-linear least squares appraoch of Hoy et al. (2014), resulting in volumetric maps of fractional anisotropy (FA) and mean diffusivity (MD). We used these two distinct diffusion modeling approaches to understand how they relate, because they are both widely used and useful points of reference. An important piece, however, is that they both include a free-water compartment, which can reduce partial volume effects due to subvoxel mixing of cerebrospinal fluid and gray matter tissue. Generally speaking, ODI and FA may reflect similar tissue properties, but they are inversely related, as lower neurite dispersion is reflected by an increase in tensor anisotropy.

We created a population-averaged dataset from 88 scans from the test-retest portion of the HCP dataset to serve as a template in our initial region-of-interest analysis. We used the tensor-based deformable registration and spatial normalization pipeline implemented in DTI-TK (Zhang et al., 2007) to produce the population averaged DTI, NODDI, and T1wMRI datasets that were aligned to the IIT template (Zhang et al., 2011). Subject data from all participants was then spatially normalized to the template and the deformable registration maps were retained for each individual. Our inital goal was to investigate gray matter microstructure parameters in frontoinsular cortex and related structures involved with decision-making and emotion regulation using a region-of-interest (ROI) approach. Guided by the definition from Allman et al. (2010), we first manually delineated ROIs on coronal slices of the template for left and right frontoinsular cortex using QIT and co-registered these in subject native space and computed region-averaged parameters. The other additional structures we examined included: the nucleus accumbens, caudate, putamen, substantia nigra (separate compact and reticular parts), amygdala, hippocampus, hypothalamus, and periaqueductal gray. ROIs were obtained from the Caltech Subcortical and Amygdala Atlases (Pauli et al., 2018; Tyszka and Pauli, 2016), and the remainder were manually drawn on the population average. The Caltech atlas data were aligned to our population average T1wMRI map using ANTs diffeomorphic registration.

Given our significant findings in frontoinsular cortex, we performed a subsequent analysis investigating microstructure properties across the entire cerebral cortex, so as to determine the anatomical specificity of our results. We used a multi-modal modeling approach, in which we combined Freesurfer cortical surface models with diffusion MRI microstructure parameter maps. We processed T1wMRI data using Freesurfer version 5.3.0 to create 3D geometric models for the inner and outer cortical surface. The cortical models were aligned with dwMRI data using ANTs to computing the optimal rigid transform between the T1wMRI and average baseline diffusion image, and microstructure parameters maps were spatially normalized in the higher resolution T1wMRI space. To estimate cortical microstructure, we took a similar approach to Fukutomi et al. (2018) and used a statistical procedure to refine the alignment of the cortical surface to better match the tissue boundaries in the diffusion scan, in the event that any subtle geometric distortions remain after artifact correction. Briefly, for each subject, we computed the weighted average microstructure parameters in each vertex of the Freesurfer cortical surface, which consisted of two stages. In the first stage, the midpoint between the pial and white matter surfaces was computed and 15 sampling points were equally spaced between them. For a given microstructure parameter, the values were measured at each of the sampling point and subsequently weighted using a Gaussian function centered at the midpoint with a weight of one, with a standard deviation that gives a weighting of 0.05 at each of the inner and outer cortical boundaries. This weighting scheme is designed to

carefully isolate gray matter voxels by reducing the influence of voxels that are closer to tissue boundaries, which are more prone to partial volume effects. In the second stage, the mean and standard deviation microstructure parameters were computed and outlier values were detected and excluded using a z-score threshold of 3.0; finally, the average value was found from points that remained after outlier rejection. We then summarized the microstructure parameters in the regions defined by the HCP multi-modal parcellation (HCP-MMP-1.0), which consists of 180 cytoarchitectonically defined parcels in each hemisphere (Glasser et al., 2016). The HCP-MMP-1.0 region most closely aligned with the manually drawn frontoinsular ROI was agranular anterior insular cortex (AAIC).

Statistical Analysis

Our statistical analysis explored the relationship among behavioral and demographic variables, how they relate to cortical microstructure, and also included a validation experiment to establish the reliability and stability of our findings, as well as tests of lateralization and heritability. We used multiple linear regression modeling to examine the relationship among variables, with the following approach. All continuous model parameters were normalized to zero-mean and unit-variance to allow their regression coefficients to be reported in standardized units. We excluded outliers using Tukey's procedure, in which high and low cutoffs were determined by 1.5 times the inter-quartile range beyond the low and high quartiles, computed using the entire cohort. We retained the R^2 coefficient of determination of the model, and the statistical outcomes of each subject variable, including the standardized regression coefficient β, t-value, standard error, and p-value. The specific steps of our analyses are described next.

The first step of our analysis examined demographic and behavioral variables by measuring distributional statistics and estimating linear regression models relating life satisfaction to basic demographics (age, sex, body mass index), other cognitive and emotional variables (memory, cognition, thought problems, meaning and purpose, and positive affect), and socioeconomic factors (relationship status, income, education, and employment). We also created plots showing the relationships.

Our second step examined the relationship between life satisfaction and frontoinsular microstructure, specifically ODI and FA, separately for each hemisphere. We estimated linear regression models in a stepwise fashion to test covariates that included the other cognitive and emotional factors, socioeconomic factors, and environmental factors. To determine the anatomical specificity of our findings, we then repeated this analysis across the entire cortex and created 3D visualizations showing statistical parameters for each brain area. We performed additional post-hoc statistical tests to determine the robustness of our findings to subject motion and validate our effects with permutation tests. We summarized the total motion for each participant by computing to total translational motion accumulated across the scanning session, computed by summing the magnitudes of the volume-to-volume translation from the output of FSL EDDY. For permutation testing, we used randomization of the life satisfaction scores with 10,000 samples to estimate the null distribution of the observed effect, including the newly added motion covariate. We computed the two-sided significance in a typical way by computing the proportion of samples with an absolute effect greater than our observed effect.

Our third step performed a validation experiment, which used a secondary test-retest dataset from the Human Connectome Project with two scans collected for 44 individuals. We first measured reliability of cortical microstructure parameters using the intraclass correlation (ICC) and the coefficient of variation (CoV), with a comparison of FA and ODI metrics. Given a mean parameter value μ, a within-session variance σ_{within}, and a between-subjects variance $\sigma_{between}$, the ICC was computed by $(\sigma_{between} - \sigma_{within})/(\sigma_{between} + \sigma_{within})$, and the CoV by σ_{within}/μ. We then repeated our life satisfaction analysis to determine the replicability of the findings within each test and retest group. We grouped left and right hemisphere variables to increase the power of the analysis, and we estimated an interaction with the timepoint variable to determine if there was a difference in effect sizes across timepoints. We also computed the correlation between test-retest pairs of life satisfaction and frontoinsular cortical microstructure parameters.

Finally, we performed laterization and heritability experiments. We compare four pairs left and right microstructure parameters, which include FA and ODI in each of frontoinsular cortex and the MMP AAIC parcel. We apply a paired t-test to assess left-right differences, and we computed the lateralization index (LI) for each parameter. The LI was found by taking the ratio of the average left-right difference over the mean value of the combined left and right values, so a positive value indicates the left hemisphere had a high parameter value than the right. We computed the heritability of each microstructure parameter in a subset of the HCP cohort that were siblings. We identified sibling pairs by matching parental identifiers and then separating based on zygosity to obtain three groups: monozygotic (identical) twins, dizygotic (fraternal) twins, and non-twin siblings. We plotted microstructural parameters for each pair of twins and computed the correlation coefficient between them to determine the degree of heritability. We also computed inter-sibling differences in life satisfaction and microstructure, and we computed their correlation to further validate our findings in this sibling cohort.

Our statistical analysis was implemented using R 3.3.3, plots were created using ggplot 3.2.1 (Wickham, 2017), and tables were created using stargazer 5.2.2 (Hlavac, 2013). 3D visualizations of statistical maps overlaid on brain anatomy were created using QIT.

Results

The results of our image analysis pipeline are illustrated in Figure 1, and our primary, test-restest, and heritability results are shown in Figures 2, 3, 4, respectively. We have shared comprehensive results in the supplemental material. Our main findings are described as follows.

Demographic and Behavioral Results

Participants were 28.7 years old on average ($\sigma = 3.67$ years) across 454 female and 355 male participants, with an average life satisfaction score of 54.36 ($\sigma = 9.39$), and normal weight with average body mass index 26.51 ($\sigma = 5.24$). Life satisfaction showed no statistically significant difference between sexes ($p = 0.786$), nor with body mass index ($p = 0.094$), but with a small decrease with age ($\beta = -0.142, p = 0.001$). All considered socio-economic factors were associated with life satisfaction to some degree: income level ($\beta = 0.127, p < 0.0001$), relationship status ($\beta = 0.465, p < 0.0001$), education level ($\beta = 0.055, p = 0.006$), and employment status ($\beta = -0.138, p = 0.004$). Other measures of well-being were associated as well: meaning and purpose ($\beta = 0.044, p < 0.0001$), positive affect ($\beta = 0.046, p < 0.0001$), thought problems ($\beta = -0.111, p = 0.0001$), and cognitive performance ($\beta = 0.134, p < 0.0001$). Relationship status was split roughly equally (344 true, 435 false), education level was relatively concentrated at 16 years of education, income was fairly evenly distributed, and most were employed in full time jobs (N = 520) and fewer were part-time (N=139). Distributional summaries of demographic and behavioral data are presented in the supplemental material.

Cortical Microstructure Results

Regarding the results from our initial manually drawn region-of-interest approach, we found that frontoinsular cortical orientation dispersion was significantly associated with life satisfaction in both hemispheres (left $\beta = -0.128, p = 0.0003$; right $\beta = -0.142, p = 0.00004$), accounting for sex, body mass index, and intracranial volume (Figure 2). Sex had a significant effect as a covariate in both hemispheres (left $\beta = 0.488, p < 0.00001$; right $\beta = 0.635, p < 0.0001$). Among other cognitive and emotional factors, the only significant covariates were thought problems (left $\beta = 0.111, p = 0.003$; right $\beta = 0.096, p = 0.009$) and meaning and purpose (right $\beta = 0.013, p = 0.009$), while no socioeconomic variables showed an effect as covariate. Among environmental factors, THC exposure (left $\beta = 0.253, p = 0.031$; right $\beta = 0.498, p = 0.00002$) and paternal alcohol exposure (right $\beta = 0.273, p = 0.006$) were significant covariates. No other manually-drawn regions of interest besides frontoinsular cortex showed a significant association with life satisfaction, and no effects were found with FICVF and MD. Distributional summaries and expanded results are presented in the supplemental material.

Our expanded analysis further looked at surface-based measures of cortical microstructure and showed that the only significant cortical parcel was agranular anterior insular cortex (left $\beta = -0.078, p = 0.026$, right $\beta = -0.143, p = 0.00003$). Other covariates showed similar results as those from frontoinsular cortex, and when examining FA, the results showed similar associations, but with inverted effect sizes of smaller magnitude. Our post-hoc statistical effects showed that the inclusion of subject motion as a covariate did not change the magnitude or significance of our effects, nor did permutation-based estimates of significance. The results of these additional tests may be found in the supplemental material.

Validation Results from Secondary Data

Our first validation experiment investigated reliability of cortical microstructure metrics using the secondary test-retest HCP dataset (Figure 3). The distribution of ODI results across the cortex had an average ICC of 0.77 ($\sigma = 0.10$) and average CoV of 2% ($\sigma = 1\%$). Agranular anterior insular cortex showed a higher than average ICC (left 0.88; right 0.86) and typical CoV (left 2.1%, right 2.4%). The manually-drawn frontoinsular region showed a high ICC (left 0.84; right 0.88) and low CoV (left 1.6%; right 1.5%). In a direct comparison of test-retest values, we found a high correlation between scanning sessions of both life satisfaction ($\beta = 0.965$) and frontoinsular cortex ($beta = 0.961$). Our second validation experiment repeated the life satisfaction analysis for each of the test and retest cohorts, and found similar effects across the primary and secondary data ($\beta = 0.220, p = 0.005$). A multiple regression model showed no significant difference in ODI between timepoints and no difference between the regression coefficients of the two models ($beta = 0.041, p = 0.787$). Similar results were found with DTI FA, though with slightly lower ICC ($\mu = 0.73, \sigma = 0.13$) and higher CoV ($\mu = 3\%, \sigma = 1\%$). We found the life satisfaction score to have an ICC of 0.87 and and CoV of 3.6%. A detailed summary of these results is provided in the supplement.

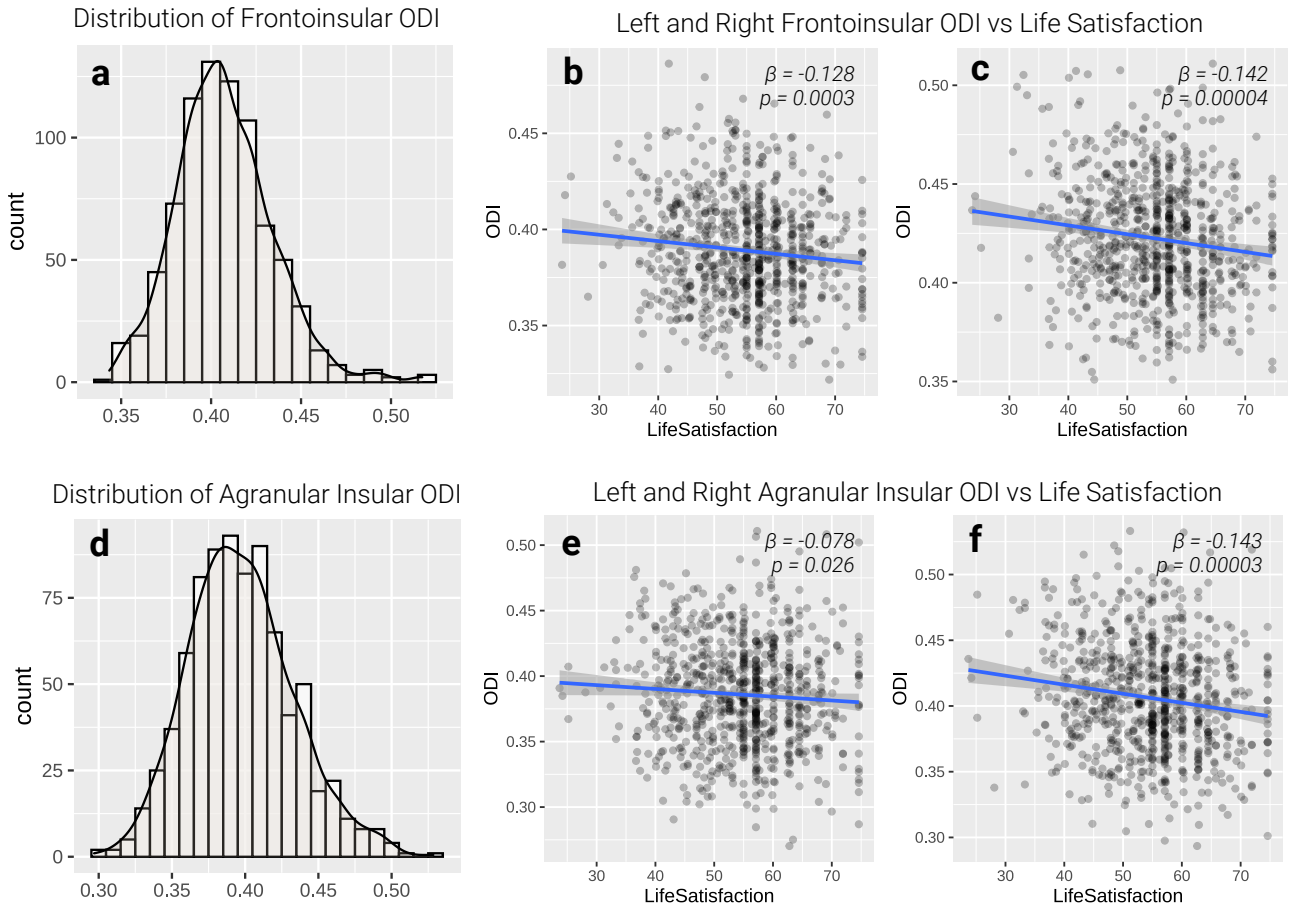

Fig. 2 Plots showing the results of our analysis comparing cortical microstructure and life satisfaction. The first panel (a) shows the overall distribution of the orientation dispersion index in frontoinsular cortex. The next two panels show the relationship between life satisfaction and frontoinsular microstructure in the left (b) and right (c) hemispheres. The first row shows results from our manually-drawn frontoinsular region, while the second row shows results from an automated surface-based approach for extracting agranular anterior insular parcel. The results show how higher life satisfaction is associated with lower dispersion, with a stronger effect in the right hemisphere. Statistical results (standardized effect size β and p-value) were obtained from multiple linear regression modeling with demographic and behavioral covariates.

Laterality and Heritability

In our tests of laterality, we found right hemisphere ODI in frontoinsular cortex to be higher than the left ($\delta = -0.033, p < 10^{-15}, LI = -0.081$), and we found right hemisphere FA in frontoinsular cortex to be lower than the left ($\delta = 0.013, p < 10^{-15}, LI = 0.071$). Similarly, we found right hemisphere ODI in AAIC to be higher than the left ($\delta = -0.020, p < 10^{-15}, LI = -0.051$), and we found right hemisphere FA in AAIC to be lower than the left ($\delta = 0.0072, p < 10^{-15}, LI = 0.045$). Thus, ODI tended to show higher lateralization than FA, and frontoinsular cortex showed higher lateralization than AAIC.

In our tests of heritability (Figure 4), we found significant heritability in ODI in frontoinsular cortex among monozygotic twins ($\beta = 0.71, p < 0.0001$), and lower heritability among non-twin siblings ($\beta = 0.244, p = 0.003$), with intermediate trend-level heritability in dizygotic twins ($\beta = 0.303, p = 0.055$). FA in frontoinsular cortex showed a similar overall trend but smaller effect sizes for all three groups: monozygotic twins ($\beta = 0.644, p < 0.0001$), dizygotic twins ($\beta = 0.275, p = 0.19$), and non-twin siblings ($\beta = 0.194, p = 0.024$). We found a similar pattern in AAIC results for ODI and FA, as well. We found life satisfaction to have significant heritability among all siblings with a lower effect size than microstructure ($\beta = 0.234, p = 0.00002$), but not when examining the twin subgroups of smaller sample size. In our comparison of inter-sibling differences in life satisfaction and microstructure, we found a significant association among all siblings ($\beta = -0.145, p = 0.008$), which is similar to our previous findings. A detailed summary of these results is provided in the supplement.

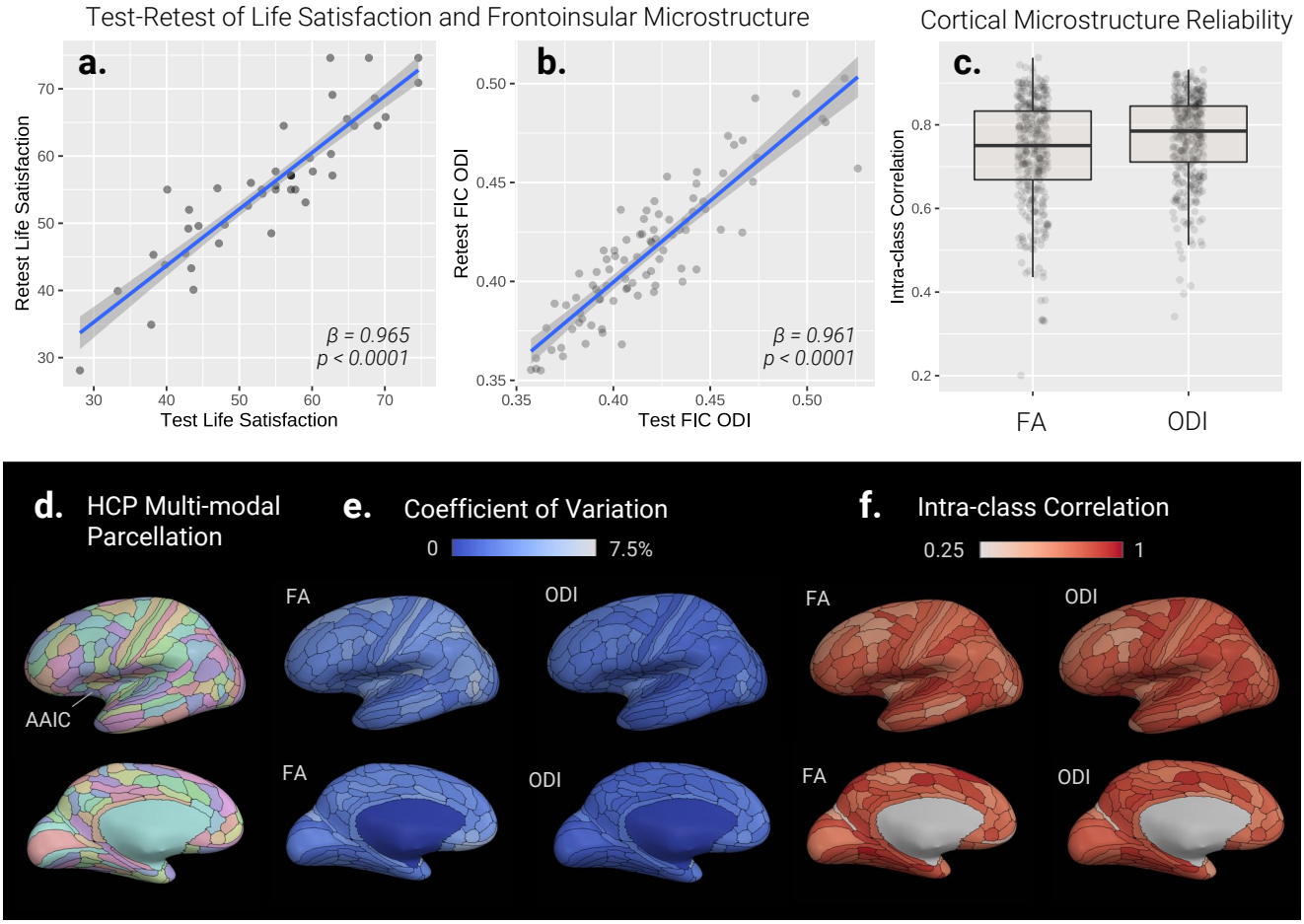

Fig. 3 Plots showing the results of our analysis of test-retest data to establish the reliability of our imaging metrics and reproducibility of our outcomes. The first row of panels shows a direct comparison between life satisfaction (a) and frontoinsular cortex (FIC) orientation dispersion (b) obtained from the same individual scanned in two different visits, where each dot represents a pair of measurements from a individual. The statistical results report the correlation β and p-value. The next panel (c) shows results from an extended reliability analysis that includes all cortical regions from the HCP multi-modal parcellation, where each dot represents the intra-class correlation of a single cortical parcel. These results are plotted on an group-averaged inflated cortical surface in the next row, showing the HCP multi-modal parcellation (d), and per-parcel reliability scores for the coefficient of variation (e) and intra-class correaltion (f). The intraclass correlation measures the inter-scan variability relative to inter-subject variability (higher values are more reliable), and the coefficient of variation is the percentage variation across multiple scans (smaller is more reliable). Overall, the results demonstrate high agreement of frontoinsular metrics between the scanning sessions, as well as generally high reliability of cortical microstructure parameters, with slightly better performance in orientation dispersion than fractional anisotropy.

Discussion

The results reported here demonstrate a robust linkage between individual judgements regarding life satisfaction and microstructural features of cortical gray matter in young adulthood. Specifically, we show these findings are specific to frontoinsular cortex, and not other cortical and subcortical brain areas; furthermore, our observed microstructural associations are independent of other behavioral and socioeconomic factors that otherwise relate to life satisfaction itself. We obtained very similar results from anterior agranular insular cortex (AAIC) which was delineated by Freesurfer and substantially overlaps with the manually defined frontoinsular cortex based on expert knowledge of the area. Further evidence for the robustness of these findings comes from a set of 40 individuals in which both the life satisfaction measure and microstructural brain imaging were repeated at varying intervals after the initial observations had been made. Both the life satisfaction measures and their relationships with ODI and FA were well maintained upon retesting and were independent of the length of the interval between the initial test and the repeat. We also showed that these cortical microstructural metrics have a moderate degree of lateralization and heritability.

Life satisfaction is understood to be multi-faceted in nature (Peterson et al., 2005), and in our examination of demographic variables we also found a diverse set of associations among behavioral and socioeconomic factors. In

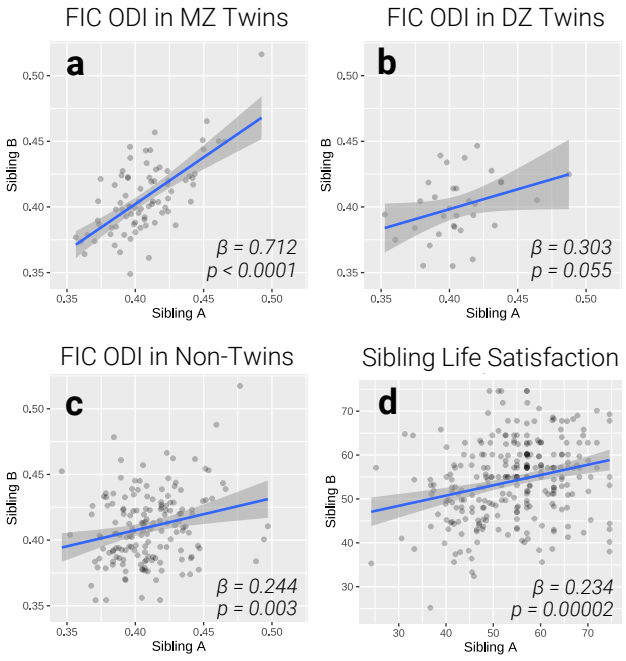

Fig. 4 Plots showing the results of our analysis of heritability in the sibling cohort. The siblings pairs were subdivided into monozygotic (MZ) twins (a), dizygotic (DZ) twins (b), and non-twin siblings (c), and the frontoinsular cortex (FIC) microstructure parameters corresponding to each twin pair are plotted. The fourth panel (d) shows the heritability of life satisfaction among all siblings. The shown statistical results report the paired correlation β and associated p-value between the siblings. Overall, the data show high heritability of microstructure in MZ twins and lower heritability in non-twin siblings, with intermediate and trend-level heritability in DZ twins. Life satisfaction showed significant heritability in all siblings, but with a lower effect size than microstructure.

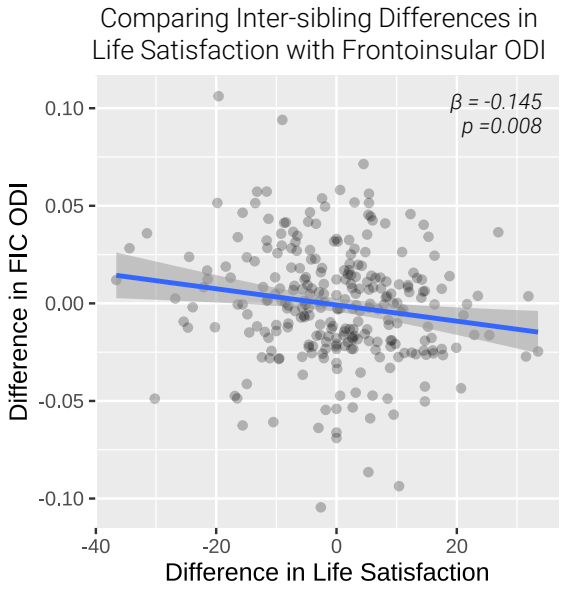

Fig. 5 A comparison of life satisfaction and microstructure in siblings. For each sibling pair, the inter-sibling differences in life satisfaction and microstructure were computed and plotted, where each dot represents a related pair of individuals. The data show an analogous pattern to our main outcome, where positive differences in life satisfaction statistically correspond to negative differences in microstructure, and vice-versa.

particular that life satisfaction reflects socioeconomic variation in income, relationship status, education, and employment, which are in line with previous findings by Melin et al. (2003), who found that education, being vocationally active, and having a steady partner were predictive of life satisfaction. Beyond this, others have found relevant mediation effects with relationship status Zhu et al. (2018), loneliness and social support (Kong and You, 2013). We further found associations with other measures of subjective well-being, findings that support previous work showing the connection of life satisfaction to different orientations to happiness (Peterson et al., 2005). In contrast, we found the microstructural association with life satisfaction to be independent of these same behavioral and socioeconomic factors. The two significant covariates explaining variance in microstructure were thought problems (negative and self-destructive thoughts) and sex, with the latter having a stronger effect. However, these factors showed no direct relation to life satisfaction, and thus the results may reflect the diverse function of frontoinsular cortex, which partly contributes to life satisfaction. These observed sex differences are notably divergent from previous work examining diffusion metrics in cortical gray matter (Schmitz et al., 2019); however, besides coming from a different population, there are methodological differences in the present work, wherein we used approaches for NODDI model fitting and surface-based cortical mapping which may provide more robust parameter maps.

Life satisfaction is often approached theoretically with the concept of a set-point, that is, there are regulatory system that maintain a constant level over time that is unperturbed by life events and changing circumstances (Fujita and Diener, 2005). Frontoinsular cortex is understood to be involved in processes of interoception, affective awareness, and error prediction, which are all critical to homeostatic regulation (Critchley, 2005; Craig, 2009). Homeostasis and set-point theory offer somewhat converging concepts, but there are open questions related to their temporal stability. Lykken and Tellegen (1996) conducted a large twin study and concluded that level of happiness is a strongly determined genetic trait (heritability = 0.44 to 0.52), suggesting a stable set-point over life. More recently, the heritability of life satisfaction specifically has been measured in 10 separate twin studies (total N=44,450). A meta-analysis of these studies found an average heritability index of 0.32 with a 95% confidence range between 0.29 and 0.35 (Bartels, 2015). While these finding indicate a moderate genetic ba-

sis for life satisfaction, thus supporting the set-point theory, they also imply a fair degree of lability over time, dependent on life circumstances. Longitudinal studies have shown that stability varies among different subsets of the subjects and tend to be less stable over time than biometric variables such as height, BMI and blood pressure (Fujita and Diener, 2005). We did not find any changes with age, but given the limited age range of our cohort, a larger study is needed to determine how microstructural parameter relate to well-being in aging. The longitudinal study of Bartels (2015) found stability only for some individuals over time, and (Kubiszewski et al., 2020) found stability only in a high life satisfaction sub-cohort. In line with these findings, we observed moderate heritability of imaging-derived microstructure parameters, which suggests the possibility of some amount of shared genetic basis for frontoinsular characteristics and life satisfaction. Our comparison of inter-sibling differences showed a similar outcome to our main findings, which provides further support.

We may consider a number of neurobiological factors that explain our findings, and as our findings were localized to only frontoinsular cortex, we may focus on diffusion MRI features of gray matter architecture. These effects were limited to differences in the orientation dispersion index, and by extension fractional anisotropy. While there are many factors that are known to affect fractional anisotropy, the biophysical and multi-compartment modeling approach of NODDI may allow for some of these to be differentiated. Specifically, this may reduce the influence of partial volume effects with cerebrospinal fluid and perivascular space effects (Sepehrband et al., 2019), and separate orientation-dependent effects from neurite density. Theoretically, the orientation dispersion index reflects the heterogeneity in the distribution in the direction taken by neurites, so increased ODI may suggest differences in dendritic complexity (Broad et al., 2019), the presence of undulating fibers (Hagslätt et al., 2010), or perhaps, relative differences in distinct morphological cell types that make up frontoinsular cortex. This last point raises a question if these findings may be explained by variation in von Economo Neurons (VENs) (Nimchinsky et al., 1999). VENs are large neurons with a distinct spindle-shaped bipolar morphology, oriented radially and extending over several cortical layers (Watson et al., 2006) (Allman et al., 2010) (Seeley et al., 2011), which presumably would decrease the orientation dispersion index and increase fractional anisotropy as their overall count increased. Previous work has found VENs to be preferentially depleted in fronto-temporal dementia (Seeley et al., 2006; Kim et al., 2012), and more prevalent in those with preserved cognition in extreme old age (Gefen et al., 2018). VENs are most abundant in frontoinsular and anterior cingulate cortices, and stereological VEN counts have also consistently shown a higher number in the right hemisphere (Allman et al., 2010), which is in accordance with the laterality observed in our findings of decreased ODI and increased FA with greater life satisfaction in frontoinsular cortex. However, VENs make up only a small portion of total cell count, so further validation work is necessary to determine the extent to which the distribution of VENs can be detected with MRI. Another factor to consider in our findings is that ODI may reflect changes in microglia density, a possibility which is supported by the observations of Yi et al. (2019) , who used genetic tools in a rodent model to demonstrate a parametric association between microglia density and NODDI parameters.

This array of possible factors may also act in concert to produce the MR observable changes, and whether alone or together, they would likely produce alterations in the function of frontoinsular cortex. Previous work has found frontoinsular cortex to be a key component of regulatory processes in the brain (Allman et al., 2010; Nieuwenhuys, 2012), including interoceptive awareness (Craig, 2009), emotional awareness (Gu et al., 2013), salience processing (Seeley et al., 2007), which each play a part in homeostasis. Life satisfaction and well-being are the products of homeostatic mechanisms. The moderate degree of heritability of life satisfaction and well-being suggest that the homeostatic mechanisms underlying them are also heritable to some degree. The findings that the relationships between ODI and FA and life satisfaction are independent of the more transitory factors contributing to life satisfaction, such as relationships and employment, imply that there might be a significant connection between these measures of cortical microcircuitry and the homeostatic bases of life satisfaction. A relevant element of life satisfaction is that it is based on an individuals own judgements and expectations, and indeed, frontoinsular cortex and anterior insular are involved in such processing, as it serves as interceptive monitor of well-being (Craig, 2011), is involved in prediction error and error awareness (Ullsperger et al., 2010), and is associated with humor and sight gags (Watson et al., 2007). Furthermore, this may extend to a more general sense of well-being, as we also found a significant microstructural association with meaning and purpose, albeit with a small effect that was limited to only right frontoinsular cortex (and not found in AAIC). Conversely, insular cortex is also related to negative thinking, through its participation in the functional salience network (Lydon-Staley et al., 2019), and insular volume is inversely related to depression (Clark et al., 2010). The aspects of insular cortex relate to our findings, as negative intrusive thinking, or thought problems, was a significant covariate in explaining microstructural variation in frontoinsular cortex.

We designed our experiments to use high quality data and methods, but they are not without limitations. MRI itself introduces a limit on the quality and specificity of our measurements. Imaging artifact was minimized to the degree possible, but it still can affect our results; for example,

diffusion imaging of orbitofrontal cortex and frontal pole is affected greatly by susceptibility artifact, and even with our correction for geometric distortion, we may not collect sufficient signal to model these areas and rule out effects that may occur there. In contrast, we found artifact to be relatively low in frontoinsular cortex, and found deformable image registration to be as effective as the multi-modal surface-based approach in this region. In fact, we found several results had a larger effect size when using the manually drawn ROI. Besides artifact, there are also limitations related to diffusion MRI modeling. Tissue microstructure is necessarily more complex than depicted by the diffusion signal, so some simplifications are required to derive useful models and to accommodate limited resources for scanning. NODDI makes simplifying assumptions regarding the diffusivities of the intra-cellular, extra-cellular, and free-water compartments, which potentially bias results if they are incorrect (Guerrero et al., 2019). However, we tried to address this by performing NODDI modeling with fixed diffusivities that are optimized for gray matter; furthermore, we added DTI analysis for comparison, as it makes fewer modeling assumptions. One interesting result was that NODDI systematically was more sensitive to our observed effects, as evidenced by greater effect sizes and smaller p-values, which may suggest that the modeling choices in NODDI are reducing the variance in microstructural parameters that are relevant to life satisfaction. Despite these limitations, there are ways to possibly address these issues in later work. For example, advanced diffusion imaging sequences, such as q-space trajectory imaging (Westin et al., 2016) and diffusion-relaxometry (Gong et al., 2020), can potentially resolve differences between microscopic anisotropy and cell size; furthermore, a combination of MRI and microscopy can reveal and validate the precise relationship between cellular level features and those observable with MRI (Goubran et al., 2019). These approaches are not yet feasible at a scale comparable to the Human Connectome Project, but future studies employing these methods could be focused specifically on frontoinsular cortex, given our results.

Conclusion

In conclusion, this study sheds new light on neurobiological factors that may underly subjective well-being in young adults. Using a large cohort of high-quality data from the Human Connectome Project and state-of-the-art image modeling and analysis techniques, our experiments identified the orientation dispersion index (and by extension, fractional anisotropy) of frontoinsular cortex as a robust anatomically-specific diffusion MRI feature that is linked to life satisfaction, independent of other demographic, socioeconomic, and behavioral factors. We further validated our finding in a secondary test-retest dataset showing high reliability of our imaging metrics and reproducibility of our outcomes. Our results suggest a possible link with microscopic features of frontoinsular cortex, which may reflect cellular morphology and architecture; more broadly, they may implicate the integrity of the homeostatic processing performed by frontoinsular cortex as an important component of an individual's judgements of life satisfaction.

Declarations

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Conflicts of interest/Competing interests. The authors have no conflict of interest to report.

Ethics approval. This project received approval from the University of Southern California Institutional Review Board and approval from the Human Connectome Project for Restricted Access from ConnectomeDB.

Consent to participant. Written informed consent was obtained from all individual participants as part of the conduct of the Human Connectome Project.

Availability of data and material. Data used in our study is available with permission from the Human Connectome Project [2]. Our data image analysis and visualization tools available online as part of the Quantitative Imaging Toolkit (QIT) [3] [4].

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