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Social network diversity and white matter microstructural integrity in humans

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Diverse aspects of physical, affective and cognitive health relate to social integration, reflecting engagement in social activities and identification with diverse roles within a social network. However, the mechanisms by which social integration interacts with the brain are unclear. In healthy adults ($N = 155$), we tested the links between social integration and measures of white matter microstructure using diffusion tensor imaging. Across the brain, there was a predominantly positive association between a measure of white matter integrity, fractional anisotropy (FA), and social network diversity. This association was particularly strong in a region near the anterior corpus callosum and driven by a negative association with the radial component of the diffusion signal. This callosal region contained projections between bilateral prefrontal cortices, as well as cingulum and corticostriatal pathways. FA within this region was weakly associated with circulating levels of the inflammatory cytokine interleukin-6 (IL-6), but IL-6 did not mediate the social network and FA relationship. Finally, variation in FA indirectly mediated the relationship between social network diversity and intrinsic functional connectivity of medial corticostriatal pathways. These findings suggest that social integration relates to myelin integrity in humans, which may help explain the diverse aspects of health affected by social networks.

Keywords: social network; diffusion tensor imaging; white matter; inflammation; connectivity; resting state fMRI

INTRODUCTION

Aspects of the social environment affect physical health in humans. For example, increasing social integration predicts greater longevity and many positive long-term health outcomes (House *et al.*, 1988; Berkman *et al.*, 2004; Cohen, 2004; Holt-Lunstad *et al.*, 2010). Emerging research also shows that social network characteristics are associated with measures of neural integrity (Yang *et al.*, 2013). For example, neuroimaging studies demonstrate that people with larger and more diverse social networks have larger brain volumes and greater functional connectivity in emotional salience processing networks (Bickart *et al.*, 2011, 2012), while larger social networks are indirectly associated with greater volume in the orbital prefrontal cortex, an area implicated in social cognition (Powell *et al.*, 2012).

The relationship between social networks and the brain is not restricted to humans. In monkeys, neocortical regions important for processing social signals, including the rostral prefrontal cortex and amygdala, increase in volume with social network size (Sallet *et al.*, 2011). Social isolation in adult mice causes reversible changes in prefrontal oligodendrocytes and hinders myelin repair in white matter (Liu *et al.*, 2012). In young mice, however, the detrimental effects of social isolation on prefrontal myelin thickness are irreversible (Makinodan *et al.*, 2012). The white matter changes in socially isolated animals associate with elevated pro-inflammatory cytokines like interleukin-6 (IL-6; Hermes *et al.*, 2006; Karelina *et al.*, 2009), suggesting a molecular basis for changes in the body with inflammation in the brain (Rosano *et al.*, 2012). With the exception of a recent study examining overall brain volume (James *et al.*, 2012), the human imaging literature has largely ignored the relationship between white matter integrity and social network structure. Yet a growing body of literature supports a connection between inflammatory markers and aspects of an individual's social network. For example, elevated IL-6 and C-reactive protein (CRP) levels are present in less socially integrated men (Häfner *et al.*, 2011).

Furthermore, inflammatory cytokines are known to have a role in initiating 'sickness behavior', which includes symptoms such as social withdrawal (Dantzer *et al.*, 1998). It is possible that inflammation leads to feelings of social disconnection and withdrawal (Eisenberger *et al.*, 2011). There is also emerging work showing a link between inflammation and white matter structure in humans (Miralbell *et al.*, 2012; Arfanakis *et al.*, 2013; Verstynen *et al.*, 2013), and this pathway mediates relationships between social factors, like socioeconomic status, and white matter integrity (Gianaros *et al.*, 2013). Taken together, these findings support the idea that aspects of the social environment relate to white matter structure in humans, possibly via inflammatory pathways.

Here, we explored whether social network characteristics are associated with inflammation and white matter structure in humans. In a sample of neurologically healthy midlife adults, we measured global white matter integrity using diffusion tensor imaging (DTI) and evaluated social network size (number of people in the social network) and diversity (number of social roles) using the Social Network Index (SNI; Cohen *et al.*, 1997). We hypothesized that more diverse and larger social networks would be associated with greater white matter integrity, i.e. larger fractional anisotropy (FA) and smaller radial diffusivity (RD), and that this relationship would be mediated by circulating CRP and IL-6. We further predicted that these social associations with white matter have corresponding implications for the functional dynamics of communication between connected brain areas.

METHODS

Participants

Participants were 155 community-dwelling adults (78 men) who were recruited via mass mailings to residents of Allegheny County, Pennsylvania (USA). Table 1 lists all relevant participant

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Table 1 Associations between demographic, socioeconomic, affective factors and health factors and each social network measure

	SNI Diversity		SNI Size	
	r	*P*	*r*	*P*
Age	**0.173**	**0.031**	**0.159**	**0.048**
Sex	−0.004	0.960	−0.123	0.126
Income	**0.273**	**0.001**	**0.319**	**<0.0001**
Education (years)	**0.205**	**0.010**	**0.257**	**0.001**
Waist	0.018	0.820	0.015	0.856
SBP	0.040	0.623	0.104	0.197
DBP	−0.025	0.760	0.050	0.536
Smoking	$\beta = -0.186$	0.104	$\beta = -0.062$	0.210
PSQI (duration)	−0.057	0.484	−0.087	0.290
PA	**0.214**	**0.008**	**0.241**	**0.003**
NA	−0.002	0.976	−0.077	0.340
ISEL	**0.187**	**0.020**	**0.170**	**0.035**

All associations, except for smoking status, were estimated using a non-parametric Spearman's rank order correlation test. Smoking status associations were determined using an iteratively reweighted binary regression routine. Statistically significant ($p < 0.05$ uncorrected) associations are indicated in bold.

demographics. A complete description of this sample is reported by Gianaros *et al.* (2013). All participants were screened for pre-existing health conditions. Informed consent was obtained before testing with approval from the University of Pittsburgh Institutional Review Board.

Social network assessment

All participants completed a questionnaire assessing the structure of their social networks. We evaluated two descriptive metrics of social networks that have been associated with neuromorphology and brain function (Bickart *et al.*, 2011, 2012).

(i) Diversity: assesses participation in 12 social roles (e.g. friends, family, church member). One point is assigned for each role (possible score of 12) for which respondents indicate that they speak (in person or on the phone) to someone in that relationship at least once every 2 weeks (Cohen *et al.*, 1997).
(ii) Size: assesses the number of people with whom the respondent has regular contact (i.e. at least once every 2 weeks). To calculate network size, we computed the number of people with whom the respondent has regular contact within each of the 12 social roles, and then summed across the 12 roles (Cohen *et al.*, 1997).

Physiological, psychosocial and health measures

We examined two markers of inflammation in a subset of subjects ($N = 135$ for CRP; $N = 126$ for IL-6).

(i) IL-6 levels in pg/ml were determined using a high-sensitivity quantitative sandwich enzyme immunoassay kit (R & D Systems). IL-6 levels were extrapolated from a standard curve with linear regression from a log-linear curve. All samples were run in duplicate, and the average coefficient of variation (CV) between samples was 10%. Prior to analysis, IL-6 values [mean = 1.79, standard deviation (s.d.) = 1.84] were natural log transformed.
(ii) Circulating levels of high-sensitivity CRP in mg/dl were assayed on a SYNCHRON LX System (Beckman Coulter, Inc., Brea, CA, with precision values of 5.0%CV within-run and 7.5%CV total for serum assays). Prior to analyses, CRP values (mean = 0.28, s.d. = 0.47) were natural log transformed.

Two measures of socioeconomic status were also assessed at the initial testing session.

(i) Education was assessed by having participants report the number of years of schooling they had completed before the time of testing (mean = 17.12, s.d. = 3.2).
(ii) Pre-tax income was assessed by having participants indicate their annual household earnings in the US dollars on a 15-point scale ranging from <$10 000/year (or $0–833/month) to >$185 000/year (or >$15 417/month). See details on scale construction and computation in Gianaros *et al.* (2013).

Four measures of general physical health were collected.

(i) Waist circumference, as a measure of central adiposity, was measured at end expiration to the nearest one-half inches with a tape measure centered at the umbilicus (mean = 35.64, s.d. = 5.17 in).
(ii) Seated, resting blood pressure (BP) was measured from the non-dominant arm with an oscillometric device (Critikon Dinamap 8100, Johnson & Johnson, Tampa, FL). Participants provided three measures taken 2 min apart after a ∼20-min acclimation period, with the average of the last two of the three BP readings serving as the resting systolic (SBP) and diastolic (DBP) BPs (SBP, mean = 121.44, s.d. = 9.48; DBP, mean = 73.25, s.d. = 8.80).
(iii) Smoking status was measured by self-report, using a binary classification variable where 0 indicates non-smoker or former smoker, 1 indicates current smoker (25 smokers total).
(iv) Quality of sleep was measured using the Pittsburgh Sleep Quality Index (PSQI; Buysse *et al.*, 1989) that ranks total sleep quality on a scale between 0 and 21, with scores 5 or less reflecting good sleep quality and scores greater than 5 reflecting poor sleep quality (mean = 4.53, s.d. = 2.52).

Finally, we assessed trait positive and negative emotionality and social support.

(i) Dispositional positive and negative emotionality were assessed using the trait positive and negative affect scales of the positive affect (PA) and negative affect (NA) schedule (Watson *et al.*, 1988; PA mean = 3.58, s.d. = 0.59; NA mean = 1.61; s.d. = 0.52).
(ii) Perceptions of social support were evaluated using the interpersonal support evaluation list (ISEL) scale (Cohen and Hoberman, 1983). This is a list of 40 statements that focus on the perceived availability of potential social resources (mean = 3.47, s.d. = 0.45).

MRI acquisition

All imaging was performed on a 3 T Trio TIM whole-body MRI scanner (Siemens, Erlangen, Germany), equipped with a 12-channel phased-array head coil. DTI was performed using a pair of pulsed-gradient, spin-echo sequences with a single-shot echo-planar imaging (EPI) readout. A parallel imaging algorithm (generalized auto-calibrating partial-parallel acquisition; GRAPPA) was applied during diffusion imaging to reduce echo-planar distortion. DTI parameters were: time-to-repetition (TR) = 5800 ms; time-to-inversion (TI) = 2500 ms; time-to-echo (TE) = 91 ms; flip angle = 90°; pixel size = 2 × 2 mm; resolution = 128 × 128 [with field-of-view (FOV) = 256 × 256 mm]; 43 slices of 3-mm thickness with no gap and total imaging time = 6 min and 19 s. Diffusion-sensitizing gradient encoding was applied in 30 uniform angular directions with a diffusion weighting of $b = 1000\ \mathrm{s/mm^2}$. A reference image with no diffusion gradient ($b = 0$) was also acquired. The acquisition sequence was repeated twice to improve the DTI signal-to-noise ratio. Usable DTI data were available for 145 participants.

Resting state functional blood oxygenation level dependent BOLD images were acquired with a gradient-echo EPI sequence (FOV = 205 × 205 mm; 64 × 64 matrix; TR = 2 s; TE = 28 ms; flip angle = 90°) for 5 min and 6 s. During scanning, participants were asked to keep their eyes open while resting quietly. Thirty-nine slices (3-mm thick, no gap) were obtained for each TR, yielding 150 images (the first three images were discarded, allowing for magnetic equilibration). A structural image used for functional image co-registration and normalization was collected using a T1-weighted 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence (FOV = 256 × 208 mm; 256 × 208 matrix; TR = 2100 ms; TI = 1100 ms; TE = 3.29 ms; flip angle = 8°; 192 slices; 1-mm thick, no gap). Usable resting state data were available for 110 participants.

DTI analysis

All DTI data were processed using the FSL Diffusion Toolbox (v2.0), which used the following steps: correction for motion and eddy current distortions by affine registration to the reference image, removal of skull and non-brain tissue, and calculation of diffusion parameters by fitting the diffusion images to a diffusion tensor model. Within each voxel three estimates of water diffusion patterns were calculated: FA, RD and axial diffusivity (AD). FA is a common white matter measure derived from DTI, and it represents the 'shape' of the underlying water diffusion in each voxel. AD and RD reflect subcomponents of the FA measure that define the length and width of the estimated tensor, respectively.

All FA images were normalized to the 1 mm^3 Montreal Neurological Institute (MNI) stereotaxic space via the FSL FA template (FMRIB58_FA). This was done by combining two transformations: (i) a non-linear registration of each participant's FA image to the FMRIB59_FA template, and (ii) an affine transformation of the template to MNI152 space. These non-linear and linear normalization parameters were then applied to the AD and RD maps. Finally, all maps for each subject were spatially smoothed using a 2 mm^3 FWHM isotropic Gaussian kernel.

To quantify head motion in each DTI scan, we used a similar procedure to Yendiki *et al.* (2013). We calculated the average volume-by-volume translation and rotation, and the percentage of slices with signal dropout. Slices with a score greater than 1 have suspect signal dropout. Signal dropout severity was calculated over all slices in the scan that were greater than 1.

Structural connectivity was assessed on a tractography template (the CMU-60 template) comprised of averaged diffusion information across 60 neurologically healthy controls (29 male, mean age = 26) that underwent a 257-direction diffusion spectrum imaging sequence. Details of this template can be found here http://www.psy.cmu.edu/~coaxlab/?page_id=423, and the general procedures are described in Yeh and Tseng (2011). Clusters that were identified from the DTI analysis as being statistically significant to either SNI factor, after adjustment for multiple comparisons (false discovery rate; FDR < 0.05) and cluster size ($k > 40$), were loaded into the CMU-60 template. A set of 20 000 streamlines was tracked through this region of interest (fiber threshold = 0.05, max turning angle = 75°, step size = 1 mm)using a modified deterministic tractography method (Yeh et al. 2013). This set of streamlines was then hand segmented into four subsets (corpus callosum, cingulum, corticostriatal and hypothalamic projections) based on pairwise start and end locations.

Resting state fMRI analysis

Resting BOLD images were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). BOLD images were realigned to the first series image, co-registered to the MPRAGE and normalized to MNI space using the SPM template. Normalized images were smoothed with a 6 mm^3 FWHM isotropic Gaussian kernel and re-sliced to 2 mm^3 voxels. The contiguous clusters of the tractography endpoints larger than 50 voxels were selected as regions of interest (ROIs) for connectivity analysis. The connectivity between each pair of ROIs was assessed by the cross-correlation of the mean BOLD time series in the regions. Before the assessment, the time series in each voxel was de-trended, de-spiked, mean-centered and adjusted for the confounding covariance due to movement, physiological noise and hemodynamic response using regression method. The parameters estimated from rigid body transformation were used as the movement regressors. The physiological noise was modeled by the component-based method (Behzadi *et al.*, 2007) with three principle components of BOLD time series from a white matter mask and two principle components from a cerebral spinal fluid (CSF) mask. The masks were constructed using the SPM MNI templates of 90 and 75% probability maps for white matter and CSF, respectively; they were further eroded to avoid partial volume effect. The hemodynamic response was modeled by the SPM default hemodynamic response function and its derivative. After the adjustment, the BOLD signals were bandpass filtered for the frequencies between 0.08 and 0.15 Hz and submitted to the connectivity analysis.

RESULTS

Social network size and diversity

We first examined the associations of network indices with various demographic, social, affective and health factors (See Table 1). In general both diversity and network size were associated with similar measures, including age, income, education, PA and ISEL scores. Only network size was associated with current smoking status. There was no difference between men and women in social network size [$t(154) = 0.029$, $P = 0.33$] or diversity [$t(154) = 0.963$, $P = 0.87$]. Moreover, neither network measure was associated with measures of physical or cardiorespiratory health. In the analyses later, we control for central adiposity, age, sex and years of education because these factors are plausible confounds of white matter structure and inflammatory measures.

Inflammation and social network structure

After controlling for central adiposity, age, sex and years of education, IL-6 was negatively associated with the diversity of a person's social network [$r(128) = -0.194$, $P = 0.027$], but uncorrelated with social network size [$r(128) = -0.088$, $P = 0.319$]. We did not find a relationship between network diversity and CRP [$r(137) = 0.04$, $P = 0.638$]. CRP was also not correlated with social network size [$r(137) = 0.125$, $P = 0.144$]. Finally, as expected CRP and IL-6 were moderately correlated with each other [$r(120) = 0.415$, $P < 0.0001$].

White matter and social network structure

We found that across all white matter voxels there was a predominant positive association between FA and diversity of a person's social network (mean = 0.012 ±0.039 s.d.; Figure 1A and B), after controlling for age, sex, education and central adiposity, which have all be found to be independently associated with measures of white matter integrity (Westlye *et al.*, 2009; Gianaros *et al.*, 2013; Verstynen *et al.*, 2013). This means that in a numerical majority of voxels, individuals with more high-contact roles had greater microstructural white matter integrity. In the uncorrected statistical maps, we found several independent clusters with strong positive associations to diversity (Figure 1A), including near prefrontal boundaries of the dorsal medial prefrontal cortex, considered part of the 'social brain' (Lewis *et al.*, 2011; Powell *et al.*, 2012).

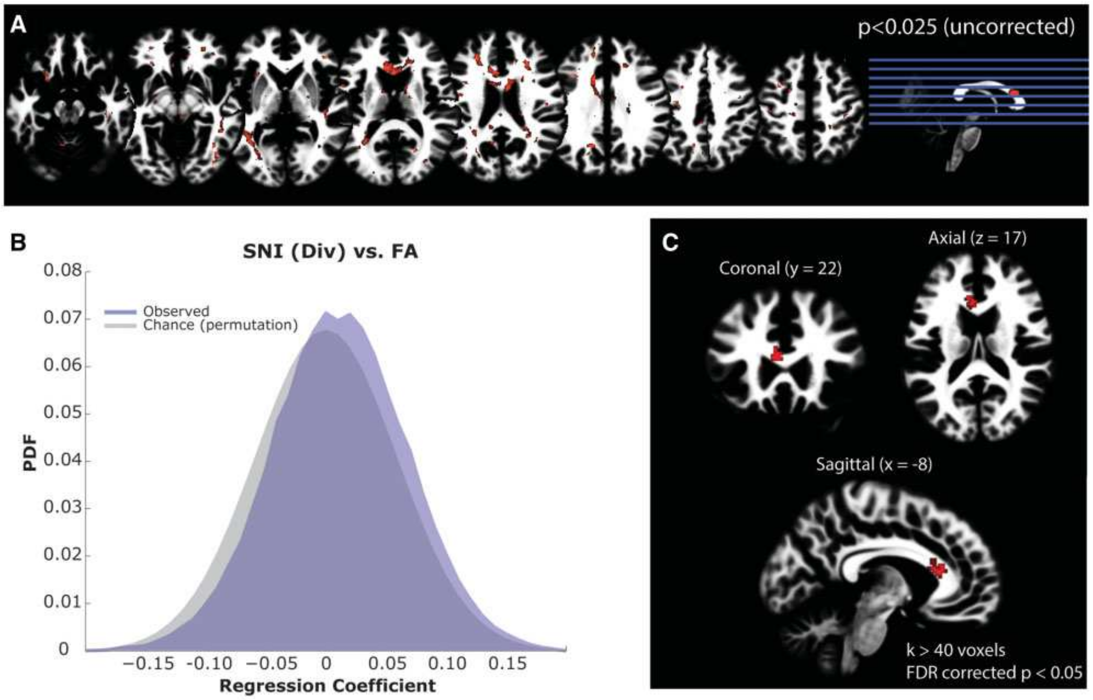

Fig. 1 (A) Uncorrected maps ($P < 0.025$) showing the voxels with strong positive (red) and negative (blue; none survive thresholding) associations with the SNI measure of diversity [SNI (Div)] and FA. (B) Probability distribution of regression coefficients between SNI (Div) and FA across all white matter voxels shown in panel A. The purple distribution shows the observed values, while the gray distribution shows the average distribution shape across a set of randomized permutation tests designed to model the null effect. (C) Location of the strongest cluster of voxels in the brain, with associations that survive multiple comparison corrections (FDR < 0.05) and clusterwise adjustments ($k > 40$).

Although there was a global positive association between network diversity and FA across a majority of voxels (Figure 1A and B), this effect was particularly strong in a cluster of voxels near the posterior section of the genu of the corpus callosum (Figure 1C). This large cluster of voxels surpassed both multiple comparison correction (FDR < 0.05) and cluster size thresholding ($k > 40$). No such patterns were observed for social network size, thus, no further exploratory analysis was done on this measure.

To ensure that head motion did not interfere with the associations between SNI and FA (Yendiki *et al.*, 2013), we ran a linear regression between the two SNI variables and head motion parameters. We found no significant correlations between SNI and head motion (all r's < -0.137, all P's > 0.11); thus, spurious differences in head movement during the scans cannot account for the relationship between SNI diversity and FA that we detected.

In order to assess whether the association between SNI diversity and FA in this cluster is driven by particularly low diversity individuals, as would be predicted by the social isolation findings in rodents (Liu *et al.*, 2012), we segmented the sample into three groups: low social diversity (<5 roles, $n = 38$), moderate diversity (between 5 and 7 roles, $n = 65$) and high diversity (8 or more roles, $n = 42$). The unadjusted FA values within the corpus callosum cluster were extracted and averaged across groups. After controlling for age, sex, education and central adiposity, FA increased consistently with each diversity group (Figure 2A), with a significant difference between low- and high-diversity individuals [$t(79) = 2.79$, $P = 0.008$] and marginal differences between low and medium diversity groups [$t(106) = 1.48$, $P = 0.14$] and medium and high-diversity groups [$t(102) = 1.46$, $P = 0.14$]. Thus, the FA associations within this cluster are not driven exclusively by low or high-diversity individuals.

Within the SNI-related cluster RD decreased as social network diversity increased, after age, sex, education and central adiposity were controlled for (Figure 2B; $r = -0.15$, $P = 0.021$). As with FA, we observed a significant difference between low and high-diversity subjects [$t(79) = 2.04$, $P = 0.044$], but no difference between low and medium diversity individuals [$t(106) = 1.55$, $P = 0.12$] or medium and high-diversity individuals [$t(102) = 0.72$, $P = 0.47$]. Unlike RD, we did not observe a significant group effect on AD within the cluster (Figure 2C; $\beta = -6.55 \times 10^{-7}$, $P = 0.45$, Spearman's $r(145) = -0.05$, $P = 0.200$). This selective association with the radial component of the diffusion signal is consistent with patterns seen in animal models of demyelination (Klawiter *et al.*, 2011).

Previous observations in rodents (Hermes *et al.*, 2006; Karelina *et al.*, 2009) predict that inflammatory factors should be moderately associated with white matter structure. Within the SNI-related cluster we found that, after controlling for age, sex, education and central adiposity, FA was negatively correlated with circulating levels of IL-6 (Figure 3; Spearman's $r(126) = -0.14$, $P = 0.017$), and trending, but not significant, when correlated against circulating CRP (Spearman's $r(135) = -0.12$, $P = 0.084$). However, no such correlation was observed between IL-6 and either RD [$r(126) = 0.07$, $P = 0.165$] or AD [$r(126) = -0.09$, $P = 0.096$]. This negative association between IL-6 and FA generally suggests that inflammation may be playing a role in white matter variation. However, this trend disappears after controlling for age and sex (all P's > 0.1), thus negating IL-6 as a mediating variable within this sample.

Finally, we expanded our analysis to include a full set of psychosocial and health factors against the cluster-wise FA values. These results are shown in Table 2. Of these factors only smoking status correlated with FA within the target cluster. This association is consistent with a possible inflammation link to the FA variation in this region. However, given the lack of association with socioeconomic and general health factors that correlated with social network measures, it is unlikely that this SNI and white matter association is the mediated by

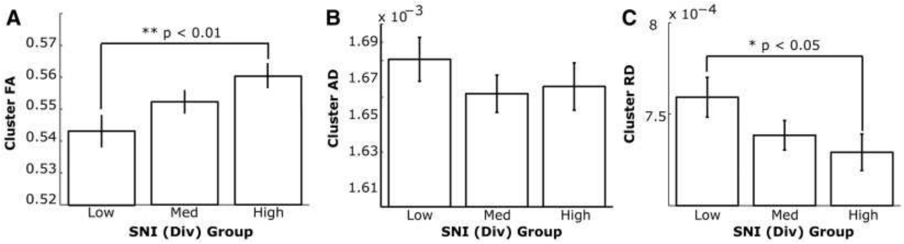

Fig. 2 (A) Average cluster FA for each SNI (Div) group. Subjects were assigned to groups based on which tertile of the social network distribution they fell into. The same values for AD and RD with the cluster are shown in panels B and C, respectively. See text for statistical results. All error bars show the standard error of the mean.

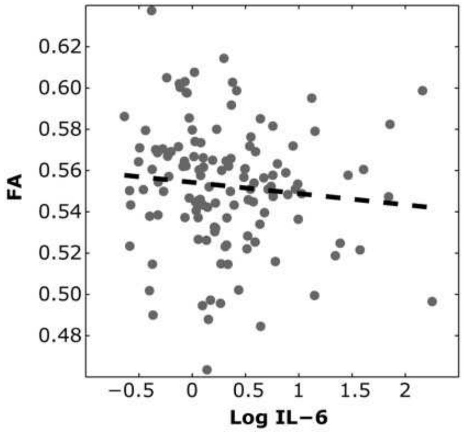

Fig. 3 Scatterplot showing the negative correlation between clusterwise FA and IL-6 (natural log transformed).

Table 2 Associations between demographic, socioeconomic, personality factors and health factors and FA within the target cluster.

	r (*N*)	*P*
Age	−0.118 (145)	0.158
Sex	−0.047 (145)	0.578
Income	0.163 (141)	0.053
Education (years)	0.106 (145)	0.206
Waist	−0.133 (145)	0.112
SBP	−0.035 (145)	0.676
DBP	−0.063 (145)	0.450
Smoking	$\beta =$ **0.198 (145)**	**<0.0001**
PSQI	−0.134 (142)	0.113
PA	0.048 (144)	0.569
NA	0.088 (144)	0.292
ISEL	0.087 (145)	0.299

Same analysis and reporting conventions as used in Table 1.

socioeconomic (Gianaros *et al.*, 2013) or physical health (Verstynen *et al.*, 2013) pathways previously reported in this sample.

Network connectivity through SNI-related voxels

To characterize the pathways running through this cluster, we performed deterministic tractography on a template of 60 neurologically healthy volunteers who were scanned using a high angular resolution form of diffusion imaging that is optimal for tractography in MNI space (see Methods). Using the SNI-related cluster as a region of interest, we found that a majority of the cluster covers interhemispheric connections between the superior and middle frontal gyrus (Figure 4). The dorsal aspects of the cluster also include projections from the left cingulum tract while the ventral aspects intersect with portions of the superior infundibulum. Thus, the voxels having particularly strong associations with social network diversity predominantly reflect pathways connecting the left and right dorsolateral prefrontal cortex, with some carry over to frontoparietal and limbic pathways.

To determine the extent that variation in the integrity of the white matter cluster associates with the functional properties of this connected circuit, we selected the cortical clusters of the tractography endpoints that had more than 50 contiguous voxels (ROIs; Figure 5A) and used resting-state BOLD time series to evaluate the functional connections between all ROIs for each subject. After correcting for multiple comparisons (FDR < 0.05) and controlling for sex, age and central adiposity, one cluster pair was found to be negatively associated with FA within the SNI-related cluster ($\beta = -1.09$, $P = 0.0146$). This region reflected functional connections between an area on the superior frontal sulcus [SFG; center of mass (COM) in MNI-space = 22, 45, 30] and the rostral striatum near the nucleus accumbens (NAcc; COM = 9, 7, 13), both in the right hemisphere. The diffusion component that explained the most variance between subjects' functional connectivity was the RD component ($\beta = 652.30$, $P = 0.0016$). Although the AD component was also associated with changes in functional connectivity ($\beta = 351.95$, $P = 0.0286$), this significance does not survive the threshold for multiple comparisons (Bonferroni adjusted $P = 0.0167$). Thus, within this corticostriatal pathway that runs through the SNI-associated cluster, we observed that individual differences in FA predict variance in functional connectivity, particularly with radial component of the DTI signal.

Although white matter integrity correlated with functional connectivity of the corticostriatal pathway, social network diversity did not have a direct association with the functional connectivity between these regions ($\beta = -0.0027$, $P = 0.36$). However, because social network diversity is associated with white matter integrity within this cluster, it is possible that white matter serves as an indirect pathway linking SNI diversity with corticostriatal functional connectivity. Using a statistical mediation analysis (Preacher and Hayes, 2008), we found that FA ($a^{*}b = -0.0049$, $P = 0.0005$) and RD ($a^{*}b = -0.0053$, $P = 0.0002$) served as significant indirect pathways linking SNI diversity with corticostriatal functional connectivity (Figure 5B). This indirect pathway was marginally significant with AD ($a^{*}b = -0.0013$, $P = 0.046$), but this does not survive multiple comparison correction and the 95% confidence interval (CI) includes zero. Therefore, only FA and RD are indirect mediators linking social network diversity to corticostriatal functional connectivity.

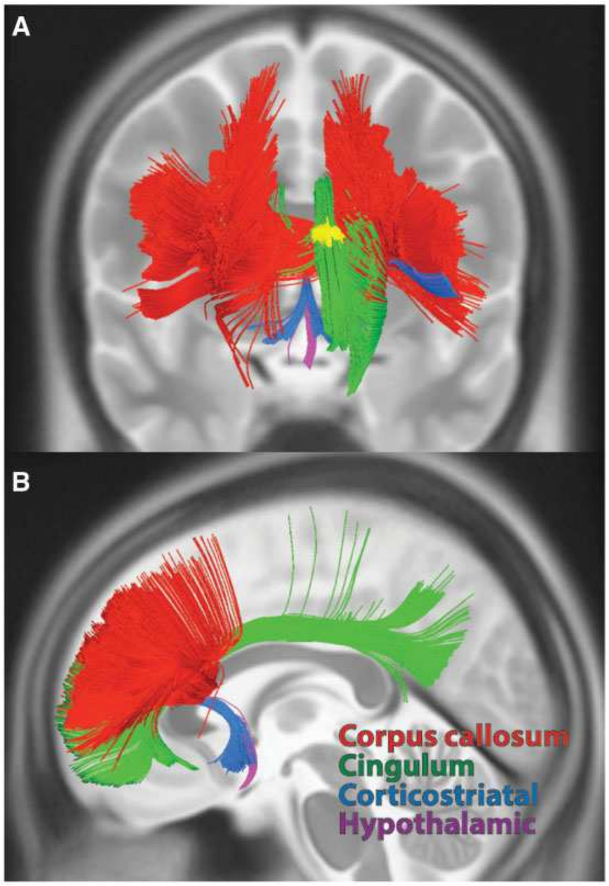

Fig. 4 Coronal, A and sagittal, B, views showing the tracked fiber streamlines that run through the SNI (Div) related cluster (yellow region). Tractography was performed on the CMU-60 template brain.

DISCUSSION

In a neurologically healthy group of midlife adults, we found that social network diversity correlated with the microstructural integrity of white matter pathways in the brain, particularly in an area near the anterior corpus callosum that includes multiple fiber pathways. This association was reflected as an increase in FA and decrease in RD as social network diversity increases. In addition, white matter integrity in these voxels was associated with levels of inflammation. Both the pattern of anisotropy changes and association with inflammation are consistent with animal studies on the influence of the amount of social contact on myelin integrity (Hermes *et al.*, 2006; Karelina *et al.*, 2009; Liu *et al.*, 2012). Any inferences between patterns in the diffusion signal and myelin or axonal changes are only speculative because the diffusion imaging signal is only an indirect measure of white matter microstructure and difficult to interpret in areas with crossing fibers (Wheeler-Kingshott and Cercignani, 2009; Jones *et al.*, 2013). Most importantly, we found that variation in SNI-related white matter indirectly mediates a relationship between social network diversity and functional connectivity of corticostriatal pathways, suggesting that the pattern of white matter variation may have an impact on functional processing as well (see also Bickart *et al.*, 2012).

Recent neuroimaging work in humans has demonstrated the relationship between social network structure and general brain morphology (Bickart *et al.*, 2012; James *et al.*, 2012). Here, we found decreased measures of white matter integrity (Liu *et al.*, 2012; Makinodan *et al.*, 2012) and increased inflammation (Hermes *et al.*, 2006; Karelina *et al.*, 2009) associated with decreased levels of social network diversity, results that are qualitatively consistent with evidence from studies of social isolation in mice. However, by assessing social network diversity as a continuous variable, our results suggest that it is not just the lack of social interaction that is associated with poorer brain health. Instead, each increment in the diversity of one's network is associated with an increase in integrity. This may have important implications for understanding why greater diversity is associated with better cognitive function (Fratiglioni *et al.*, 2000; Seeman *et al.*, 2001; Zunzunegui *et al.*, 2003; Tilvis *et al.*, 2004; Beland *et al.*, 2005; Bennett *et al.*, 2006; Ertel *et al.*, 2008).

Mechanistically, rodent models have shown that inflammation acts as a mediator between the amount of social isolation and reduced white matter integrity (Hermes *et al.*, 2006; Karelina *et al.*, 2009). Our results are also qualitatively consistent with this pathway in that reduced social network diversity correlated with reduced white matter integrity and increased systemic inflammation. Although inflammation did not serve as an indirect mediator between white matter and social network structure, previous reports have found a direct link between white matter integrity and systemic inflammation throughout the human brain (Brück, 2005; Wersching *et al.*, 2010; Miralbell *et al.*, 2012; Arfanakis *et al.*, 2013; Verstynen *et al.* 2013). Inflammatory pathways reflect a general mechanism through which peripheral systems can interact with the central nervous system by visceral afferent transmission or by crossing the blood brain barrier (Banks and Kastin, 1991; Tracey, 2002; Hampel *et al.*, 2005; Ek *et al.*, 2001; Yirmiya and Goshen, 2011; Trapero and Cauli, 2014). Pro-inflammatory cytokines such as IL-6 are produced by microglia as part of a normal brain cell functioning (Shigemoto-Mogami *et al.*, 2001; Nakanishi *et al.*, 2007). If the normal inflammatory immune response becomes chronic, increased levels of cytokines in the local microenvironment can lead to neuronal and glial dysfunction and death (Ramesh *et al.*, 2013). Oligodendrocytes in particular may be more sensitive to raised levels of pro-inflammatory cytokines (Di Penta *et al.*, 2013). Furthermore, inflammatory cytokines are known to have a role in initiating 'sickness behavior', which includes social withdrawal as a symptom (Eisenberger *et al.*, 2011), and acute social stress leads to increased levels of IL-6 and Tumor necrosis factor (TNF)-α (Slavich *et al.*, 2010). Inflammation could therefore have potential social psychological consequences, possibly playing a role in social withdrawal. With larger sample sizes, it may be possible to detect such relationships. Also, it should be noted that the white matter structural changes that occur as a result of inflammation in socially isolated rodents are observed under a more extreme measure of social integration than is used in humans. The stricter isolation that the rodents experience may have more observable consequences than measuring social diversity and number of contacts in a normal human population. Low power is likely a significant reason why we did not detect the same inflammation-mediated relationship between social network measurements and white matter integrity.

Previous human studies have also demonstrated a provisional association between measures of social network structure and both neuromorphology and brain function. In particular, Bickart *et al.* found that, in humans, as social network size increases the volume of the amygdala is larger (Bickart *et al.*, 2011) and the intrinsic functional dynamics between the amygdala and cortical areas related to social processing increases (Bickart *et al.*, 2012). We found no correlation between social network size and pathways that directly innervate the amygdala itself. Instead, the portion near the corpus callosum most strongly associated with social network diversity appears to interconnect the prefrontal, medial parietal and limbic areas. Functionally, this cluster is associated with differences in functional connectivity of corticostriatal pathways. However, the current findings are not necessarily mutually exclusive from the findings of Bickart and colleagues as the prefrontal cortex, striatum and amygdala are all known to have strong functional

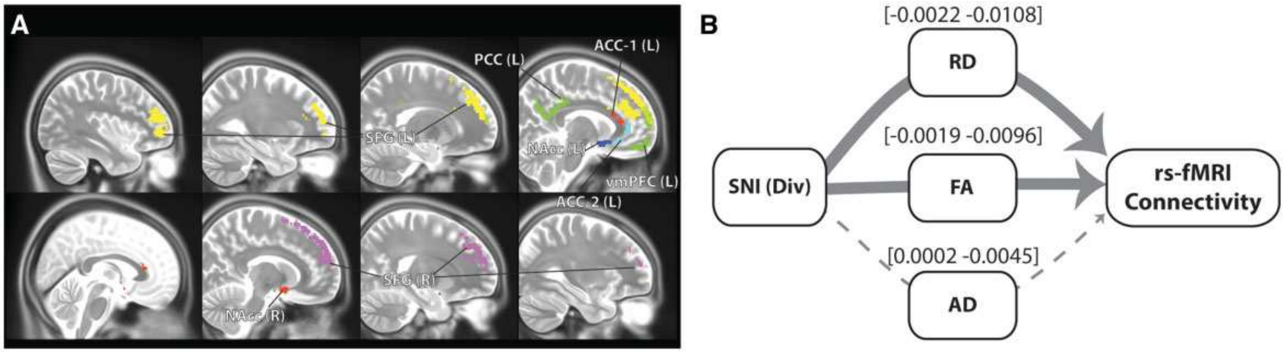

Fig. 5 (A) Sagittal slices showing the eight ROIs masks generated from cortical endpoints of tracked fiber pathways from analysis shown in Figure 4. These ROIs were used as masks for resting state functional connectivity analysis on the subset of the sample ($N = 110$) that had viable resting state fMRI data. Variation in FA within the SNI (Div) related cluster correlated with variation in functional connectivity between a region on the right medial wall of the SFG and a region near the right NAcc (lower row). ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; NAcc, nucleus accumbens; vmPFC, ventromedial prefrontal cortex; SFG, superior frontal gyrus; R, right; L, left. (B) Mediation analysis showing how FA and RD served as indirect pathways linking SNI (Div) to functional connectivity of the significant corticostriatal pathway identified in A. Size of the lines represents the magnitude of the indirect ($a*b$) pathway. Dashed lines indicate non-significant results after correcting for multiple comparisons. Bracketed numbers indicate the upper and lower bound of the bias corrected and accelerated 95% CI for the indirect pathway.

associations (Ochsner and Gross, 2005; Dolcos and McCarthy, 2006; Golkar *et al.*, 2012; Kim *et al.*, 2012; Lee and D'Esposito, 2012). Therefore, the gray matter and functional network differences in amygdala processing may not be detectible in the white matter pathways that innervate the nucleus. It is also possible that we did not have sufficient power in our sample to detect differences in the white matter pathways to the amygdala. More work is needed to bridge our white matter findings with the gray matter and functional network findings previously reported.

The fact that diversity-related variation in FA-mediated corticostriatal functional connectivity implies that differences in social structure may have functional consequences for basal ganglia processing. Indeed, the dopaminergic pathways within cortico-basal ganglia loops have been indicated as being a key part of the so-called 'social brain' (Skuse and Gallagher, 2009). According to this model, inherent variation in sensitivity to feedback signals impacts an individual's likelihood to engage in social interactions. Unfortunately, given the cross-sectional nature of the current study, we cannot tell whether inherent differences in corticostriatal connectivity predisposes an individual to a particular social network structure or whether exposure to many high-contact social roles modulates corticostriatal connectivity itself. Inferring the causal direction of these associations is left to future intervention or longitudinal studies.

Nonetheless, the current findings suggest that, like in rodents, reduced social network structure in humans is linked to the health of myelin in the brain. Our findings from the DTI analysis are largely consistent with variation in myelin integrity, and the simple correlation between FA and inflammation hints that similar molecular mechanisms may be mediating this effect in humans as in non-human animals. Although previous work has linked both socioeconomic status (Gianaros *et al.*, 2013) and physical health (Verstynen *et al.*, 2013) to white matter integrity via inflammatory pathways, we believe that the social network associations reported here reflect an independent social-white matter link. This is supported by the fact that the voxels with the strongest network diversity and FA associations do not correlate with measures of socioeconomic status or general physical health (Table 2). Considering our current results in the context of previous findings suggests that different social factors can relate to brain morphology in different ways, but possibly through shared molecular pathways (e.g. inflammation). Thus, complex features of the broader social environment previously implicated in physical health (House *et al.*, 1988; Cohen, 2004; Uchino, 2006; Holt-Lunstad *et al.*, 2010) may also relate to the health of the brain. The extent to which these associations with neural integrity influence behavior should be a focus of future work.

CONFLICT OF INTEREST

None declared.

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