Social Regulation of the Neural Threat Response Predicts Subsequent Markers of Physical Health

Jingrun Lin
Dalian, China

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Committee Members:
James A. Coan, PhD
Joseph P. Allen, PhD

Abstract

Social support has been linked to a vast range of beneficial health outcomes. However, the specific nature of social support processes is not well characterized. Drawing on fMRI and health-related outcome data, this study aimed to understand how neural measures of "yielding" – the reduction of brain activity during social support – moderates the link between social support and health. We employed a longitudinal dataset where eighty-three participants around the age of 24 were exposed to the threat of shock when holding the hand of a partner. At around age 28 – 30, and then again at around age 30 – 32, participants returned for health visits where inflammatory activity and heart rate variability were recorded. Greater perceived social support was associated with lower inflammatory activity and greater heart rate variability, among individuals who had been more likely to yield to social support in the hypothalamus, dlPFC, and dACC years earlier. Our pre-registration is available online (https://osf.io/za4ud/).

Keywords*:* social support, fMRI, yielding, physical health, cardiovascular health, inflammatory activity

Proximity to social resources corresponds with positive health outcomes by attenuating cardiovascular arousal (Grewen et al., 2003), reducing glucocorticoids during stress (Weaver et al., 2004; Heinrichs et al., 2003), and modulating threat-related neural activation (Coan et al., 2017). Social Baseline Theory (SBT, Beckes & Coan, 2011) states that human brains have been shaped by natural selection to *assume* proximity to other humans—their primary ecological niche or habitat. When this assumption fails, humans perceive an increased demand on their personal resources. The brain adapts to the lack of social resources by optimizing metabolic and vascular resources for rapid responses to potential threats via unassisted labor. If maintained for long periods, health and longevity are compromised.

In previous work, we have used functional magnetic resonance imaging (fMRI) to operationalize *neural yielding* as instances when neural activity in prespecified areas (e.g., the prefrontal cortex) *decreases* in the presence of a supportive partner. Here, we propose that neural yielding will moderate the relation between perceived social support and physical health outcomes assessed up to eight years after fMRI data were collected. Physical health outcomes span cardiovascular health and immune functioning.

Social Support and Health

Social support is a key element in social relationships and an integral part of people's everyday life. Positive impacts of social support and negative consequences of social strain on health outcomes have been observed through decades of research (Lyyra & Heikkinen, 2006; Reblin & Uchino, 2008; Holt-Lunstad et al., 2015).

According to the stress "buffering" model, social support indirectly improves physical well-being by reducing negative responses to stressful events (Cohen & Wills, 1985), as it provides an alternative solution to stressful events, changes the perception of the threat, and desensitizes the physiological response. The stress "buffering" model receives major support from literature that focuses on cortisol levels (Ditzen et al., 2008; Steptoe et al., 2004), autonomic activation (Kamarck, Manuck, & Jennings, 1990; Fleming et al., 1982), and cardiovascular reactivity (Gerin et al., 1992; Lepore, Allen, & Evans, 1993).

Consistent with the stress buffering model, physiological stress responses (i.e., HPA-axis, sympathetic nervous system) can exacerbate inflammatory activity throughout the body (Black & Garbutt, 2002; Cohen et al., 2012; Miller et al., 2002). When stress-induced inflammation has no pathogenic targets, exposure to prolonged inflammatory responses damages tissues over time (Ershler & Keller, 2000). C-reactive protein (CRP) and interleukin-6 (IL-6) are two inflammatory markers commonly used in studies that assess the link between social strain and inflammation. Research has recognized inflammation as a major physiological consequence of persistent marital distress (Kiecolt-Glaser et al., 2005), adolescent relationship conflicts (Allen et al., 2018), social isolation (Heffner et al., 2011), and perceived loneliness (Steptoe et al., 2004).

Another pathway that links social support to physical health is via the cardiovascular system (Uchino, Cacioppo, & Kiecolt-Glaser, 1996; Uchino, 2006). Among physiological markers of cardiovascular health, heart rate variability (HRV) is associated with lifetime cardiovascular risk factors (Kubota et al., 2017) and cardiovascular disease itself (Dekker et al., 2000). Theories suggest that social support may influence heart rate variability by activating parasympathetic nervous system. For example, difficulties in establishing and maintaining social relationships from adolescence had been linked to lower vagal tone, a marker of the extent to which the parasympathetic system controls heart rate variability (Allen et al., 2022). A recent meta-analysis that reviewed relationship between social support and heart rate variability suggests that higher perceived social support was associated with higher levels of heart rate variability during rest, stress induction, and recovery phases (Goodyke et al., 2021).

Individual differences in Seeking and Perceiving

Broad literature on social support and health focuses on intervening mechanisms and on the other hand, many of the existing research also focuses on potential moderators by sociodemographic or individual differences within this process. For example, the link between social support and health outcomes is moderated by individual differences such as sex, socioeconomic status, attachment styles, and personality traits. For example, as compared to men, women are more likely to seek out and receive help, be satisfied with the help they receive, and benefit from the buffering effect of social resources (Copeland & Hess, 1995; Ptacek, Smith, & Zanas, 1992; Walen & Lachman, 2000). Similarly, socioeconomic status affects the harshness and instability an individual is likely to experience, which through a measure of life history, interacts with genetic predispositions and culminate in unique mental and physical adaptations (Gonzalez, Wroblewski, et al., 2021; Neff & Karney, 2017; Randall & Bodenmann, 2009). Individuals with secure attachment styles are more likely to seek out social support and perceive that support as positive (Collins & Feeney, 2004) while self-reported attachment anxiety was associated with a stronger relationship between emotional overinvolvement and blood pressure reactivity after marital separation (Lee et al., 2011). Likewise, extroverts are more likely to seek social support and perceive them as more available in their social circle (Swickert et al., 2002). Thus, the vast majority of theoretical models of social support and health include that any given mechanism linking social support and health can be moderated by person- and situation-level variables (e.g. gender, socioeconomic status, individual differences).

Yielding – An Opportunity to Conserve Personal Resources

To conceptualize the moderators in this process found so far, to some extent, Bayesian model suggests that our brain utilizes prior social experiences to place "bets" on whether and the degree to which we should invest personal resources (e.g. vigilance vs. foraging) in the presence of social resources that may be capable (and willing) to provide those resources for us. Sociodemographic and individual difference variables seen so far as moderators within the process served to some extent as either past experiences of direct consequences of past experiences. From a theoretical model perspective on relationship, Butler (2011)'s model of temporal interpersonal emotional systems (TIES) stated that components of relationship should be conceptualized as a dynamical system such that one's affective experience should be connected to that of another and also changes as a function of their past states. So here, individual differences and sociodemographic moderators could be viewed as past states or factors of past relationships that will continue to exert effects on one's current psychological functioning. From both perspectives, a definition categorizing past experiences related to close relationships, or factors that affected past states of relationship is greatly needed to conceptualize the individual and demographic differences observed in a simpler term.

Here previous work has conceptualized "yielding" as an individual's willingness (or ability) to relax physiological investments when the opportunity arises to depend on the labor (cognitive, emotional, physiological) of others (Gonzalez, Coppola, et al., 2021). Yielding related processes are well documented in animal literature where animals use social resources to decrease time spent on the "lookout" and increase opportunities for foraging (Ridley, Raihani, & Nelson‐Flower, 2008; Lanham & Bull, 2004; Kutsukake, 2007). On the other hand, reliance on social resources facing threats can be risky (Robinette & Ha, 2001). Accordingly, our brain utilizes prior social experiences to place "bets" on whether and the degree to which we should invest personal resources (e.g. vigilance vs. foraging) in the presence of social resources that may be capable (and willing) to provide those resources for us. Individual differences in yielding are hypothesized to correspond with differences in the physical and psychosocial health one is likely to enjoy.

In past work, we have observed that the presence of a relational partner corresponds with less activation of a participant's threat-responsive neural circuits compared to when the participant is alone, an observation we now characterize as an instance of yielding. These effects are observed most consistently in the dorsal anterior cingulate cortex (dACC) and dorsolateral prefrontal cortex (dlPFC), regions commonly associated with emotion, cognitive-control, and self-regulation (MacDonald et al., 2000; Coan et al., 2017, 2006; Gonzalez et al., 2015), and differentially linked to health outcomes via modulated neural reactivity (Eisenberger et al., 2007; Morys, Bode, & Horstmann, 2018). As an individual difference variable, yielding in the hypothalamus corresponds with higher self-ratings of general health (Brown et al., 2017). Thus, the association between health and social support is also partly mediated through the social regulation of threat-related hypothalamic activations—yielding in the hypothalamus.

Yielding and Perceived Social Support – An Interaction Effect

Few research has examined the relationship between yielding and perceived social support directly. However, past research indicated that this relationship is plausible from various sources of findings. For example, Farrell and colleagues (2019) tested adult attachment style as a mediator between maternal sensitivity and cardiometabolic risk in middle adulthood. The researchers found that secure-base script knowledge partially mediated the path between maternal sensitivity in infancy and cardiometabolic risk in middle adulthood, suggesting that awareness and engagement of successful support seeking may be one way relationship experience can be translated into health related outcomes.

One potential mechanism linking social support and health is through attachment orientations, representing internal working models developed in childhood on the basis of experiences with one's primary caregiver. Continuously shaped by relationship experiences, attachment orientation formed intenral models guided cognition, affect, and behaviors and ininfluence how people assess and cope with stressors and how they effectively seek support in romantic relationships (Ehrlich, Miller, Jones, & Cassidy, 2016). The brain has shifted from a solely reactive role to being as a predictive organ. Yet, we know surprisingly little about the neurocognitive processes linking social support and health. Past research examined the brain as a mechanism linking psychological stress and inflammation in cancer patients (Leschak et al., 2020), and early life trauma, inflammation and symptoms of PTSD and depression in Black women (Mehta et al., 2019), and responses to painful or emotionally salient content underlying self affirmation (Dutcher et al., 2020). For instance, Inagaki and Meyer (2019) showed that task based activations in dorsal anterior cingulate, anterior insula, and amygdala in response to people in need are negatively related, suggesting that social experience contribute to health by altering activity in these regions, and thus, assessing established neural processes in close relationships, social influence, self-regulation might help explore the mediating process associating between social support and health.

Purpose of the Present Study

As discussed, prior research has revealed many instances of yielding using fMRI; At a group level, neural activations in response to threat are reduced in the presence of a social resource. In the current study, we employed a longitudinal dataset consisting of individual differences across a variety of brain regions in yielding as measured by fMRI, along with self report measures of perceived social support, and both self-reported and independently evaluated health outcomes across an eight-year span. The aim of the study was to understand how yielding as an individual trait interacts with perceived social support and subsequent health outcomes, including cardiovascular health and immune system health.

Methods

Participants

Scanned participants were drawn from a larger longitudinal study, which has been tracked annually for over a decade (Allen et al., 2007). The VIDA longitudinal sample initially recruited adolescents from the 7th and 8th grades of a public middle school at suburban and urban Southeastern United States. At around age 24 (Wave I of the current study), participants from the longitudinal sample were recruited via telephone or email to participate in the neuroimaging task. To be included, participants were asked to bring a willing romantic partner or friend to provide supportive handholding during the scanning sessions. Participants who were pregnant or exhibited any risk of danger in the scanning environment were excluded. The final neuroimaging sample included 86 participants. Of scanned participants, 27 identified their dyads as friends, 29 as dating, 27 as cohabitating, and 3 as married.

From around age 28 – 30 (Wave II) and age 30 - 32 (Wave III), participants were contacted to complete two rounds of subsequent health visits. 3 participants were excluded for failing to complete both subsequent health visits. The final analyses included 83 participants (46 female, 37 male; 24 African American, 1 Hispanic/ Latinx, 49 White/European, 6 Mixed Race, 3 Others).

Power for this study is greater than 80% to detect effect sizes as small as f^2 =.098 (d = 0.6). The power is considered good given the relatively large effect size (e.g. average odds ratios was 1.5, equivalent to effect sizes d > .80) calculated by meta-analysis examining social relationships and mortality risks (Holt-Lunstad, Smith, & Layton, 2010).

Procedure

Handholding fMRI task at Wave I (Around Age 24). Participants brought an opposite-gender romantic partner or same-gender friend who were willing to visit the lab and provided handholding while participants were in the scanner. Before participants entered the scanner, two Ag-AgCI shock electrodes were applied to the participants' ankle. Each participant underwent three blocks of "threat of shock paradigm" in counterbalanced order, where they held the hand of their partner, an unseen confederate, or were alone. Each block was composed of 24 trials, including an equal number of threat and safety trials. A threat trial is consisted of 1-second threat cue (a red "X" on a black background), followed by 4 – 10 seconds of anticipation period (a fixation cross), and 17% chance of receiving electric shock, prior to the end cue (a small dot). A safety trial is consisted of 1-second safety cue (a blue "O" on a black background), followed by 4 – 10 seconds of anticipation period, with no chance of shock, prior to the end cue. The shock was administered by an isolated physiological stimulator and lasted for 20ms at 4mA (Coulbourn Instruments, Allentown, PA, USA). Following the completion of the handholding task, participants rated their perceived level of support using the Multidimensional Scale of Perceived Social Support Scale (MSPSS).

Health Visits \. Participants came back for two subsequent health visits. A variety of health-related outcomes were measured, including participants' interleukin-6 level, C-Reactive Protein level and heart rate variability at four conditions. Participants also reported height and weight at Wave II and their Body Mass Index was calculated. Due to the length of the main text, the results were reported in the Supplementary Materials.

All experiments in the study were approved by the Institutional Review Board at the University of Virginia. Participants' data were protected by a Confidentiality Certificate issued by the U.S. Department of Health and Human Services, which protected information from subpoena by federal, state, and local courts. However, analysis code is available online: https://osf.io/za4ud/. Adult participants and participating dyads provided informed consent and were all paid for participation.

Image Acquisition

Functional images were acquired using Siemens 3 Tesla MAGNETOM Trio High-speed imaging device, with a 12-channel head-coil with integrated mirror. Before functional images were obtained, a total of 176 anatomical T1-magnetization-prepared rapid-acquisition gradient echo images were acquired (TE = 2.53 ms; TR = 1900 ms; flip angle = 9°; FOV = 250 mm; voxel size = 1mm x 1mm x 1mm; image matrix = 256 mm x 256 mm; slice thickness = 1mm), to determine the localization of function. After the anatomical scan, a total of 216 functional T2*-weighted echo planar images were collected for each block (TE = 40 ms; TR = 2000 ms; flip angle = 90°; FOV = 192 mm; voxel size = 3mm x 3mm x 3.5 mm; image matrix = 64 mm x 64 mm; slice thickness = 3.5 mm; slice gap = 1mm). T2*-weighted echo planar images were collected in volumes of 28 slices, each slice with 3.5 mm thickness and 1 mm gap, covering the whole brain.

Imaging data were preprocessed and analyzed using FMRIB's Software Library (FSL) software (Version 5.98; www.fmrib.ox.ac.uk/fsl, Worsley, 2001). fMRI images were skull-stripped to eliminate non-brain material voxels using Brain Extraction Tool (BET; Smith, 2002).

Functional images were corrected for motion using FMRIB's Linear Image Registration Tool and intra-modal correction algorithm tool (MCFLIRT; Jenkinson et al., 2002), with slice scan time correction, a high-pass filtering cutoff point of 100s, and smoothed using a 5 mm full width at half minimum Gaussian kernel to remove irrelevant signals. Functional images were registered on the individual T1 images and then to the Montreal neurological Institute (MNI) space using FLIRT (Jenkinson et al., 2002). Trials where participants received shock were deleted to remove movement artifacts.

First and second-level analyses were conducted using FMRI Expert Analysis Tool (FEAT; Version 6.00). First level analyses began with a threat minus safety contrast applied separately to each handholding condition for each subject. During second-level analyses, data were collapsed across the three handholding conditions using a fixed effects model. Additional contrasts comparing each handholding condition in all possible combinations were employed, including alone minus partner condition (Detailed pre-processing and higher-level analyses, see Coan et al., 2017).

Predictors

Regions of Interest (ROIs). We focused on dACC, dlPFC, and hypothalamic ROIs. dACC and dlPFC were functionally defined metanalytically using neurosynth.org. The terms "dACC" and "dlPFC" were searched individually and reverse inference statistical maps were extracted at the FDR corrected $p > 0.01$ level. FSL's cluster command was used to generate binary mask of these regions. The masks were then coregistered with the anatomical Harvard Oxford Cortical and Subcortical atlases using fsleyes and fslmaths, and clusters with the greatest overlap were extracted and used as the dACC and dlPFC ROIs. The centroid and size for each ROI are as follows: dACC, $x = -1.31$ $y = 27$ $z = 26.3$, $k = 466$; dlPFC, Left: $x = -40.2\ 3$, $y = 30.1$, $z = 32.3$, Right: x = 38.9 y = 37.3 z = 27.1, k = 1345 (see Gonzalez, Coppola, et al., 2021). The hypothalamic ROI was created by deriving the peak hypothalamus coordinates from an independent sample of participants who completed the same hand-holding paradigm (Coan et al., 2006). The derived coordinates were used to create a 3x3x3 voxel region of interest (see Brown et al., 2017).

Yielding (see Gonzalez, Coppola, et al., 2021). Yielding is operationalized as decreased activity in any neural or physiological system in the presence of a social resource, in reference to activity in the same neural or physiological system while alone. The value of yielding was extracted by applying the dACC, dlPFC, and hypothalamic masks to the second-level threat minus safety, alone minus partner condition contrasts. The value of yielding across three ROIs was averaged by multiplying respective Z scores with the number of voxels in each mask and dividing by the total number of voxels. Yielding is indexed as threat-safety Z scores to the alone-partner condition, with higher scores indicating a greater difference between threat-related activity while alone versus with a relational partner, hence greater yielding.

Multidimensional Scale of Perceived Social Support (MSPSS). The Multidimensional Scale of Perceived Social Support (Zimet et al., 1988) is a 12-item questionnaire which assesses participants' perceived support from friends, family, and significant others. It uses a 7-point Likert scale, in which higher score indicates higher perceived support. Historically, the MSPSS has excellent internal consistency (Cronbach's α = .88) and test-retest reliability (Cronbach's α ~ .85; Zimet et al., 1988). The current study uses the total MSPSS score ($M_{MSPSS} = 6.12$; $SD_{MSPSS} = 0.90$).

Outcomes

Heart Rate Variability (HRV). Heart rate variability was assessed in terms of heart interbeat intervals obtained from an electrocardiogram at rest (baseline HRV), while giving a stressful speech imagining that they were department store shopping and the security guard falsely accused them of shoplifting a belt (speech HRV; see Cacioppo et al., 1995; Kirschbaum et al., 1993), while completing a math subtraction task where they were asked to subtract numbers out loud for 6 minutes as quickly as they could (math HRV), and at recovery (recovery HRV). Heart rate variability was monitored using a Mindware 2000D module with five-lead electrodes placed according to standard ECG placement recommendations (Hoetink et al., 2002). One participant with a history of heart disease was excluded from the respective model.

Interleukin-6 (IL-6) and C-Reactive Protein (CRP). Both Interleukin-6 and C-Reactive Protein levels were assessed from drawn blood. To assess circulating concentrations of inflammatory cytokines, approximately 20 ml of blood were collected and treated with EDTA (to prevent clotting). Plasma was separated via centrifugation, aliquoted, and stored at –80 °C. IL-6 and CRP were measured by ELISA (limit of detection = 0.3 pg/ml; R&D Systems, San Diego, CA). Intraassay and interassay coefficients of variation (%CV) are 2.8% and 5.2% for C-Reactive protein, and 3.6% and 8.6% for IL-6, respectively. Resulting scores were then log-transformed, as is typical with this measure to address skewness.

Body Mass Index (BMI). Participants' height (in inches) and weight (in pounds) was assessed by trained research assistants. BMI was calculated by using the formula: BMI = weight / height, which was then multiplied for a conversion factor of 703. Resulting scores were then log-transformed to address skewness. Analyses involving Body Mass Index were included in the

Supplementary Materials. All other numerical data were mean centered to address multicollinearity.

Covariates

Analyses were adjusted for the following variables.

Baseline family income. Parents of participants self-reported their estimated annual household income before taxes in 1998. Their baseline income was transformed to an eight-point categorical variable (ranging from 1 = *under $5,000* to 8 = *$60,000 or more*), with higher score indicating higher baseline income. Adolescents' parents reported a median family income in the $40,000 - $59,999 range (M = $43,600; *SD* = $22,400) at the initial assessment, which resembles the national median household income of $39,000 in 1998.

Sex. Sex is coded as a binominal categorical variable, in which Male is recorded as 1 and Female is recorded as 2.

Race. Race is coded as a binominal categorical variable, in which White/European is recorded as 1 and others were recorded as 0.

Age. Age is recorded as a continuous variable and participants' age at Wave I was entered into the model.

Season. Season is recorded by converting the date of the health visits to season time of the year (Spring, Summer, Autumn, Winter).

Statistical Analyses

Statistical analyses were conducted using R statistical software (3.6.3). We used generalized linear models to examine the interacting effect of Yielding and MSPSS score at Wave I on inflammation markers (IL-6 and CRP levels) and resting and state heart rate variability at Waves II and III. These models were adjusted for age, sex, race, baseline family income, and season when the health data was recorded. When heart rate variability under stress and recovery was the predicted outcome, the respective models also adjusted for baseline heart rate variability. To interpret the interaction effect, we used PROCESS v4.1 for R (Hayes, 2017) with bias-corrected 95% confidence intervals (n = 10000). To best address any potential biases due to missing data, full information likelihood (FIML) method was employed, using *lavaan* in R (Rosseel, 2012), to yield the least biased estimates. Because PROCESS currently has no internal procedure to deal with missingness other than listwise deletion (Hayes, 2017), the values obtained via PROCESS are for interpretation purposes, and significance of terms should be derived from the main model.

Results

Descriptive Statistics

Means and standard deviations for primary study variables (before transformations) are presented in **Table 1**. In Wave II, around 86% - 94% participants' health data were recorded and in Wave III, 42% - 64% participants' health data were recorded. Intercorrelations among study variables are presented in Supplementary Materials (see Supplementary Table 1).

Variable	*n*	*M*	*SD*
Wave I:			
1. Perceived Support (MSPSS):			
Wave I	82	6.12	0.90
2. dACC Yielding	83	0.01	0.49
3. dlPFC Yielding	83	0.05	0.51
4. Hypothalamus Yielding	83	-0.02	0.75
5. Yielding across ROIs	83	0.02	0.39
Wave II:			
6. IL-6 Level	71	1.89	2.03
7. CRP Level	71	5.76	10.66
8. Baseline HRV	77	6.26	1.25
9. Recovery HRV	77	6.37	1.07
10. Speech HRV	77	6.18	1.04
11. Math HRV	77	6.40	1.04
12. BMI	78	28.68	10.06

Wave III:			
13. IL-6 Level	53	2.51	2.73
14. CRP Level	55	6.44	14.82
15. Baseline HRV	35	6.24	1.33
16. Recovery HRV	35	6.33	1.20
17. Speech HRV	35	6.17	1.11
18. Math HRV	35	6.23	0.96

Table 1. Sample characteristics and descriptive statistics

Interaction effect of yielding and support on Immune system: Interleukin-6 (IL-6)

The interaction between yielding and perceived social support assessed at Wave I did not predict subsequent IL-6 level at Wave II after adjusting for age, sex, race, baseline income, and season (dACC: β = -0.11, se = 0.20, z = -0.55, p = 0.580, 95% CI [-0.50, 0.28]; dlPFC: β = -0.28, se = 0.28, z = -0.99, p = 0.324, 95% CI [-0.83, 0.27]; hypothalamus: β = -0.16, se = 0.15, z = -1.03, p = 0.305, 95% CI [-0.46, 0.14]). The interaction was also not significant when yielding was averaged across three ROIs (β = -0.33, se = 0.32, z = -1.04, p = 0.301, 95% CI [-0.96, 0.30]), The rest of the results were all reported after adjusting for respective covariates.

The interaction between dACC and hypothalamus-related yielding and perceived support predicted IL-6 level assessed at Wave III: across two ROIs, greater perceived social support was associated with less subsequent IL-6 concentration (dACC: β = 0.48, se = 0.23, z = 2.07, p = 0.039, 95% CI [0.03, 0.93]; **Figure 1A;** hypothalamus: β = -0.46, se = 0.15, z = -3.01, p = 0.003, 95% CI [-0.77, -0.16]; **Figure 1B).** Within hypothalamus, the effect was strongest in the high yielding group (1 SD above the mean of yielding: β = -0.70, se = 0.21, t = -3.26, p = .003, 95% CI [-1.13, -0.26]), and then in the average yielding group (β = -0.40, se = 0.14, t = -2.86, p = .008, 95% CI [-0.68, -0.11]). This effect was the weakest in the low hypothalamus yielding group (1 SD below the mean of yielding: β = - 0.10, se = 0.18, t = -0.54, p = .593, 95% CI [-0.46, 0.27]). In contrast, within dACC, the effect was strongest in the low yielding group (β = -0.54, se = 0.18, t = -2.97, p = 0.006, 95% CI [-0.92, -0.17]), weaker in the average yielding group (β = -

0.29, se = 0.14, t = -2.11, p = 0.043, 95% CI [-0.58, -0.01]), and the weakest in the high yielding group (β = - 0.05, se = 0.20, t = -0.23, p = 0.823, 95% CI [-0.46, 0.37]). This effect was not significant in other ROIs (dlPFC: β = -0.26, se = 0.37, z = -0.70, p = 0.484, 95% CI [-0.98, 0.46]; average: β = -0.12, se = 0.50, z = -0.24, p = 0.813, 95% CI [-1.14, 0.90]).

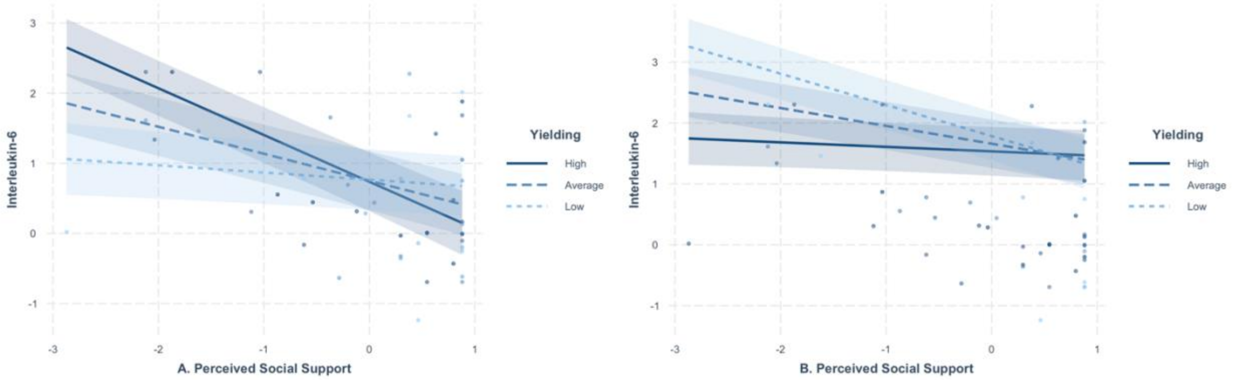

Figure 1A-B. The interaction between yielding and perceived social support predicted IL-6 level assessed at Wave III. Figure 1A: Across the three ROIs, the interaction between yielding and perceived support was significant within **hypothalamus**: higher perceived social support was associated with lower IL-6 level and this prediction was strongest in the high yielding group. **Figure 1B:** The effect was also significant within **dACC**: higher perceived social support was associated with lower IL-6 level but this prediction was strongest in the low yielding group. The values of IL-6 and perceived support were after transformations. Shading represents 95% CIs.

Interaction effect of yielding and support on Immune system: C-Reactive Protein

The interaction between dACC-related yielding and perceived social support predicted CRP level assessed at Wave II: greater perceived social support was associated with lower CRP level (β = -1.02, se = 0.44, z = -2.33, p = 0.020, 95% CI [-1.88, -0.16]; **see Supplementary Figure 1)**. The effect was strongest in the high yielding group (β = -0.56, se = 0.35, t = -1.62, p = 0.112, 95% CI [-1.26, 0.14]), and then in the average yielding group (β = 0.00, se = 0.25, t = -0.01, p = 0.994, 95% CI [-0.51, 0.51]), and in the opposite direction in the low yielding group (β = 0.56, se = 0.37, t = 1.49, p = 0.143, 95% CI [-0.19, 1.31]). The interaction was not significant within other ROIs: (dlPFC: β = -0.73, se = 0.63, z = -1.16, p = 0.245, 95% CI [-1.97, 0.50]; hypothalamus: β = -0.15, se = 0.35, z = -0.43, p = 0.671, 95% CI [-0.84, 0.54]; average: β = -1.36, se = 0.71, z = -1.91, p = 0.056, 95% CI [-2.75, 0.04]).

At Wave III, the interaction between yielding and perceived social support did not predict subsequent CRP level (dACC: β = -0.30, se = 0.46, z = -0.67, p = 0.505, 95% CI [-1.20, 0.59]; dlPFC: β = -0.53, se = 0.68, z = -0.78, p = 0.436, 95% CI [-1.87, 0.81]; hypothalamus: β = -0.05, se = 0.31, z = -0.15, p = 0.883, 95% CI [-0.66, 0.57]; average: β = -0.63, se = 0.71, z = -0.90, p = 0.369, 95% CI [-2.02, 0.75]).

Interaction effects of yielding and support on heart rate variability: resting

At Wave II, the interaction between hypothalamic yielding and perceived social support predicted baseline heart rate variability: greater perceived social support was associated with greater baseline HRV (β = 0.49, se = 0.23, z = 2.12, p = 0.034, 95% CI [0.04, 0.94]; **Figure 2A**). The effect was strongest in the high yielding group (β = 0.63, se = 0.25, t = 2.48, p = 0.017, 95% CI [0.12, 1.13]), weaker in the average yielding group (β = 0.20, se = 0.17, t = 1.15, p = 0.254, 95% CI [-0.15, 0.54]), and in the opposite direction in the low yielding group (β = -0.23, se = 0.27, t = -0.86, p = 0.395, 95% CI [-0.78, 0.31]). The interaction was not significant at other ROIs (dACC: β = 0.37, se = 0.28, z = 1.34, p = 0.181, 95% CI [-0.17, 0.92]; dlPFC: β = 0.19, se = 0.35, z = 0.54, p = 0.591, 95% CI [-0.50, 0.88]; average: β = 0.35, se = 0.39 z = 0.90, p = 0.369, 95% CI [-0.42, 1.12]).

The interaction between yielding and perceived social support did not predict baseline HRV at Wave III (dlPFC: β = -0.26, se = 0.69, z = -0.37, p = 0.712, 95% CI [-1.61, 1.10]; dACC: β = -0.60, se = 0.50, z = -1.21, p = 0.225, 95% CI [-1.58, 0.37]; hypothalamus: β = -0.27, se = 0.31, z = -0.88, p = 0.382, 95% CI [-0.88, 0.34]; average: β = -0.34, se = 0.69, z = -0.50, p = 0.620, 95% CI [-1.69, 1.01]).

Interaction effects of yielding and support on heart rate variability: giving a speech

Across three ROIs, the interaction between yielding and perceived social support did not predict heart rate variability at Wave II when giving a speech (dACC: $\beta = 0.07$, se = 0.12, z = 0.55, p = 0.582, 95% CI [-0.17, 0.31]; dlPFC: $\beta = -0.14$, se = 0.15, z = -0.92, p = 0.358, 95% CI [-0.43, 0.16]; hypothalamus: $\beta = -0.16$, se = 0.11, z = -1.48, p = 0.139, 95% CI [-0.37, 0.05]; average: $\beta = -0.08$, se = 0.16, z = -0.48, p = 0.632, 95% CI [-0.40, 0.24]).

At Wave III, the interaction between dlPFC-related yielding and perceived social support predicted heart rate variability when giving a speech: greater perceived social support was associated with greater speech HRV ($\beta = 0.80$, se = 0.33, z = 2.44, p = 0.015, 95% CI [0.16, 1.44]; **Figure 2B)**. The effect was strongest in the high yielding group ($\beta = 0.34$, se = 0.30, t = 1.14, p = 0.272, 95% CI [-0.30, 0.98]), weaker in the average yielding group ($\beta = 0.09$, se = 0.16, t = 0.60, p = 0.558, 95% CI [-0.24, 0.42]), and in the opposite direction in the low yielding group ($\beta = -0.16$, se = 0.24, t = -0.65, p = 0.522, 95% CI [-0.66, 0.35]). The interaction was also significant at hypothalamus, following a similar trend ($\beta = 0.51$, se = 0.13, z = 3.82, $p < 0.001$, 95% CI [0.25, 0.77]; **Figure 2C**). This effect was strongest in the high yielding group ($\beta = 0.47$, se = 0.24, t = 1.95, p = 0.069, 95% CI [-0.04, 0.98]), and then in the average yielding group ($\beta = 0.15$, se = 0.15, t = 0.98, p = 0.341, 95% CI [-0.17, 0.46]), and in the opposite direction in the low yielding group ($\beta = -0.18$, se = 0.16, t = -1.07, p = 0.301, 95% CI [-0.52, 0.17]). The interaction was also significant when averaged across three ROIs, following a similar trend ($\beta = 0.75$, se = 0.32, z = 2.32, p = 0.021, 95% CI [0.12, 1.38]); **see Supplementary Figure 2**): This effect was strongest in the high yielding group and in the opposite direction in the low yielding group (high yielding: $\beta = 0.31$, se = 0.28, t = 1.10, p = 0.288, 95% CI [-0.28, 0.90]; average yielding: $\beta = 0.09$, se = 0.15, t = 0.59, p = 0.564, 95% CI [-0.24, 0.42]; low yielding ($\beta = -0.12$, se = 0.22, t = -0.56, p = 0.584, 95% CI [-0.59, 0.35]). The interaction was not significant within dACC (β = 0.31, se = 0.26, z = 1.20, p = 0.231, 95% CI [-0.20, 0.82]).

Interaction effects of yielding and support on heart rate variability: math subtraction task

The interaction between yielding and perceived social support did not predict heart rate variability during a math subtraction task at Wave II (dACC: β = -0.15, se = 0.16, z = -0.91, p = 0.362, 95% CI [-0.50, 0.17]; dlPFC: β = -0.14, se = 0.20, z = -0.69, p = 0.493, 95% CI [-0.53, 0.26]; hypothalamus: β = -0.03, se = 0.14, z = -0.21, p = 0.832, 95% CI [-0.30, 0.24]; average: β = -0.19, se = 0.22, z = -0.85, p = 0.394, 95% CI [-0.62, 0.25]).

At Wave III, the interaction between hypothalamic yielding and perceived support predicted heart rate variability at math subtraction: greater perceived social support was associated with greater math HRV (β = 0.36, se = 0.13, z = 2.77, p = 0.006, 95% CI [0.11, 0.62]; **Figure 2D**). This effect was strongest in the high yielding group (β = 0.38, se = 0.26, t = 1.46, p = 0.163, 95% CI [-0.17, 0.94]), and then in the average yielding group (β = 0.11, se = 0.16, t = 0.69, p = 0.502, 95% CI [-0.23, 0.45]), and in the opposite direction in the low yielding group (β = -0.16, se = 0.18, t = -0.89, p = 0.386, 95% CI [-0.54, 0.22]). This effect was not significant within other ROIs (dlPFC: β = 0.17, se = 0.31, z = 0.55, p = 0.585, 95% CI [-0.44, 0.78]; dACC: β = -0.07, se = 0.23, z = -0.28, p = 0.781, 95% CI [-0.52, 0.39]; average: β = 0.12, se = 0.31, z = 0.40, p = 0.691, 95% CI [-0.48, 0.73]).

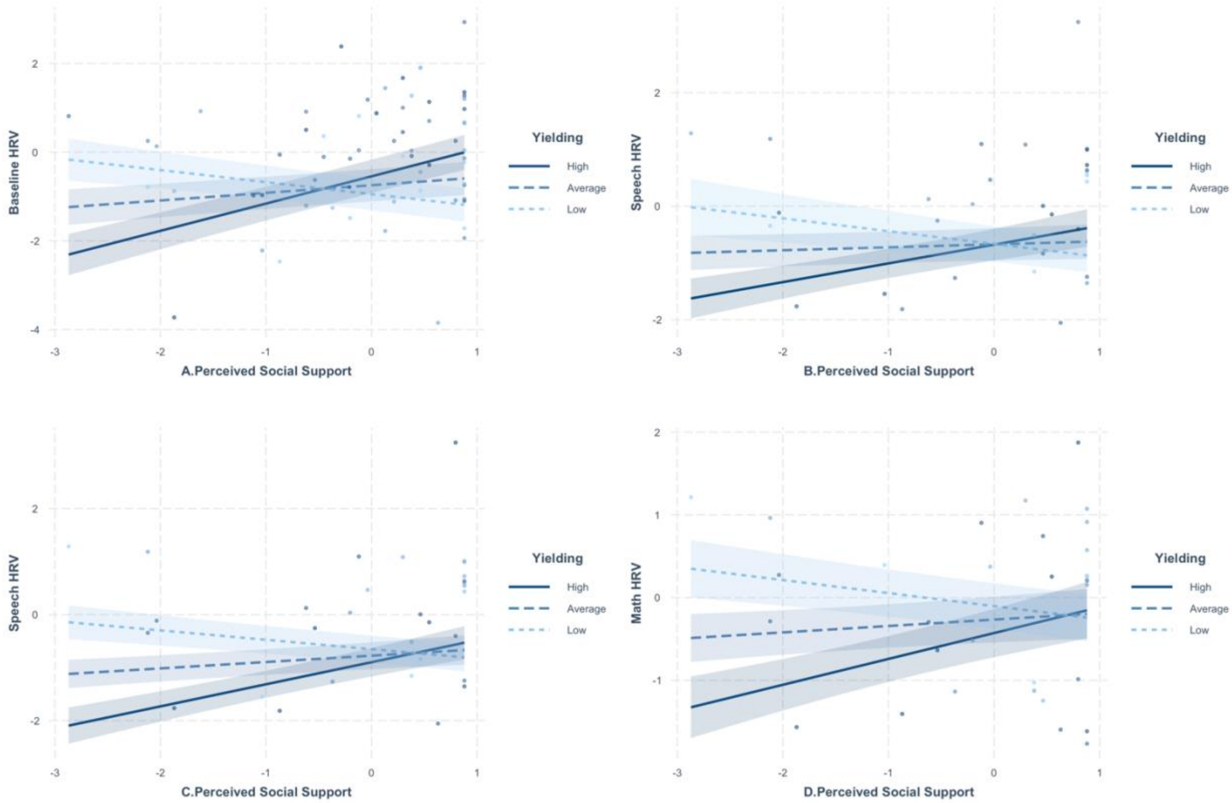

Figure 2A-D. The interaction between yielding and perceived social support predicted baseline, speech, and math heart rate variability assessed at Wave II and III. Figure 2A: The interaction assessing baseline heart rate variability was significant at **hypothalamus at Wave II**: higher perceived social support was associated with greater baseline heart rate variability and this prediction was strongest in the high yielding group. **Figure 2B:** The interaction assessing speech heart rate variability was significant within **dlPFC at Wave III**, in a similar trend. **Figure 2C:** The interaction assessing speech heart rate variability was also significant at **hypothalamus at Wave III**, following a similar trend. **Figure 2D:** The interaction assessing math heart rate variability was significant within **hypothalamus at Wave III**, in a similar trend. The values of heart rate variability and perceived support values were after transformations. Shading represents 95% CIs.

Interaction effects of yielding and support on heart rate variability: recovery

There was a significant interaction between hypothalamic yielding and perceived support on recovery heart rate variability at Wave II: greater perceived social support was associated with greater recovery HRV (β = -0.24, se = 0.11, z = -2.08, p = 0.038, 95% CI [-0.46, -0.01]; **see Supplementary Figure 3A**). This effect was strongest in the low yielding group (β = 0.12, se = 0.13, t = 0.91, p = 0.368, 95% CI [-0.14, 0.37]), and then in the average yielding group (β = 0.01, se = 0.08, t = 0.09, p = 0.929, 95% CI [-0.15, 0.17]), and in the opposite direction in the high yielding group (β = -0.10, se = 0.13, t = -0.82, p = 0.418, 95% CI [-0.35, 0.15]). This effect was not significant within other ROIs (dACC: β = 0.04, se = 0.14, z = 0.30, p = 0.767, 95% CI [-0.23, 0.31]; dlPFC: β = -0.004, se = 0.17, z = -0.03, p = 0.980, 95% CI [-0.34, 0.33]; average: β = 0.02, se = 0.19, z = 0.09, p = 0.927, 95% CI [-0.35, 0.39]).

At Wave III, there was a significant interaction between dACC-related yielding and perceived support on recovery heart rate variability: greater perceived social support was associated with greater recovery HRV (β = -0.36, se = 0.12, z = -3.02, p = 0.002, 95% CI [-0.60, -0.13]; **see Supplementary Figure 3B**). This effect was strongest in the low yielding group (β = 0.12, se = 0.11, t = 1.11, p = 0.285, 95% CI [-0.11, 0.34]), and then weaker in the average yielding group (β = -0.05, se = 0.08, t = -0.58, p = 0.573, 95% CI [-0.22, 0.12]), and in the opposite direction in the low yielding group (β = -0.21, se = 0.12, t = -1.72, p = 0.104, 95% CI [-0.47, 0.05]). This effect was not significant within other ROIs (dlPFC: β = -0.15, se = 0.17, z = -0.89, p = 0.375, 95% CI [-0.48, 0.18]; hypothalamus: β = 0.09, se = 0.08, z = 1.17, p = 0.242, 95% CI [-0.06, 0.24]; average: (β = -0.28, se = 0.16, z = -1.73, p = 0.083, 95% CI [-0.61, 0.04]).

Discussion

This study examined the interaction between perceived social support and tendency to yield to one's partner for help on subsequent health outcomes. Specifically, we looked at two inflammatory markers, including Interleukin-6 (IL-6) and C-Reactive Protein (CRP) and a physiological marker of cardiovascular health—heart rate variability (HRV)—while giving a stressful speech, while doing a math subtraction task, and during a recovery period across two waves. Our results showed that greater perceived social support corresponded with lower inflammatory activity and greater resting, stress, and recovery heart rate variability, especially among individuals who showed less activity in the hypothalamus, dlPFC, and dACC during the provision of actual social support, a process we have called "yielding" (Gonzalez, Coppola, et al., 2021).

As expected, the relationship between perceived social support and physical health was robust: greater perceived social support was associated with beneficial health outcomes, including inflammatory responses (measured by IL-6 and CRP) and heart rate variability. This is consistent with the extant literature (Goodyke at al., 2021; Steptoe et al., 2004), and replicated past studies employing the same dataset (vagal tone, Allen et al., 2022; IL-6, Allen et al., 2018; subjective health, Brown et al., 2017).

More importantly, we observed an interaction between perceived social support and yielding in predicting both inflammatory responses and heart rate variability. For the majority of our findings, individuals displaying a high degree of yielding across dlPFC, dACC, and hypothalamus and perceiving themselves to enjoy higher levels of social support had lower inflammatory responses as measured by IL-6 and CRP, and greater resting and stress heart rate variability. In other words, perceived social support was associated with lower subsequent inflammatory activity and greater heart rate variability, but only among individuals who actually yielded to a source of social support while under threat. In the low yielding group, where individuals were less likely to yield to their partner under threat (compared to the sample average), the amount of support one perceived did not have a strong effect on subsequent inflammatory activity and heart rate variability or the effect was even in the opposite direction.

In addition, we observed that hypothalamus-related yielding interacted with perceived social support across a range of health outcomes involved in inflammatory and cardiovascular reactivity responses. Given the vital role of hypothalamus in response to perceived stressor via the HPA-axis and corticosteroid release, our data provides additional neuroimaging evidence to a large literature supporting the stress buffering model: higher perceived social support corresponds with better health outcomes via modulated responses to stress (Gerin et al., 1992; Cohen et al., 2012). Higher perceived social support has also corresponded with greater resting heart rate variability, suggesting a link between access to social resources and parasympathetic nervous system devoted to the maintenance of bodily welfare and reduced energy expense. According to the ecological perspective, yielding utilizes prior social experiences to place "bets" on the deployment of personal resources; when threat-related tasks (e.g., vigilance, contingency planning) can be outsourced to others, resources devoted to those tasks can be conserved or applied to other tasks that could benefit an individual's health (Gonzalez, Coppola, et al., 2021).

Although numerous researchers suggested that *perceived* social support and *received* social support are separate concepts (Wills & Shinar, 2000), others argue that they are conceptually related and may even interact under some contexts (Uchino, 2009 for review). Uchino (2009) hypothesized that individuals with higher perceived support may benefit more from received support, via positive interpretations of schema-relevant information (Holmes, 2000); conversely, in the absence of one's receptibility to support seeking, individuals may discount the support received as it conflicts with other co-developed positive psychological factors (Bolger et al., 2000). Data presented here, as with other findings in our laboratory [masked for review] support this prediction: it was those who yielded to *received* social support who showed the strongest links between *perceived* social support and health.

Note that despite the majority of the interaction effects displaying a similar pattern, there are three findings that reversed the pattern. For example, the effect of perceived support on IL-6 level at Wave III was the strongest in the low dACC-related yielding group and the weakest in the high dACC-related yielding group. These findings add to the complexity of the relationship between social support, yielding, and health. Possible limitations of the current study are discussed below.

Strengths and limitations

The experimental manipulation of threat and social support increases our understanding of neurobehavioral mechanisms linking social support to physical health, addressing an important gap in the existing literature. Furthermore, by using a longitudinal design and a multilevel approach (behavioral, physiological, and neural), the current study adds to our general understanding of the social, psychological, physiological, and neural mechanisms of human health.

Nevertheless, limitations of the study include potential issues with our sample characteristics, data analytic approach, and the complexities inherent in measuring complex social phenomena. For example, our measurement of the MSPSS has introduced a ceiling effect ($M = 6.12$, $SD = 0.89$), suggesting they were heavily skewed towards perceiving (or reporting) a high degree of social support. In addition, our neuroimaging data was measured years before the health outcomes, so whether the participants' ability to yield changed as a function of the support they perceived remains a question. Future research should investigate the stability of yielding through repeated measures. Finally, although we adjusted for demographics based on existing literature, there might still be other covariates that we have not adjusted for. We also did not record participants' baseline health outcomes and for all these reasons, causal relationships from the results must be drawn with caution.

In addition, to ensure consistency with previous research findings from our lab, we limited our neural hypothesis preregistrations to the hypothalamus, dACC, and dlPFC. Future research may benefit from careful hypotheses involving other ROIs (e.g. ventromedial prefrontal cortex, amygdala, etc.), or exploratory whole-brain analyses. Finally, associations between seeking social support, giving social support, perceiving social support, and the amount of support actually received, is likely to be complex and is in any case still poorly understood. Existing research indicates that prosocial behaviors – support giving has emerged as a health promoting behavior (Inagaki, MacCormack, Muscatell, 2022). Future research could benefit by examining the additional role of support giving to fully examine and capture such complexity (Inagaki et al., 2017). Other physical health outcomes and measures could also be employed to examine other areas of health of interests that could be influenced by social support and yielding. Farrell and colleagues (2021) suggested that although research exploring changes in inflammation, autonomic nervous system, and neuroendocrine activity grew over the past decade, it might become increasingly important to connect these changes in the system to clinical endpoints such that the association is demonstrated with risk for clinical dysfunctions (e.g. coronary heart disease), worth future researchers to explore.

Conclusions

The current findings suggest that greater perceived social support is associated with better health outcomes, examined across inflammatory activity and heart rate variability. This association is stronger among individuals who “yield” to that source of support, measured by their neural activity across dACC, dlPFC, and hypothalamus. The results are consistent with a large existing literature on the link between social support and physical health. In addition, the current study highlights the role of *yielding*, which we have characterized as one’s likelihood to relax one’s efforts (or in this case one’s threat-related neural activity) in the presence of supportive social resources. Applying an ecological lens, yielding helps clarify the link between social support and health outcomes—that it involves the conservation or alternative application of physiological and attentional resources potentially critical to survival. Future research could benefit by investigating other regions of interests in the brain and an expanded view of socially supportive behavior. We await this research with interest and enthusiasm.

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