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

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Abstract

Objective: Social support has been linked to a vast range of beneficial health outcomes. However, the physiological mechanisms of social support are 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.

Methods: We employed a dataset where seventy-eight participants around the age of 24 were exposed to the threat of shock when holding the hand of a partner. At age 28 – 30, participants returned for a health visit where inflammatory activity and heart rate variability were recorded.

Results: Findings showed a significant interaction between dACC-related yielding and perceived social support on C-reactive protein levels ($\beta = -0.95$, se = 0.42, $z = -2.24$, $p = 0.025$, 95% CI [−1.77, −0.12]). We also found a significant interaction between hypothalamus-related yielding and perceived social support on baseline heart rate variability ($\beta = 0.51$, se = 0.23, $z = 2.19$, $p = 0.028$, 95% CI [0.05, 0.97]).

Conclusions: Greater perceived social support was associated with lower CRP levels and greater baseline heart rate variability among individuals who were more likely to yield to social support in the dACC and hypothalamus years earlier. The current study highlights the construct of *yielding* in the link between social support and physical health.

Keywords

social support; fMRI; yielding; physical health; cardiovascular health; inflammatory activity

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Conflicts of Interest, Source of Funding, and Data Transparency

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INTRODUCTION

Proximity to social resources corresponds with lower cardiovascular arousal (1), reduced glucocorticoid activity during and following stressful events (2,3), and decreased threat-related neural activation (4). Social Baseline Theory (SBT; 5) 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 and capabilities. 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 (6).

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 years after fMRI data were collected. Physical health outcomes span cardiovascular health and immune functioning.

Social Relationships, Health, and Wellbeing

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 (7–9). While a broad literature now clarifies the link between social support, physiological dysregulation, and health outcomes (10,11), another line of research has focused on individual differences that may moderate this process. For example, adults with different attachment styles differ in the nature and quality of their social interactions with others. In general, secure adults perceive their support figures as available and are satisfied with the support they receive (12–14). In contrast, insecure adults are less satisfied with the support they receive and estimate higher risks associated with seeking help from others (15). Attachment theory suggests that attachment represented working models contain information about the *expected likelihood* that others will be emotionally available in times of need (16), and when activated, these working models guide physiological and cognitive resources to direct decision making in support seeking behaviors (17). Other individual differences that moderate the link between social support and health outcomes include early life stability (18) and personality traits (19). 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 culminates in unique mental and physical adaptations (18). Individuals who are extroverted are also more likely to seek social support and perceive them as more available in their social circle (19). In short, prior research demonstrates that individual differences, largely derived from prior support-related information, affect the extent to which one is likely to seek and receive help, be satisfied with the help one receives, and benefit from the buffering effect of social resources. This is consistent with a larger area of research in social perception that suggests the role of top-down processes of individual schemas in

shaping one's cognition, affect, and behaviors, and construing supportive interactions with close others (20).

Yielding – Social Support as the Conservation of Personal Resources

We conceptualize "yielding" as an individual's willingness (or ability) to "yield" to available sources of support by relaxing physiological responses to perceived demands when the opportunity arises to depend on the labor (cognitive, emotional, physiological) of others (21). Yielding-related processes are well documented in the animal literature, where animals use social resources to decrease time spent on threat vigilance in order to increase opportunities for foraging (22–24). On the other hand, reliance on social resources in threatening contexts can be risky (25). Social Baseline Theory (SBT; 5) suggests that human brains draw on prior social experiences to place "bets" on whether, and the degree to which, we should invest *personal* resources (e.g., in vigilance or. foraging) when dependable *social* resources are available. 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 (4), an observation we now characterize as *instances* of yielding (21). 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, self-regulation, and self-reported pain unpleasantness (26–28). If yielding reflects a willingness (or ability) to seek and accept social support, we hypothesize that yielding can be conceptualized as a moderator of long observed links between social support and health such that individuals with a greater tendency to yield benefit more from the salubrious effects of social relationships.

There is reason to suspect this is so. First, literature reviewed above demonstrated that individual differences exist and moderate the link between social support and health. These factors utilize support-related schemas and shape how one assesses risks and seeks support in close others–similar to the construct of yielding. Reporting on the same fMRI sample as that reported on here, researchers observed a significant interaction between degrees of social support (handholding by a familiar partner, stranger, or no one) and concurrent *self-reported* general health measured via the Short Form Health Survey (SF-36) (29). Specifically, greater hypothalamic yielding while holding hands with a familiar partner, but not while alone or holding hands with a stranger, corresponded with greater concurrent self-reported general health. Similarly, Lee and Cichy (2020) assessed relationship quality, frequency of physical touch, and cardiovascular risk in adults participating in the National Social Life Health and Aging Project (30). Their results showed that relationship quality was differentially associated with cardiovascular risk depending on the level of physical touch: higher relationship quality was more strongly associated with lower cardiovascular risk among partners with more frequent physical touch. Both studies provided preliminary evidence consistent with the moderating effect of yielding. Although no other research has directly tested yielding as a moderator of social support and health, research in other areas could offer some additional clues. For example, Inagaki and Meyer (2020) reported that resting state and task-based activations in the dorsomedial (DMPFC) default network subsystem were associated with greater concurrent and subsequent tendency to provide (though not receive) social support (31). More pointedly, the DMPFC default network

subsystem moderated associations between observing negative emotional cues in others and activations in the dorsal anterior cingulate, anterior insula, and amygdala, suggesting that withdrawal-related brain activity is less likely to inhibit helping behavior among persons with relatively greater DMPFC default network subsystem activity.

Purpose of the Present Study

As discussed, prior research has revealed many instances of yielding, per se, using fMRI; it is now clear that, at a group level, threat-related neural activations are reduced in the presence of a social resource (32,4). In the current study, we employed a 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 independently evaluated health outcomes. The aim of the study was to understand how yielding in key brain regions may moderate the association between perceived social support and subsequent health outcomes, including measures of cardiovascular health and immune system health.

Methods

Participants

Scanned participants were drawn from the Kids, Lives, Families, and Friends/Virginia Institute for Development in Adulthood (Kliff/Vida) longitudinal study of adolescence, which has been tracked annually for over a decade (33). Participants were initially recruited from the 7th and 8th grades of a public middle school at suburban and urban Southeastern United States in 1998. From the winter of 2009 to the spring of 2012, participants (M_{age} = 23.53, SD_{age} = 1.04) from the sample were recruited via telephone or email to participate in the neuroimaging task at the University of Virginia. To be included, participants were asked to bring a partner or friend of the opposite sex 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. For the current study, “partner” refers to any of these types of relationships, as contrasted with “stranger,” an anonymous member of the opposite sex.

From the winter of 2013 to the spring of 2017, participants (M_{age} = 28.65, SD_{age} = 1.25) were contacted to complete a subsequent health visit. Study exclusion criteria include failing to complete the health visit, current cardiac problems (34), and acute inflammation (CRP > 10.0 mg/dL; 35). 8 participants were excluded for failing to complete the health visit. 1 participant was excluded from the respective model with a history of heart disease. The final analyses included 78 participants (44 female, 34 male; 22 African American, 1 Hispanic/Latinx, 46 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 (36).

Procedure

Handholding fMRI task I (Age 24).—Participants brought a romantic partner or 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 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 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 Visit (Age 28 – 30).—Participants came back for a subsequent health visit. A variety of health-related outcomes were measured, including participants' interleukin-6 level, C-reactive protein level, height and weight, and heart rate variability at rest.

All experiments in the study were approved by the Institutional Review Board at the University of Virginia. Participants' data are 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. The current dataset was derived from a larger study, but the analysis plan was pre-registered. Pre-registration and analysis code are available online: https://osf.io/za4ud/[1]. Adult participants and participating dyads provided informed consent and were 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.

[1]Discrepancy between pre-registration document and in-text analysis plan includes adding BMI as a covariate and limiting the outcome variable of heart rate variability to baseline heart rate variability only. These changes are made according to comments from reviewers.

Imaging data were preprocessed and analyzed using FMRIB's Software Library (FSL) software (Version 5.98; www.fmrib.ox.ac.uk/fsl; 37). fMRI images were skull-stripped to eliminate non-brain material voxels using Brain Extraction Tool (BET; 38). Functional images were corrected for motion using FMRIB's Linear Image Registration Tool and intra-modal correction algorithm tool (MCFLIRT; 39), 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 (39). 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 trial contrast applied separately to each handholding condition (alone, partner, stranger) for each subject. During second-level analyses, data were collapsed across the three handholding conditions using a fixed effects model. Contrast comparing alone minus partner handholding condition was made.

Predictors

Regions of Interest (ROIs).—We focused on dACC, dlPFC, and hypothalamic ROIs. dACC and dlPFC were functionally defined meta-analytically using neurosynth.org (see 21). 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 co-registered 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. The hypothalamic ROI was created by deriving the peak hypothalamus coordinates from an independent sample of participants who completed the same hand-holding paradigm (32). The derived coordinates were used to create a 3×3×3 voxel region of interest.

Yielding (21).— *Yielding* is operationalized as decreased activation of any neural or physiological system in the presence of a social resource, as compared to activity in the same neural or physiological system while alone. The metric of yielding was calculated by applying the dACC, dlPFC, and hypothalamic masks to the second level alone minus partner condition contrast. Yielding is thus indexed as the difference in threat-safety Z scores between the alone and partner condition (alone-partner). Higher scores indicate greater differences, hence greater yielding.

Multidimensional Scale of Perceived Social Support (MSPSS).—The Multidimensional Scale of Perceived Social Support (40) 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. In the current

study, the total MSPSS score (M_{MSPSS} = 6.09; SD_{MSPSS} = 0.91) demonstrated high internal consistency (Cronbach's α = .92).

Outcomes

Heart Rate Variability (HRV).—Heart rate variability was assessed in terms of heart rate reactivity while participants were resting in a comfortable chair, watching a soothing outdoor video for ten minutes (41,42). The assessment of heart rate variability was averaged over the final three minutes of this period. Heart rate and breathing were continuously monitored using a Mindware 2000D module. Five-lead electrodes were placed according to standard ECG placement recommendations (43) and each waveform was verified or edited prior to analyses.

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. Data associated with yielding, MSPSS, and HRV were mean centered according to common approach in neuroimaging and social science research broadly (44).

Covariates

Analyses were adjusted for the following variables. Socioeconomic status (45,46), sex (47,48), race (49,50), age (51,52), seasonality (53,54), and BMI (55,56) have all been associated with varying degrees of influence on inflammatory markers and heart rate variability index.

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 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).

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.

Statistical Analyses

Statistical analyses were conducted using R statistical software (3.6.3). We used general linear models to examine the interacting effect of Yielding and MSPSS score on inflammation markers (IL-6 and CRP levels) and heart rate variability. These models were adjusted for age, sex, race, baseline family income, BMI, and seasonal time when the health data was recorded. To interpret the interaction effect, we used PROCESS v4.1 for R (57) 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 (58), to yield the least biased estimates. Because PROCESS currently has no internal procedure to deal with missingness other than listwise deletion (57), the values obtained via PROCESS are for interpretation purposes, and significance of terms should be derived from the main model.

Results

Main effects for the handholding contrast have been reported elsewhere (4). Briefly, compared to either being alone or being with a stranger, main effects of partner handholding showed diminished activations in the dACC, the dlPFC, the posterior cingulate cortex (PCC), the posterior parietal cortex (PPC), and the right ventrolateral prefrontal cortex (vlPFC).

Descriptive Statistics

Descriptive statistics and correlations for primary health variables (before transformations) are presented in Table S1, Supplemental Digital Content. Around 91% - 99% participants' health data were recorded. For those participants who did not have their IL-6 and CRP level measured, their missingness does not relate to demographic information (i.e., sex, race, age, socioeconomic status) or outcomes from neuroimaging assessment ($p = 0.14 – 0.90$), suggesting that missingness was not likely to have distorted the findings reported.

Interaction effect of yielding and support on immune system: interleukin-6 (IL-6) and C-reactive protein (CRP)

The interaction between dACC-related yielding and perceived social support predicted CRP level assessed: greater perceived social support was associated with lower CRP level ($\beta = -0.95$, se = 0.42, $z = -2.24$, $p = 0.025$, 95% CI [−1.77, −0.12]; Figure 1). The effect was strongest in the high yielding group ($\beta = -0.46$, se = 0.35, $t = -1.31$, $p = 0.20$, 95% CI [−1.16, 0.25]), flattened in the average yielding group ($\beta = 0.09$, se = 0.26, $t = 0.33$, $p = 0.74$, 95% CI [−0.43, 0.60]), and reversed direction in the low yielding group ($\beta = 0.63$, se =

0.37, t = 1.70, p = 0.096, 95% CI [−0.12, 1.37]). The interaction was not significant in other ROIs (all βs ≤ −0.28, all ses ≥ 0.34, all zs ≤ −0.83, all p values ≥ 0.40). No interactions were observed between yielding in any of our ROIs and perceived social support in predicting subsequent IL-6 levels (all βs ≤ −0.08, all ses ≥ .15, all zs ≤ −0.43, all p values ≥ 0.21).

Interaction effects of yielding and support on baseline heart rate variability

In general, greater perceived social support was associated with greater baseline HRV (β = 0.51, se = 0.23, z = 2.19, p = 0.028, 95% CI [0.05, 0.97]; Figure 2). An interaction effect between hypothalamic yielding and perceived social support revealed the effect was strongest in the high yielding group (β = 0.63, se = 0.26, t = 2.44, p = 0.018, 95% CI [0.11, 1.15]), weaker in the average yielding group (β = 0.16, se = 0.18, t = 0.88, p = 0.38, 95% CI [−0.20, 0.52]), and reversed direction in the low yielding group (β = −0.31, se = 0.29, t = −1.06, p = 0.29, 95% CI [−0.90, 0.28]). This interaction was not significant in other ROIs (all βs ≤ 0.38, all ses ≥ 0.28, all zs ≤ 1.35, all p values ≥ 0.18). Though we did observe a main effect of dlPFC-related yielding on subsequent baseline HRV (β = −0.77, se = 0.28, z = −2.77, p = 0.006, 95% CI [−1.31, −0.22]) such that higher dlPFC-related yielding was associated with *lower* baseline heart rate variability.

Discussion

This study examined the effect on subsequent health outcomes of the interaction between perceived social support and the tendency to yield to a relational partner's presence, presumably on the assumption that the partner is an available resource. 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)—during baseline.

As expected, the association between perceived social support and physical health was robust: greater perceived social support was associated with beneficial health outcomes. This is consistent with the extant literature (11,59) and replicated past studies employing the same dataset where adolescent relationship quality and their conflict resolution skills were significant predictors of adult vagal tone (60) and IL-6 concentration (61). Additionally, our results showed that greater perceived social support corresponded with lower CRP concentration and greater baseline heart rate variability, and that this was especially true for individuals who showed less activity in the dACC and hypothalamus respectively during the provision of actual social support, a process we have called "yielding" (21).

To break down the findings of the current study, first, we observed that yielding at hypothalamus moderated the link between perceived social support and baseline heart rate variability. Heart rate variability is the beat-to-beat variability between consecutive normal-to-normal (RR) intervals during sinus rhythm–an indirect measure of sympathetic and parasympathetic modulation of heart rate (62). Theories suggest that social support may influence heart rate variability by activating the parasympathetic nervous system, suggesting in turn a link between access to social resources and physiological regulation of the body's energy expenditures. Ecologically speaking, yielding reflects "bets" made on the budgeting and deployment of personal bioenergetic resources in the presence of others,

based at least in part on past social support experiences; when the brain "bets" that threat-related tasks (e.g., vigilance, contingency planning) can be outsourced to others, resources devoted to those tasks can be applied to other tasks that could benefit an individual's health (21). Importantly, our findings showed that yielding measured at a neural level (hypothalamus) moderated the effect of perceived social support on baseline HRV *years* after the neuroimaging task was completed, suggesting yielding is trait-like.

We also found that the interaction between social support and neural yielding predicted CRP, but not IL-6 level. This discrepant finding may be due to the differential effects of cortisol on inflammatory markers. When stress becomes chronically sustained in the absence of inflammation, pCRP, the only isoform of CRP measured in most physiological research, is active in the resolution phase of inflammation and promotes tissue repair and wound healing (63). Cortisol is an important signaling pathway through which IL-6 produces CRP, but IL-6 itself may not be elevated due to the suppressive effects on IL-6 of cortisol. As such, in the absence of inflammation, chronic stress upregulates CRP without necessarily changing IL-6 levels. Indeed, one study that focused on prolonged stress with no exposure to early adversity found that individuals such as familial caretaker of cancer patients showed nearly twice as high CRP concentration compared to controls but no significantly higher levels of IL-6 (64). Furthermore, Giudice and Gangestad (2018) argued that both IL-6 and CRP are not unambiguous inflammatory markers but serve more accurately as physiological markers of energy allocation (65,66). In the absence of energy resources, investment in innate immunity increases in response to perceived threats, consistent with a life history perspective (67,68). In other words, our findings suggest that individuals who were low on social support *and* yielding may have showed high CRP concentration years later due to upregulated tissue repair in the face of sustained stress. Such sustained coping is energy-intensive, potentially jeopardizing health and wellbeing (6).

Our findings also point to the possibility the brain regions involved may play distinct roles in respective health outcomes. Neural yielding at the hypothalamus, for example, is distinctly associated with the baseline heart rate variability. As part of the hypothalamic-pituitary adrenal axis (HPA), the hypothalamus is considered to play a crucial role in stress responsiveness. Past research examining HPA axis and baseline HRV suggests that HPA axis stimulation is associated with reduced hear rate variability, suggesting a role for the HPA-axis in the modulation of stress related cardiovascular responsiveness (69). This is consistent with findings reported here that reduced hypothalamic activity in the presence of a relational partner interacted with perceived social support and predicted higher baseline heart rate variability.

We did observe one result apparently contrary to our original hypothesis, which was that greater yielding in the dlPFC was associated with *lower* baseline heart rate variability. The prefrontal cortex, especially the dlPFC, has numerous regulatory effects on the HPA axis (70). Specifically, the dlPFC indirectly inhibits the amygdala via projections to the hypothalamus (71). Our unexpected result might be related to a general functional association between the dlPFC and HRV. A growing literature suggests that greater prefrontal cortex activity corresponds with greater HRV, presumably reflecting the role dlPFC plays in regulating negative affect. Of course, our experimental paradigm explicitly

aims to reduce dlPFC-related emotion regulation; yielding entails *less* activation of the dlPFC on the grounds that social resources render it less necessary. SBT predicts this because the inhibitory or emotion-regulatory role of the dlPFC is resource-intensive and even subjectively experienced as effortful (72–74). Thus, expressed in terms of yielding, the previously reported main effect associating greater dlPFC activity with greater HRV may have been preserved as a main effect across conditions, with the sign reversed; greater dlPFC yielding is synonymous with less dlPFC activation in the presence of a social resource, and so greater yielding is associated with lower HRV. If true, the association between yielding and HRV is likely to be complex in ways that require more and better research.

By contrast, our observation that yielding in the dACC potentiated the long-term effects on CRP levels of perceived social support is more straightforwardly interpretable. A robust line of research highlights the role of dACC in modulating CRP levels. For example, Liu and colleagues (2020) found that in anticipation of a reward, individuals with reduced activation in dACC had lower CRP levels (75). CRP levels in adults are inversely associated with dACC thickness (76). Anatomically, dACC acts as an important hub within the salience network. The salience network informs goal-directed behaviors as to the value of a stimulus and identifies internal and external cues that signal attentional deployment (77), including attention devoted to threat detection and preparation (78). Thus, the current study also speaks to the central role of dACC as part of the salience network that, when directing attention to threat-relevant stimuli, prepares the body for potential threats by stimulating the release of (bioenergetically costly) inflammatory resources, including CRP.

The current findings are relevant to a variety of theoretical views on the association between relationships and health. For example, the stress-buffering hypothesis (79) suggests that social support may desensitize physiological responses to stress. Nevertheless, neural mechanisms underlying the stress-buffering hypothesis remain largely speculative. One potential mechanism of the stress-buffering hypothesis may be yielding as we have defined it: the ability to reduce task-relevant activity in a neural system or circuit in the presence of a social resource. Thus, social support may buffer stress through yielding in a variety of systems, including somatosensory activity, threat detection and sensitivity, self-regulatory activity, physiological redistribution of bioenergetic resources throughout the body, and more–all depending on situational demands. Yielding as a neural and physiological mechanism of the stress-buffering model provides specific and testable hypotheses that can aid our understanding of social support, health, and their relation.

Lastly, although numerous researchers have suggested that perceived social support and received social support are separate concepts (80), others argue that they are conceptually related and may even interact under some conditions (81). Uchino (2009) has hypothesized that individuals with higher perceived support may benefit more from received support, via positive interpretations of schema-relevant information (82); conversely, individuals who predict less potential access to social support may discount any support received as it conflicts with other task-relevant psychological factors (83). Data presented here, as with other findings in our laboratory (4), support this view; it was those who yielded to available social support who showed the strongest links between perceived social support and health.

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. The current study crosses many levels of analysis, adding to our general understanding of the social, psychological, physiological, and neural mechanisms of human health.

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 = 6.09, *SD* = 0.91), suggesting they were heavily skewed towards perceiving (or reporting) a high degree of social support. In addition, 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 this reason, conclusions drawn from the study should be made with caution. 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.). Finally, associations between seeking social support, giving social support, perceiving social support, and the amount of support actually received, are likely to be complex and are in any case still poorly understood. For example, recent research indicates that among prosocial behaviors, support giving has emerged as an important health promoting behavior (84). Future research could benefit by examining the additional role of support giving to fully examine and capture such complexity. Many other potential health outcomes related to yielding are of interest as well. For example, Farrell and colleagues (2019) suggested that although research exploring changes in inflammation, the autonomic nervous system, and neuroendocrine activity grew over the past decade (85), it might become increasingly important to connect these changes in the system to clinical endpoints (e.g., coronary heart disease).

Conclusions

The current findings suggest that greater perceived social support is associated with better health outcomes, examined across CRP level and baseline heart rate variability. This association was stronger among individuals who relax their own responses to stress when a source of support is available, operationalized especially as decreases in neural activity across dACC and hypothalamus. Our results are consistent with a large existing literature on the link between social support and physical health. In addition, the current study highlights the construct of *yielding*, which we have characterized as a trait-like likelihood or ability 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—in that it (yielding) affects the 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Glossary

SBT	Social Baseline Theory
fMRI	functional magnetic resonance imaging
dACC	dorsal anterior cingulate cortex
dlPFC	dorsolateral prefrontal cortex
ROI	region of interest
IL-6	Interleukin-6
CRP	C-reactive protein
HRV	Heart Rate Variability
BMI	Body Mass Index

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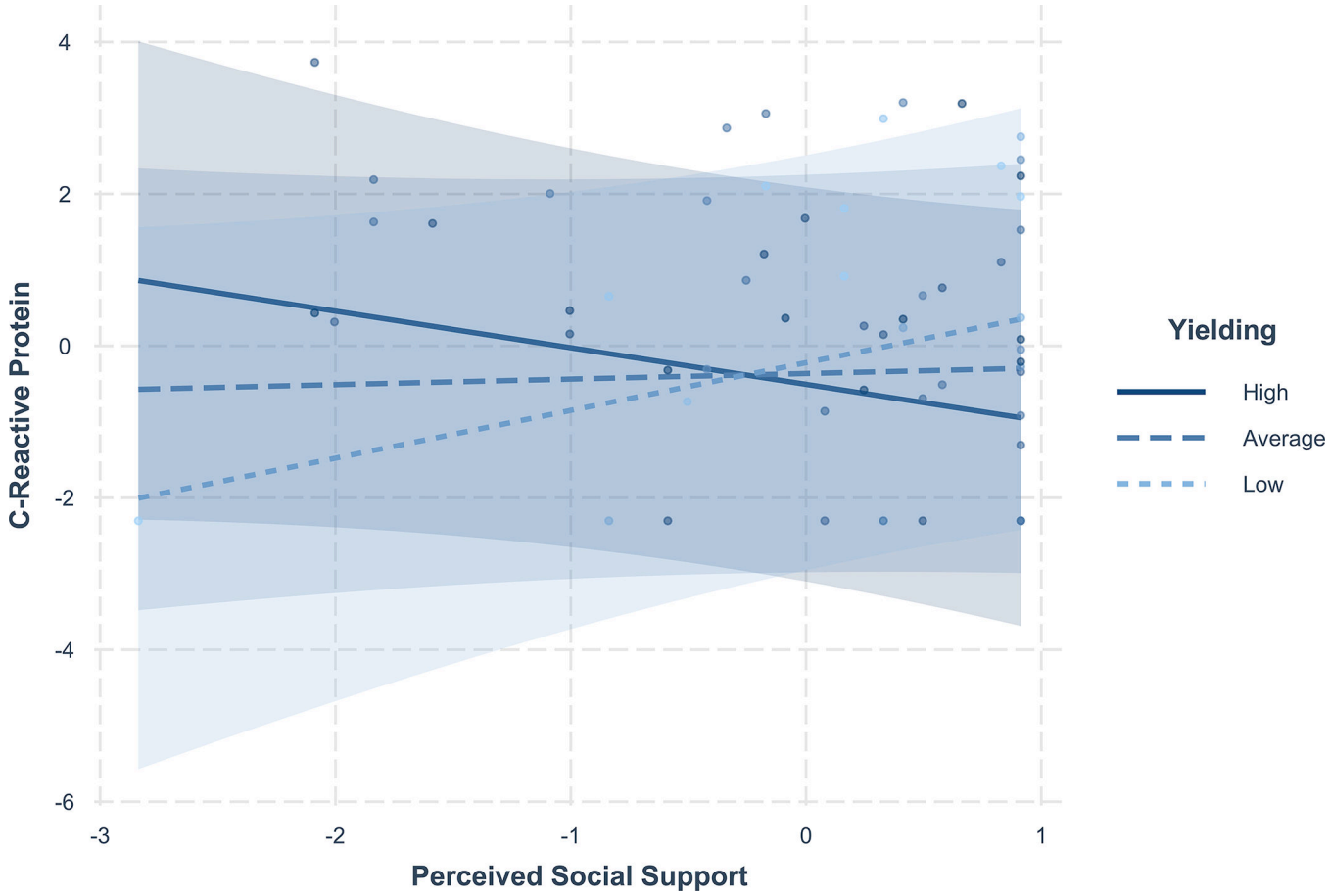

Figure 1. The interaction between yielding and perceived social support predicted CRP level.

Across the three ROIs, the interaction between yielding and perceived support was significant within **dACC**: higher perceived social support was associated with lower CRP level and this prediction was strongest in the high yielding group. The values of CRP and perceived support were after transformations. Shading represents 95% CIs. Color image is available online only at the Psychosomatic Medicine web site.

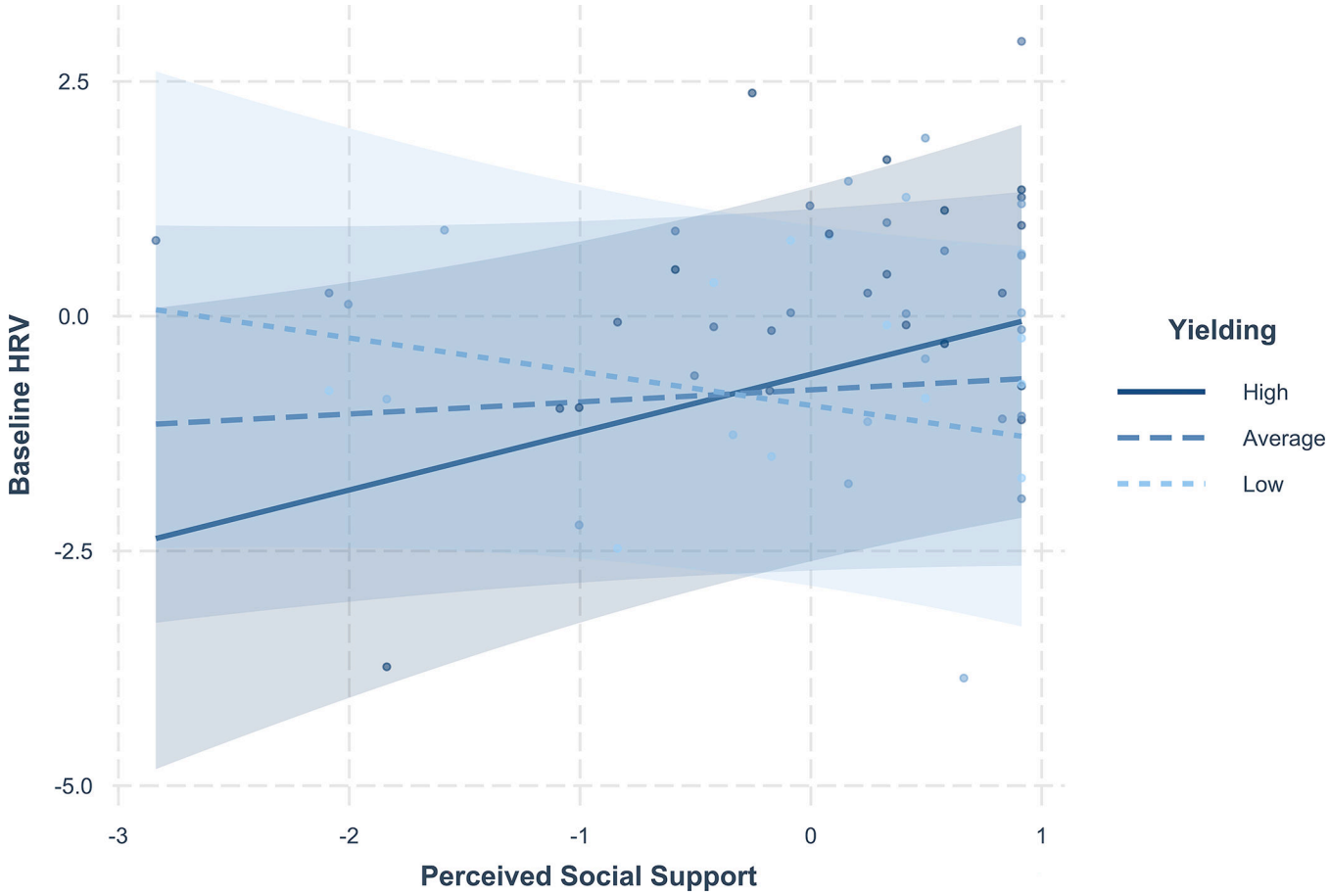

Figure 2. The interaction between yielding and perceived social support predicted baseline heart rate variability assessed.

The interaction assessing baseline heart rate variability was significant at **hypothalamus**: higher perceived social support was associated with greater baseline heart rate variability and this prediction was strongest in the high yielding group. Shading represents 95% CIs. Color image is available online only at the Psychosomatic Medicine web site.