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Stress and the brain: Emotional support mediates the association between myelination in the right supramarginal gyrus and perceived chronic stress

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ABSTRACT

Perceived stress, which refers to people's evaluation of a stressful event and their ability to cope with it, has emerged as a stable predictor for physical and mental health outcomes. Increasing evidence has suggested the buffering effect of social support on perceived stress. Although previous studies have investigated the brain structural features (e.g., gray matter volume) associated with perceived stress, less is known about the association between perceived chronic stress and intra-cortical myelin (ICM), which is an important microstructure of brain and is essential for healthy brain functions, and the role of social support in this association. Using a sample of 1076 healthy young adults drawn from the Human Connectome Project, we quantified the ICMby the contrast of T1w and T2w images and examined its association with perceived chronic stress during the last month and social support. Behavioral results showed that perceived chronic stress was negatively associated with both emotional support and instrumental support. Vertex-wise multiple regression analyses revealed that higher level of perceived chronic stress was significantly associated with lower ICM content of a cluster in the right supramarginal gyrus (rSMG). Interestingly, the emotional support, but not the instrumental support, significantly mediated the association of perceived chronic stress with ICM in the rSMG. Overall, the present study provides novel evidence for the cortical myelination of perceived chronic stress in humans and highlights the essential role of the rSMG in perceived chronic stress and emotional support.

1. Introduction

Stress is an inherent part of everyone's life, and probably the one which cannot - or should not - be eliminated. Moderate and controlled levels of stress are beneficial to our physical and mental health (Hostinar and Gunnar, 2015). However, severe, overloading and uncontrolled stress can harm us and cause increased risks of illnesses (e.g., cardiovascular disease and stroke) (Aggarwal et al., 2014; Tsutsumi et al., 2009) and mental disorders (e.g., depression and posttraumatic stress disorder) (Catabay et al., 2019; Bryant, & psychology, 1998; Vaidya, 2000). There is a consensus that the impact of objective stressful events on people is determined to some extent by one's subjective perception of the stressful event, namely perceived stress (Cohen, Kamarck, Mermelstein, & behavior, 1983). Perceived stress refers to people's evaluation of a stressful event and their ability to cope with it (Cohen et al., 1983). Events are perceived as stressful only when the demands placed by the event exceed the person's ability to cope or available resources (Cohen et al., 1983; Schiffrin and Nelson, 2010).

Social support, as a psychological or material resource provided by a network of social relationships, plays an important role in the maintenance of human health. Social support can be further divided into two main types: emotional support and instrumental support (Cohen and Wills, 1985; Mathieu et al., 2019; Park et al., 2010). Emotional support makes the recipient feel valued and loved by providing affective comfort and caring; while instrumental support is the provision of helpful behaviors such as providing financial assistance, spending time with others, or giving of one's skills (Cohen and Wills, 1985; Rueger et al., 2016). Although the two types of social support differ in form, they are

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not separate from each other, as sometimes instrumental support is provided along with some emotional support (Mathieu et al., 2019). Ample studies have found that people with few social supports reported higher levels of stress (Hostinar and Gunnar, 2015; Southwick et al., 2005), depression (Rueger et al., 2016), and mortality (Barth et al., 2010) than those who receive much support from family members and friends. Cohen et al. (1983, 2004) described the protective effect of social support on health as *stress-buffering model* and proposed two possible mechanisms underlying this relationship. First, the belief that others will provide social support enhances one's ability to cope with stress and alters the evaluation of potentially stressful situations so that they are no longer perceived as threatening (Cohen and Wills, 1985; Cohen, 2004). Second, social support serves the purpose of maintaining health by dampening emotional and physical reactivities to stressful events. That is, even if the event is assessed as stressful, people with supportive relationships are empowered to cope with the stress, negative emotional experiences, and calming of the neuroendocrine system, thereby reducing the overreaction to stress (Cohen and Wills, 1985; Eisenberger et al., 2007).

There is growing evidence that stress might be associated with specific neurobiological factors in addition to psychosocial factors. In particular, studies have provided more consistent evidence for the association of limbic system (e.g., hippocampus, amygdala) and prefrontal cortex (e.g., medial prefrontal cortex, orbitofrontal cortex) with stress (Li et al., 2021; McEwen et al., 2015; Sherman et al., 2016). The hippocampus is considered a central brain region in relation to stress because of its presence of a great number of receptors for stress hormones (e.g., glucocorticoids), which can regulate the release of stress hormones through action on the hypothalamic-pituitary-adrenal axis to promote individual adaptation to stressors (Bremner, 1999; Klaming et al., 2019; McEwen et al., 2015). However, it is a fact that stress may involve a much broader brain network involving memory processing, social cognition, inhibitory control. In a sample of adult, Li et al. (2014) found that perceived stress levels were associated with larger gray matter volumes in the bilateral parahippocampus, fusiform cortex, and entorhinal cortex, and with smaller gray matter volumes in the right insula. A longitudinal study by Papagni et al. (2011) showed the impact of life stress on human brain structure, with individuals who endured higher levels of life stress exhibiting significant alterations in areas of the anterior cingulate, hippocampus and parahippocampal gyrus. Another yoga-based intervention study found that yoga practice, which is believed to contribute to a reduction in the stress response, increased activity of the superior parietal gyrus and the supramarginal gyrus (SMG) in response to emotion evoking stimuli (Wadden et al., 2018). The majority of previous research has focused on the typical brain imaging measures (e.g., gray matter volume, cortical thickness, white matter volume, brain function), yet it is unclear whether intra-cortical myelination (ICM), a microstructure that captures brain growth and maturation, could reflect inter-individual differences in stress levels.

Myelin is a multilaminar sheath of oligodendrocytes wrapped around axons in the nervous system that greatly accelerates nerve conduction and provides nutritional support for axons (Fünfschilling et al., 2012; Nave, 2010). It is essential for maintaining proper brain function, and changes in myelin are likewise part of normal brain functioning (Dong et al., 2021). Studies have found that myelin undergoes continuous changes even in adulthood, and these changes could be critical for people's learning and memory formation (Lazari and Lipp, 2021; McKenzie et al., 2014; Pan et al., 2020; Sampaio-Baptista et al., 2013). Evidence from animal and human studies suggests that behavioral trainings or interventions can induce experience-dependent changes in myelin structure in both childhood and adult individuals (Purger et al., 2016). Also, the experience of adverse events (e.g., social isolation) can have an impact on brain myelination (Liu et al., 2012; Makinodan et al., 2012). Furthermore, a growing body of evidence from molecular and morphological studies supports the important role of sleep for brain myelination (de Vivo and Bellesi, 2019). Gene expression studies have shown that sleep deprivation in rodent can result in downregulation of several myelin-related transcripts (Bellesi et al., 2013; Cirelli et al., 2006; Mongrain et al., 2010). Bellesi et al. (2018) found that chronic lack of sleep (about 5 days) in mice reduced myelin thickness and increased the length of Ranvier's nodes in highly myelinated white matter tracts. Human studies have also revealed that sleep quantity and quality is related to white matter integrity and ICM (de Vivo and Bellesi, 2019; Elvsåshagen et al., 2015; Sexton et al., 2017; Toschi et al., 2021). Considering the reciprocal relation between sleep loss and stress (Nollet et al., 2020; Prather, 2019), it would be important to investigate the association of perceived stress with ICM in humans.

Myelinated axons are most abundant in the white matter of the brain, but are also widely distributed in the gray matter of the cerebral cortex (Nieuwenhuys, 2013). ICM is regarded as a marker of the degree of axonal myelination in the cerebral cortex, which is closely related to individual cognitions, behaviors, and emotion (Grydeland et al., 2019; Toschi and Passamonti, 2019). ICM varies across cortical areas, with primary sensory cortex being heavily myelinated and higher cognitive functional areas such as the prefrontal lobe being lightly myelinated (Glasser and Van Essen, 2011). Moreover, the myelination of specific brain regions varies between individuals (Glasser et al., 2014; Grydeland et al., 2013). Whether ICM differs between individuals at different stress levels is one of the issues of interest in this study.

Stress early in life can lead to changes in myelin sheaths in humans and rodents (Breton et al., 2021; Long et al., 2021). Several studies have revealed changes in oligodendrocytes and their myelin under chronic stress exposure and in stress-related psychiatric disorders such as post-traumatic stress disorder (PTSD), major depressive disorder, and child abuse (Boda, 2021; Chao et al., 2015; Lutti et al., 2014; Lutz et al., 2017; Poggi et al., 2022). For instance, Chao et al. (2015) found that veterans with PTSD showed significantly more hippocampal myelination than those without PTSD, and that there was a positive correlation between estimates of hippocampal myelination and severity of PTSD and depressive symptoms (Chao et al., 2015). In another animal experiment with rats, it was revealed that juvenile exposure to acute traumatic stress can lead to a decrease in gray matter myelination in the amygdala, hippocampus, and prefrontal cortex in adult female rats (Breton et al., 2021). Moreover, some studies have demonstrated that patients with major depression have significantly lower levels of myelin in the whole brain and the nucleus accumbens than healthy individuals (Lutti et al., 2014), and that patients who experience more depressive episodes also have reduced myelin in the lateral prefrontal cortex (Sacchet and Gotlib, 2017).

However, there have been few studies examining the relationship between ICM and stress, possibly due to limitations in the means of measuring ICM content *in vivo*. Researchers have been developing non-invasive MR-based measures of ICM, and proposed that the ratio between T1-and T2-weighted MRI signal can be a reliable indicator of ICM (Glasser and Van Essen, 2011; Nerland et al., 2021). This approach has been used to characterize age-related differences in cortical myelin content across the lifespan (Grydeland et al., 2013; Rowley et al., 2017). Moreover, the myelin mapping derived from the T1w/T2w signal ratio have been shown to match well with histological maps of cortical myelination (Nieuwenhuys, 2013). Empirical studies have also found that the levels of ICM, as indicated by the T1w/T2w signal ratio, are associated with multiple sclerosis (Trapp et al., 2018), schizophrenia (Insel, 2010), bipolar disorder (Jørgensen et al., 2016), sleep (Toschi et al., 2021), and obesity (Dong et al., 2021). It is evident that ICM measured by T1w/T2w signal ratio can provide valuable information about the relationship between brain myelination and stress.

In the present study, we took advantage of the Human Connectome Project (HCP) database, a large, homogeneous as well as well-characterized sample, to explore the psychosocial and neurobiological correlates of participants perceived chronic stress during the last month, that is, the relationship between stress and social support and ICM. This database provides behavioral indicators of emotional and instrumental support, perceived chronic stress, and neuroimaging data with high-resolution and image quality, which contribute to the objectives of this study. Based on the above evidence, we predict that social support can reduce the levels of stress perceived by individuals and that the ICMbrain regions associated with stress are mainly located in the limbic, prefrontal, and socioemotional systems. Moreover, given the widely established relationship between social support and social-emotional functioning (Park et al., 2015; Salimi and Bozorgpour, 2012), we additionally examined the possibility of a mediating role for social support in the relationship between stress-rel ated ICM brain regions and perceived chronic stress.

2. Materials and methods

2.1. Participants

The sample included in the present study was drawn from the 1200 Subjects Release of the HCP (Van Essen et al., 2013), a large dataset that provides open access to high-quality behavioral and neuroimaging measures of healthy young adults (age range = 22–35 years old). Details of inclusion and exclusion criteria see Van Essen et al. (2012). We first included a group of participants (n = 1112) for which the T1w/T2w-derived myelin map and the behavioral data for perceived stress and social support were available. Of these participants, we further excluded 36 participants based on the following criteria: (1) missing intermediate files for space transformation (n = 17); (2) missing measures on family income (n = 7), family information (n = 3) or fluid intelligence (n = 8); (3) outliers in region-of-interest analyses using a threshold of four standard deviations above or below the mean (n = 1). As a result, the sample for present study consisted of 1076 participants, whose demographics can be seen in Table 1.

2.2. Behavioral measures

The perceived stress, perceived emotional support and perceived instrumental support of the participants in the HCP were assessed by the subscales in the NIH-Toolbox Emotion Measures that has been widely used to examine emotion function and dysfunction. Perceived stress refers to people's evaluation of a stressful event and their ability to cope with it (Cohen et al., 1983). The perceived stress scale in the NIH toolbox consists of 10 items to measure the degree of stress a person feels during the last month (Kupst et al., 2015). Respondents rate the items on a 5-point Likert scale with options ranging from “Never” to “Very Often”. The sum score of the 10 items was used to determine the participants' perceived chronic stress, with a higher score indicating higher level of perceived stress.

The emotional support scale measured how often participants felt that there was someone available to listen to their problems with empathy, caring and understanding in the past month. Instrumental support referred to the perception of available people who can provide material or functional aid when needed in the past month. 8 items were included in each survey and were rated by participants on a 5-point Likert (1 = *never* and 5 = *always*). The total score of the 8 items was used to denote the perceived emotional or instrumental support, with a higher score indicating more perceived support for the participants.

The final score of each scale was converted to the T score with the mean of 50 and the s.d. Of 10 based on item response theory (for details, see https://www.healthmeasures.net/score-and-interpret/interpret-scores/nih-toolbox), which was used in the subsequent analyses.

In addition, a number of demographic variables, fluid intelligence, personality traits, and sleep quality were also retrieved from the HCP database due to their close relation with perceived chronic stress or cortical myelination. Of these, participants' fluid intelligence was assessed via Penn Progressive Matrices test (Bilker et al., 2012), in which the raw number of correct responses was selected as the level of fluid intelligence. The five-factor model (FFM) personality traits were assessed using the NEO Five-Factor Inventory (Costa and McCrae, 2008), which comprises of 60 items and consists of five scales: Neuroticism, Extraversion, Openness, Agreeableness, Conscientiousness. The raw scores for each of five-factor personality traits were used. Finally, the Pittsburgh Sleep Quality Index (PSQI) questionnaire was used to assess participants' sleep quality (Buysse et al., 1989). The total PSQI scores is calculated by summing the seven components' scores, with lower scores denoting better sleep quality.

Table 1
Demographic characteristics of participants (N = 1076).

Demographic Characteristic	M (SD) or %
Sex	
Male	45.9%
Female	54.1%
Age	28.8 (3.7)
Race	
White	75.2%
Black or African American	14.6%
Asian American, Native Hawaiian, or other Pacific Islander	5.9%
Native American	0.2%
More than one race	2.5%
Unknown or not reported	1.7%
Ethnicity	
Hispanic or Latino	8.6%
Not Hispanic or Latino	90.1%
Unknown or not reported	1.2%
Income	
$1000-$9999/year	7.0%
$10,000-$19,999/year	7.8%
$20,000-$29,999/year	12.5%
$30,000-$39,999/year	11.7%
$40,000-$49,999/year	10.3%
$50,000-$74,999/year	21.3%
$75,000-$99,999/year	13.7%
$100,000-$149,999/year	15.7%
Years of Education	14.9 (1.8)
Handedness	66.2 (43.7)

2.3. MRI acquisition

High-resolution T1w and T2w images were collected on a 3 T Siemens Tim Trios with a 12-channel head coil at the Washington University in St. Louis and at the Northwestern University. T1w images were acquired with the MPRAGE sequence with the following scanning parameters: TR = 2400 ms; TE = 2.14 ms; flip angle = 8°; FOV = 224 × 224; voxel size = 0.7 × 0.7 * 0.7 mm^3; 256 slices. While T2w images were acquired using the SPACE sequence with the following scanning parameters: TR = 3200 ms; TE = 565 ms; variable flip angle; FOV = 224 × 224; voxel size = 0.7 × 0.7 * 0.7 mm^3; 256 slices.

2.4. Intra-cortical myelin mapping

The preprocessed ICM maps were downloaded from the HCP consortium database (https://db.humanconnectome.org, accessed on September 21, 2021). The myelin maps were generated using T1w and T2w contrasts following the standard, state-of-the-art HCP pipeline (Glasser et al., 2013). In brief, the FreeSurfer software suite (version 5.2, http://surfer.nmr.mgh.harvard.edu) was first used to build white, pial, and mid-thickness surfaces, which are then projected onto a 164 k vertex fs_LR mesh using Caret and the Connectome workbench. During this procedure, the T2w map was registered to the T1w map using the affine registration tool in FSL (FLIRT) and mutual information cost function. It is worth noting that the signal ratio of T1w and aligned T2w image increases susceptibility of probing intra-cortical myelin while decreases signal intensity biases. The contrast associated with myelin content (m) is approximately proportional to the intensity in the T1w image and approximately inversely proportional to the intensity (1/m) in the T2w image, and the receive bias can be represented by b in both images.

Thus, the generated contrast (T1w/T2w signal ratio) will be approximately proportional to m^2. Furthermore, the T1w/T2w signal ratio can result in an enhanced contrast-to-noise ratio for myelin since the both images are influenced by uncorrelated noise. Finally, ICM maps for all participants were converted to Freesurfer fsaverage 164 k surface space for statistical inference using Connectome workbench.

2.5. Statistical analysis

We first performed vertex-wise regression analyses using general linear model (GLM) to identify regional cortical myelin content that associated with perceived stress. The regression model included age, gender, handedness, household income, fluid intelligence, FFM personality traits, sleep quality, and total intracranial volume (TIV) of participants as covariates of no interest. All these factors can individually affect perceived chronic stress and myelination (Grydeland et al., 2013; Schmitt et al., 2020; Toschi and Passamonti, 2019; Zhu et al., 2022), thus they were treated as "nuisance" of confounding variables in the GLM. In order to avoid collinearity between these covariates, TIV was orthogonalized to gender before inclusion in the GLM ($r = -0.014$, $p = 0.669$ after orthogonalization). For all vertex-wise comparisons, the Monte Carlo simulation was used to control for type I error rate and multiple comparisons (Long, 2022). In this process, a null distribution of maximum cluster size with an initial cluster forming threshold of $p < 0.001$ was first tested and then a threshold of cluster-wise p-value (CWP) < 0.05 was used to determined brain regions in which ICM content was correlated with perceived stress.

Furthermore, we performed powerful nonparametric permutation analyses of linear model as implemented in FSL's PALM software (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM) (Winkler et al., 2015) to re-estimated the statistical significance for the corresponding statistical model. Permutation inference for GLM relies only on weak assumptions about the data and provides excellent type I error rate control in a wide range of imaging studies (Winkler et al., 2014). Since participants in the HCP dataset consist of twins and non-twin siblings, we used multilevel block permutation analysis to test the association between cortical myelin and perceived stress while control for biases induced by the family structure. To do this, we generated exchangeability blocks with the HCP2Blocks MATLAB script available at https://raw.githubusercontent.com/andersonwinkler/HCP/master/share/hcp2blocks.m (Winkler et al., 2015), which designed to separately capture the unique variance within dizygotic twins, monozygotic twins, and non-twin siblings while simultaneously accounting for family structure (i.e., family size and type). PALM shuffles the data within and between blocks according to the HCP kinship/pedigree structure, avoiding relatedness confounding the results. Significant clusters were determined using 10, 000 permutations with multiple comparisons correction by family-wise error (FWE) at vertex-wise $p < 0.001$ and CWP <0.05.

2.6. Mediation analysis

Given the importance of social support for stress reduction, we next aimed to test whether the relationship between ICMand perceived chronic stress was mediated by perceived emotional or instrumental support of participants. Specifically, we first defined the right supramarginal gyrus identified in the above vertex-wise regression analysis as the region-of-interest (ROI) and calculated the mean value of myelin content within it. We then examined whether ICM content in this ROI was significantly correlated with emotional or instrumental support. Finally, mediation analysis was conducted using the Hayes's (2013) PROCESS macro. The mediation model was estimated to derive the total, direct, and indirect effects of ICM in the right supramarginal gyrus and perceived chronic stress. A bootstrapping procedure with 5000 bootstrap samples was used to estimate the indirect effect of the mediation model. The 95% confidence interval (CI) for the product of indirect path that does not include zero provides evidence of a significantly indirect effect (Hayes, 2009).

3. Results

3.1. Behavioral performance

Our final sample included in this study comprised 582 women and 494 men with a mean age of 28.8 ± 3.7 years, while some other demographic characteristics are shown in Table 1. The T score for perceived chronic stress ranged from 22.4 to 80.5 with 105 participants scoring ≥60 (indicating "high levels of perceived stress", Fig. 1A), for emotional support ranged from 15.9 to 62.5 and for instrumental support ranged from 22.1 to 62.9. The gender differences were not significant for perceived chronic stress ($t = 1.436$, $p = 0.151$) and instrumental support ($t = 0.700$, $p = 0.484$), but significant for emotional support ($t = 4.111$, $p < 0.001$), with females receiving more emotional support than males. Perceived chronic stress scores were negatively correlated with emotional support ($r = -0.414$, $p < 0.001$, Fig. 1B) and instrumental support ($r = -0.315$, $p < 0.001$, Fig. 1C). The correlations of perceived chronic stress with fluid intelligence, FFM personality traits, and sleep quality are shown in Table 2. In addition, gender did not moderate the correlations between perceived chronic stress and emotional support ($p = 0.552$) and between perceived stress and instrumental support ($p = 0.202$). Hierarchical regression analysis further showed that the perceived chronic stress was significantly predicted by the emotional support ($b = -0.156$, $t = 5.702$, $p < 0.001$) and instrumental support ($b = -0.071$, $t = 2.807$, $p = 0.005$) after adjusting participants' age, gender, household income, fluid intelligence, five-factor model personality traits, and sleep quality. The final model included emotional and instrumental support and covariates accounted for 52.1% of the total variance in perceived chronic stress.

Notably, there is one set of participants with the highest value in the emotional support (n = 304) and instrumental support (n = 156), indicating a possible ceiling effect. We conducted additional exploratory analyses to examine whether the peculiar distribution of social support data had an impact on our results. After removing these participants (n = 347), correlation analysis also showed that perceived chronic stress scores were negatively correlated with emotional support ($r = -0.362$, $p < 0.001$) and instrumental support ($r = -0.219$, $p < 0.001$). Hierarchical regression analysis showed that the perceived chronic stress was significantly predicted by the emotional support ($b = -0.145$, $t = 4.570$, $p < 0.001$), but not the instrumental support ($b = -0.024$, $t = 0.790$, $p = 0.430$) after controlling for the same covariates. These results suggest that the emotional support is a stable predictor of perceived chronic stress.

3.2. Intra-cortical myelin content in relation to perceived chronic stress

We first identified brain regions in which ICM content measured by the T1/T2 signal ratio was significantly correlated with perceived chronic stress using vertex-wise multiple regression analysis. Cortical surface analysis showed a significantly negative association between the perceived chronic stress and ICM content of a cluster in the right supramarginal gyrus (rSMG; peak MNI: 47–36 44; 74 mm^2; partial correlation coefficient r = −0.151; CWP: 0.002; Fig. 2) after adjusting participants' age, gender, handedness, household income, fluid intelligence, FFM personality traits, sleep quality, and TIV and performing Monte Carlo simulation correction. Individuals with lower ICM content in the rSMG show higher level of perceived chronic stress. Nonparametric multilevel block permutation test was further used to confirm the validation of the above association while accounting for the family structure in the HCP dataset. The statistical results from permutation test revealed a similar cluster in the rSMG (peak MNI: 45–36 41; 74 mm^2; FWE-corrected CWP: 0.047) in which ICM content was significant in association with perceived chronic stress.

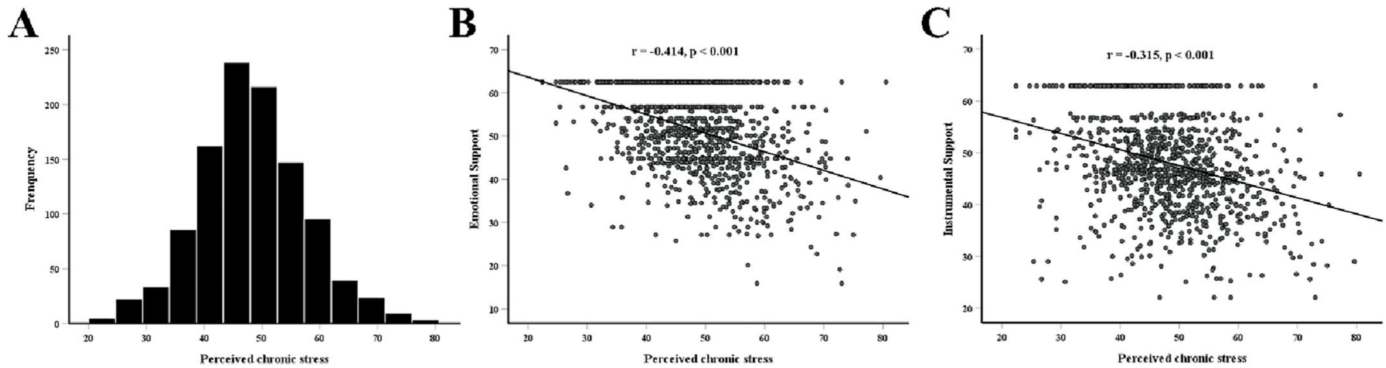

Fig. 1. Frequency distribution of perceived chronic stress (A) and its correlation with emotional support (B) and instrumental support (C).

Table 2
Correlations of perceived chronic stress with social support, fluid intelligence, FFM personality traits, and sleep quality.

	Perceived chronic stress	
Emotional support	r = −0.414	p < 0.001
Instrumental support	r = −0.315	p < 0.001
Fluid intelligence	r = −0.121	p < 0.001
FFM-Agreeableness	r = −0.246	p < 0.001
FFM-Openness	r = 0.015	p = 0.621
FFM-Conscientiousness	r = −0.330	p < 0.001
FFM-Neuroticism	r = −0.684	p < 0.001
FFM-Extraversion	r = −0.237	p < 0.001
sleep quality	r = 0.297	p < 0.001

3.3. Relations between cortical myelin, perceived chronic stress, and social support

We first defined the rSMG that showed correlation of its ICM content with perceived chronic stress from the vertex-wise regression analysis as ROI and followed the ROI-based analysis. We then used hierarchical regression analysis to text the relationship between ICM in the rSMG and social support. In the regression model, participants' age, gender, handedness, household income, fluid intelligence, FFM personality traits, sleep quality, and TIV were entered as a block of variables, and the emotional and instrumental support were entered as another block. Regression analysis showed that ICM in the rSMG was significantly correlated with emotional support ($b = 0.123$, $t = 3.097$, $p = 0.002$, Fig. 3A), but was not correlated with instrumental support ($b = -0.004$, $t = 0.097$, $p = 0.923$, Fig. 3B). In addition, due to the possible ceiling effect in the data of social support, we re-ran the regression model after excluding the participants with the highest value in emotional or instrumental support. Results also showed that ICMin the rSMG was significantly correlated with emotional support ($b = 0.170$, $t = 3.845$, $p < 0.001$), but was not correlated with instrumental support ($b = -0.002$, $t = 0.049$, $p = 0.961$) after controlling for the covariates.

We finally conducted mediation analysis to further characterize the relations between ICM in the rSMG, perceived chronic stress, and social support. We tested the hypothesis that lower ICM content in the rSMG was associated with higher level of perceived chronic stress via perception of less social support. Mediation analysis found a significant indirect effect of the emotional support (indirect effect = 0.013, 95% percentile $CI = -0.023$ to -0.005, Fig. 3C), but not instrumental support (indirect effect = 0.003, 95% percentile $CI = -0.008$–0.001, Fig. 3C), in the association between ICMin the rSMG and perceived chronic stress after adjusting individuals' age, gender, handedness, household income, fluid intelligence, FFM personality traits, sleep quality, and TIV. The indirect effect accounts for 14.8% of the total effect of ICM in the rSMG on perceived stress. We also examined the indirect effect of the social support after excluding the participants with the highest value in the emotional or instrumental support, and again found a significant indirect effect of the emotional support (indirect effect = 0.015, 95% percentile $CI = -0.027$ to -0.006), but not instrumental support (indirect effect = 0.001, 95% percentile $CI = -0.006$–0.002). Mediation result indicated that emotional support plays a partially mediating role in the association of ICMin the rSMG with perceived chronic stress.

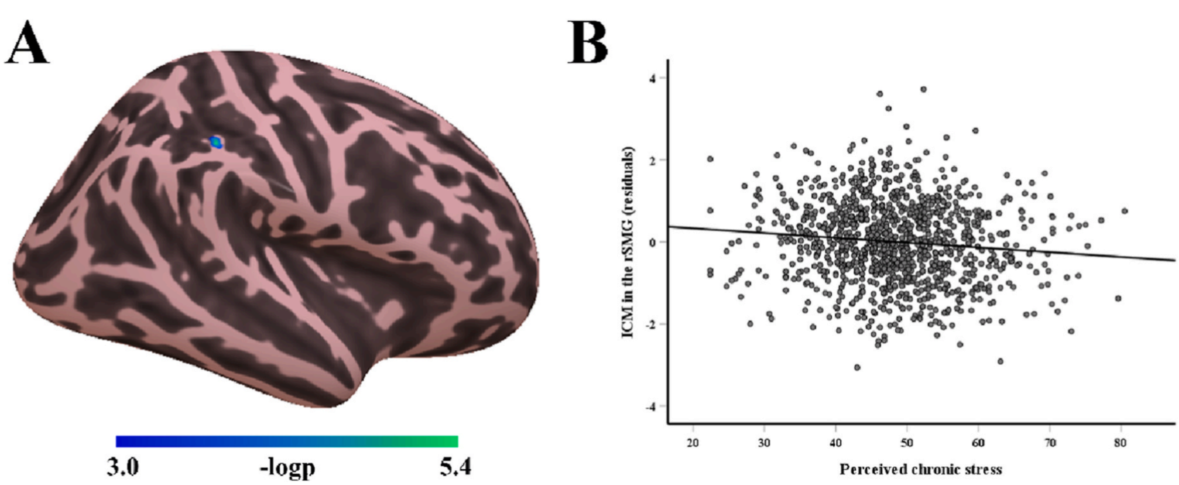

Fig. 2. Vertex-wise multiple regression analyses revealed that ICM content in the rSMG was significantly correlated with perceived stress after performing Monte Carlo simulation correction (A). Scatter plot was used for visualization purposes and not to be used for statistical inference (B).

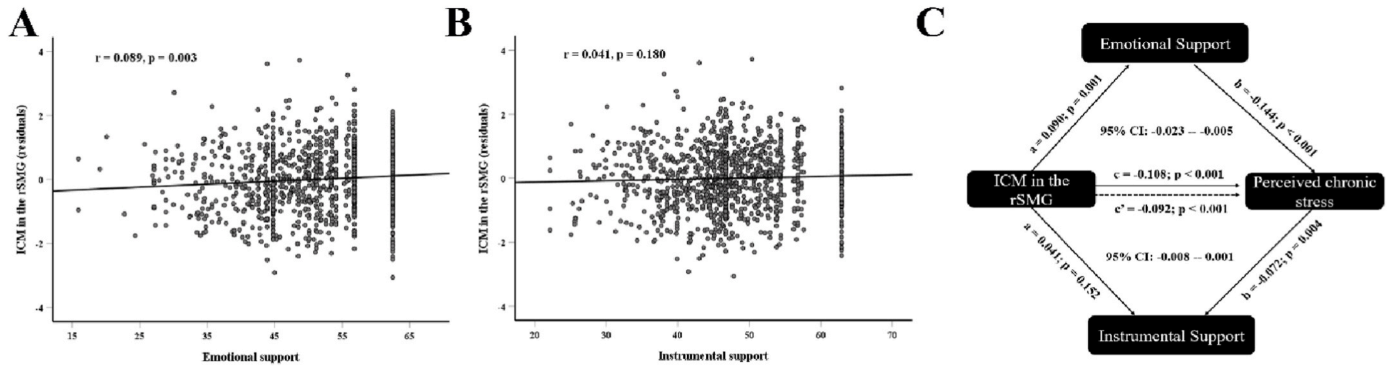

Fig. 3. Scatter plots showing the correlation of ICM in the rSMG with emotional support (A) and instrumental support (B). (C) The mediation model, in which both the emotional and instrumental support are used as mediators, shows that emotional support, but not instrumental support, significantly mediated the association between ICM content in the rSMG and perceived chronic stress.

4. Discussion

In the present study, we quantified the ICM using the T1w/T2w signal ratio and examined the associations of ICM with perceived chronic stress, but not perceived acute stress, and social support in a large and well-characterized sample of healthy young adults from the HCP (n = 1076). Behavioral results found that both emotional support and instrumental support were negatively associated with perceived chronic stress, suggesting the protective effect of social support on stress. Vertex-wise multiple regression analysis showed a negative association of perceived chronic stress with ICM content in the rSMG, such that lower ICM content in the rSMG corresponded to higher level of perceived chronic stress. ROI analysis further revealed a significant correlation between ICM in the rSMG and emotional support, rather than instrumental support. The final mediation analysis found a partially mediating effect of emotional support in the association between ICM in the rSMG and perceived chronic stress. Taken together, our results provide initial evidence that perceived stress is associated with cortical myelination of the rSMG and highlight the important role of emotional support in this association.

As anticipated, our behavioral findings revealed the protective effect of social support on perceived chronic stress. Accumulating evidence has suggested perceived social support is one of the most well-documented psychosocial factors influencing human physical and mental health (Barth et al., 2010; Berkman et al., 2000; Cohen, 2004; Holt-Lunstad et al., 2012; Rueger et al., 2016). Individuals with high levels of social support reported low levels of stress than those who perceive much support from family members and friends (Hostinar and Gunnar, 2015; Southwick et al., 2005). In addition, lack of social support has been identified as one of the risk factors for the development of PTSD (Brewin et al., 2000; Trickey et al., 2012). Although emotional support and instrumental support are conceptually independent and provide distinct resources, they both serve a similar buffering effect on stressors (Armstrong-Carter and Telzer, 2021; Catabay et al., 2019; Cohen and Wills, 1985; Mathieu et al., 2019). Previous theoretical work has suggested that social support can reduce stress reactivity by altering the appraisal or perception of potentially stressful situations or enhancing the abilities to actively cope with stressful events (Cohen and Wills, 1985; Cohen, 2004; Eisenberger et al., 2007).

Our neuroimaging results found an association between higher level of perceived chronic stress and lower ICM content in the rSMG. The SMG is a portion of the posterior parietal lobe and has been identified the key hub for bodily self-consciousness (Limanowski and Blankenburg, 2015). In addition to its involvement in perception of self-location in space (Blanke et al., 2015; Brozzoli et al., 2012), the SMG was also associated with monitoring one's peripersonal space (Di Pellegrino and Làdavas, 2015). The peripersonal space is believed to be the "margin of safety" around the body, which, when invaded, arouses discomfort and triggers appropriate defensive responses (Bogdanova et al., 2021; Lloyd, 2009; Serino, 2019). Neuroimaging evidence has shown that the SMG is engaged in the processing of threatening, painful, and stressful stimuli in the peripersonal space network (Costantini et al., 2008; de Borst et al., 2018; Grivaz et al., 2017; Kogler et al., 2015; Lloyd et al., 2006). Kogler et al. (2015) conducted a meta-analysis of neuroimaging studies and identified the SMG as a key brain region activated during physiological stress. Patients with PTSD were shown to have alterations in neural activity and functional connectivity of the SMG as compared to healthy controls (Bastos et al., 2022; Dossi et al., 2020; Felmingham et al., 2009; Rabellino et al., 2018). In addition, preliminary evidence has suggested that the associations of ICM with cognitive function may be through its importance for the integrity of neural connections and neural synchrony of cerebral cortex, particularly the facilitation of local brain synchrony (Grydeland et al., 2016; Vandewouw et al., 2021; Yang et al., 2020). Demyelination has been considered as a biomarker for some neurological diseases such as multiple sclerosis (Lucchinetti et al., 2011). Taken together, lower intra-cortical myelin may provide a novel micro-structural substrate underlying previously observed associations between perceived stress and brain neural activity in SMG under stress.

Importantly, we found that individuals perceived emotional support, but not instrumental support, partially mediated the association of ICM content in the rSMG with perceived chronic stress. Previous studies have also shown that the SMG, particularly the right-hemisphere SMG, is associated with some social cognitions including theory of mind or empathy (Kogler et al., 2020; Lamm et al., 2011), perspective taking (Besharati et al., 2016), and self-other distinction (Hoffmann et al., 2016). It has been suggested that the rSMG serves as a central hub selectively engaged in affective self-other distinct (Riva et al., 2022; Silani et al., 2013; Steinbeis et al., 2015; Zhao et al., 2021). The function and structure of the rSMG has been shown to be associated with overcoming emotional egocentricity bias that refers to the tendency to project one's own mental states onto others (Riva et al., 2022; Silani et al., 2013; Steinbeis et al., 2015). Moreover, the use of repetitive transcranial magnetic stimulation to temporarily disrupting the function of the rSMG leads to a substantial increase of emotional egocentricity bias in social judgments (Silani et al., 2013). Hence, our mediating result suggests that individuals with higher level of ICMin the rSMG may have less emotional egocentricity that enables them to be more empathic and avoid biased social judgments, which in turn might make them perceive stronger emotional support from others in their social network when dealing with stressful events.

Given the fact that small samples might lead to insufficient statistical power, inflated effect sizes and replication failures in studies of brain-wide brain-behavior association (Marek et al., 2022; Masouleh et al., 2019), a key strength of our study was its use of a large and well-characterized sample that facilitated the identification of reliable association of individual differences in perceived chronic stress with

ICM content. However, several limitations related to our findings need to be considered. First, the cross-sectional study design limits our ability to draw the causal conclusion among ICMcontent in the rSMG, emotional support, and perceived stress. Although our mediation analysis provided useful insights into this regard, another mediation model that differs from our hypothesis but could also be true is that ICM content in the rSMG mediates the effect of emotional support on perceived stress (indirect effect = 0.011, 95% percentile CI = −0.020 to −0.004). Future researchers can adopt a longitudinal study design to address this question. Second, although the myelin maps derived from the contrast of T1w and T2w images have been shown to match well with histological maps of cortical myelin (Nieuwenhuys and Broere, 2017), the underlying biology of this contrast is unclear and the mechanisms involved may be complex. The T1w/T2w ratio probably reflect some other microstructural factors beyond myelin content. Future studies are still needed to further verify the current findings using multiple ICM measures (e.g., magnetization transfer ratio and myelin water fraction). Finally, the participants included in this study were mainly comprised of a group of young healthy adults, which may limit the generalizability of our findings to diverse populations (e.g., patients with PTSD).

In conclusion, we demonstrated for the first time that variations in perceived chronic stress have significant association with cortical myelin measured by the T1w/T2 ratio. Individuals reporting higher level of perceived chronic stress show lower ICM content in the rSMG. Interestingly, perceived emotional support from others in one's social network significantly mediated the link between ICM in the rSMG and perceived stress. Our findings provide preliminary evidence for understanding microstructural substrate underlying stress-related cognition in humans and reveal an essential mediating role of emotional support in the association of ICM in the rSMG with perceived chronic stress.

Ethical approval statement

The study is approved by the ethical committee of Chongqing University of Posts and Telecommunications. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Submission declaration and verification

The authors declare that the work has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language.

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Data availability

The data utilized in this study are available for download from the Human Connectome Project (www.humanconnectome.org/). Users must agree to data use terms for the HCP before being allowed access to the data and ConnectomeDB, details are provided at https://www.humanconnectome.org/study/hcp-young-adult/data-use-terms.

CRediT authorship contribution statement

Yiqun Guo: Conceptualization, Formal analysis, Funding acquisition, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Huimin Wu:** Conceptualization, Writing – original draft, Writing – review & editing. **Debo Dong:** Formal analysis, Writing – review & editing. **Feng Zhou:** Writing – review & editing. **Zhangyong Li:** Funding acquisition, Writing – review & editing. **Le Zhao:** Writing – review & editing. **Zhiliang Long:** Methodology, Validation.

Declaration of competing interest

The authors assert that they have no competing financial or personal interests.

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