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The Social Regulation of Pain: Autonomic and Neurophysiological Changes Associated With Perceived Threat

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Abstract: **The analgesic effect of social support is proposed as a function of social support modulating perceived threat of painful stimuli. In the current study, we directly examined the social buffering effect in the context of the threat of pain. Eighteen healthy participants were subjected to the threat of pain while they held the hand of a close other, a stranger, or not at all. Neural and autonomic responses were recorded using electroencephalogram and heart rate, respectively. Close other hand-holding reduced pain perception. This was accompanied by decreased heart rate and frontal theta oscillation (4–8 Hz) during the threat phase preceding painful stimulation. Interestingly, decreased heart rate and frontal theta in the close other hand-holding condition were uniquely associated with greater pain reduction during subsequent nociceptive stimulation. Neural changes were source-localized to the insular cortex and the rostral-ventral portions of anterior cingulate cortex, regions involved in the processing of threat and pain. Together, our data build upon work to date linking social support to pain by showing autonomic and neurophysiological changes associated with pain reduction.**

Perspective: ***Social support may reduce pain through buffering the autonomic and neurophysiological response to the threatening quality of noxious stimuli. Results implicate that in clinical settings the caregiver could help people with chronic pain reappraise pain and related conditions as less stressful.***

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Key words: *Social support, pain, stress, heart rate, theta oscillation.*

Supportive relationships with others have substantial benefits for individuals.[11,57] These benefits arise through forms of social support including the structure of one's social relationships (eg, having intimate relationships with others), or the explicit functions performed by others[10] (eg, emotional, economical, informational support). In the context of pain research, literature has largely suggested that social support, in its various forms, has analgesic effects for pain patients[7,33,36] as well as in experimental settings with healthy individuals.[6,17,31,39] Thus, social connectedness may play an important role in the perception of pain.

Preliminary evidence in this area has indicated a "stress-buffering" process in which social support may reduce pain-related threat response that in turn decreases pain.[25,51,60] For example, one study identified that perceived threat of pain mediated the influences of social support on pain reduction.[59] Several imaging studies have also suggested that social support may prime safety or reward themes that in turn result in the reduction of pain and related threat response.[19,62] However, a limitation of current investigations into the buffering effect on pain is the simultaneous assessment of the painful sensation and threat of pain, in which the buffering effect suffers from an indirect manner of examination (eg, Eisenberger et al,[19] and Younger et al[62]). In addition, where the threat of pain has been specifically addressed, it has been assessed through a self-report dichotomous variable (ie, yes or no; eg, Corley et al,[12] and Vlaeyen et al[59]). However, the social buffering effect involves not only the subjective,

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self-reported experience of threat or stress, but (albeit related) neural, cardiovascular, and neuroendocrine dimensions of perceived threat, which are closely associated with health outcomes.[56]

In the current investigation, we build upon the literature of social support and pain to date by using electroencephalogram (EEG) and heart rate measures to assess neural and autonomic changes during the threat of pain and its relationship to pain reduction. To do so, we used a novel manipulation to introduce 6-second continuous threat of pain leading up to painful stimulation. It is important to note that EEG and heart rate offer high temporal resolution. In the present paradigm, this allowed us to reveal the dynamic increase in neural and autonomic response during pain-related threat, and crucially, directly show the buffering effect of social support on threat and pain experience as well as the graded influence of social support depending on the quality of the relationship (ie, close acquaintance vs stranger). Because EEG theta oscillation (4–8 Hz[8]) is suggested as one potential neural correlate of the perception of threatening cues,[15,43] we hypothesized that social support would reduce theta activity and autonomic heart rate in the threat stage leading up to painful stimulation. Importantly, we anticipated that these changes during the threat of pain would be related to decreased pain ratings after noxious stimulation.

Methods

Subjects

Eighteen healthy adults participated in this study (8 male and 10 female, age range = 18–35 years, mean = 25.2, SD = 5.7). All participants were right-handed, not taking any medication, and had no history or current diagnosis of a neurological or a psychiatric disorder, assessed using the Mini International Neuropsychiatric Interview.[53] Involvement in the study required inclusion of a participant's close other (romantic partner, family member, or close friend). All study participants and their close other provided informed consent and the experiment was approved by the Alfred Hospital and Monash University Human Research and Ethics Committee. This study was conducted in accordance with the Declaration of Helsinki.

Experimental Design and Procedure

Noxious electrical stimuli were delivered under 3 conditions: during hand holding of 1) the subjects' close acquaintance ("close other" condition), 2) a stranger ("stranger" condition), and 3) in the absence of hand-holding ("no-holding" condition). The stranger was a staff member who was gender-matched to the close other (a total of 2 staff members only were used for this role). The close other/stranger was only present during the relevant experimental condition and was instructed not to talk or have any eye contact during the recording.

As shown in Fig 1, the experimental task consisted of 30 trials in each condition. Each trial started with the presentation of a fixation cross for 1 second. This was followed by the presentation of numbers in center-screen

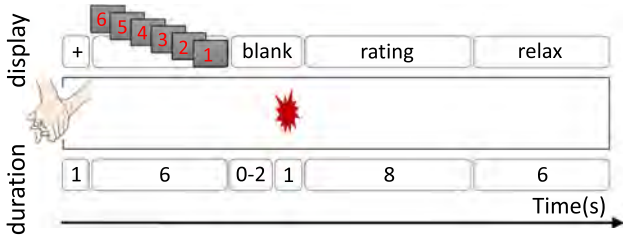

Figure 1. Illustration of the experimental design.

counting down from 6 to 1, at the rate of 1 number per second. A blank screen was then shown for between 0 to 2 seconds, which was followed by a train of painful stimuli lasting for 1 second. This jittered interval was designed to control for the habituation to the impending stimuli. Immediately after the stimulation participants were asked to rate pain intensity and then pain unpleasantness aroused by the stimuli. Participants gave a verbal rating within 8 seconds (described in *Trial-by-Trial Rating of Painful Sensation*). The participant was allowed to relax for a further 6 seconds before commencement of the subsequent trial. The duration of each condition was approximately 10 minutes. The participant held the hand throughout the condition when relevant. The order of conditions were pseudorandomized and counterbalanced across participants.

Painful Stimuli

Before the start of each condition, individual current levels were determined. Small electrical stimuli were applied to the dorsum of the left little finger (Stimulus Isolator; ADInstruments, Sydney, Australia). Trains of fifty 500-μs (frequency = 50 Hz, total time = 1 second) stimuli were applied. After each train of stimuli participants gave a verbal pain rating between 0 and 10 (0 = no pain; 10 = worst pain imaginable). The calibration procedure started from a very low current, for which the participants could barely feel the stimulation, then the current was gradually increased. The calibration process was halted when participants rated the intensity as 7.[26] We then repeated the current 10 more times to see if it can consistently create a painful feeling of 7 for at least 8 times. If not, the current was increased again until it did elicit a painful rating of 7 for 8 od 10 stimuli. This method of pain calibration has been used in previous studies,[32,35,52] and was chosen to avoid habituation to perceived threat of pain. The calibration procedure was performed in the absence of the close other or the stranger to avoid any confounding influence.

Trial-by-Trial Rating of Painful Sensation

To assess perceived pain after the offset of each train of stimuli, subjects provided pain intensity and unpleasantness ratings on a numerical scale ranging from 0 to 10 (pain intensity: no pain to worst pain imaginable; pain unpleasantness: not unpleasant to most unpleasant pain

imaginable). To associate decreased neurophysiological threat response with pain relief (ie, a measurement of pain reduction induced by holding the hand of a close other or stranger compared with no-holding), we specifically computed the difference between the mean of pain intensity in no-holding trials and the mean of pain intensity in close other trials[19,62] (or stranger trials) and then correlated to changes in heart rate and EEG theta activity.

Heart Rate Recording

Heart rate was monitored continuously during each of the 3 conditions using electrocardiogram (PowerLab/4SP; ADInstruments, Sydney, Australia). Three electrodes were administrated to the volar surface of bilateral forearms and the calf muscle of the right leg, respectively. Data were recorded with LabChart (version 5.5.6, ADInstruments) in the sampling rate of 1,000 Hz on a separate computer.

EEG Recording

Recordings took place in a sound-attenuated, temperature-controlled, and electrically shielded room. Subjects were seated in a slightly reclined chair with face approximately 50 cm from the computer monitor. Continuous EEG was recorded using a 64-channel Quickcap (Neuroscan Inc, Victoria, Australia) with CPZ as the reference electrode. Vertical electro-oculogram activity was monitored with electrodes attached above and below the left eye, and horizontal electro-oculogram activity was monitored with electrodes located at the outer canthus of both eyes. Data were sampled at 1,000 Hz with impedances below 5 kΩ throughout the testing.

Data Analysis

For the electrocardiogram data, interbeat interval series were derived using Pan-Tompkins algorithm that identifies the peak of the R wave as the fiducial point.[46] Artifacts were checked visually and edited as necessary according to published guidelines.[3] Then interbeat interval series were transformed to beat-per-minute (BPM) series and baseline corrected (–500 to 0 ms, where time 0 represents the onset of the first countdown number) for each trial. Specifically, percent change of BPM was calculated using the Equation 1. This method is believed to control for individual differences in baseline heart rate, and capture the dynamics of event-related heart rate change in a short period.[4] Percent change of BPM series were then averaged across trials for each participant in each condition, and area under the curve (AUC) was calculated with the linear trapezoidal rule to measure event-related heart rate change during the presentation of countdown numbers (0–6,000 ms).[34,37] For 2 participants, heart rate recordings were unavailable due to technical issues.

$$\text{Percent change of BPM} = (\text{BPM at each time point} - \text{BPM mean}\,[-500 \text{ to } 0 \text{ ms}])/\text{BPM mean}\,(-500 \text{ to } 0 \text{ ms}) \times 100 \quad (1)$$

We then examined the correlation between heart rate change and pain relief in the close other (or stranger) compared with the no-holding condition. Because of the dynamic changes of heart rate, we were particularly interested in investigating the specific time windows in which those two would correlate. To this end, a sliding window method was used. The window length was set as 1,000 ms with 50% of overlapping. This was chosen as each countdown number was presented for 1,000 ms. In each window, heart rate reduction was computed as the difference of AUC between the no-holding and the close other (or stranger) condition. Pearson correlations were further computed to assess the relationship of heart rate reduction and pain relief.

Offline EEG data were preprocessed using custom-written scripts that implement functions from EEGLAB (version 13.6.5b; see Delorme and Makeig[16]) running under Matlab R2016b (The MathWorks, Inc, Natick, MA). Bad channels were first removed. Data were then filtered (Butterworth filter, band-pass = .5–100 Hz, band-stop = 48–52 Hz), referenced to the average reference, and corrected for stereotyped artifacts including eye blinks, lateral eye movements, muscle, and line noise using the FastICA algorithm.[30] Stereotyped artifacts were identified by visual inspection of the spatial and temporal representation of the independent components. Continuous data were then segmented into 7,000-ms nonoverlapping epochs spanning from 1,000 ms before to 6,000 ms after the onset of the first countdown number. Missing channels were interpolated, and epochs were inspected again to remove any anomalous activity in the signal.

Time–frequency representations were calculated with Hanning tapered "mtmconvol" method (7 cycles per time window), as implemented in FieldTrip toolbox.[45] This method can convolve dynamic EEG time–frequency data with a complex wavelet, and has the advantage that the temporal spread is fully confined to the time window of interest. We calculated power for frequencies ranging from 1 to 100 Hz in the time window of –1,000 to 6,000 ms. Power values were calculated for each trial, and averaged across trials for each subject in each condition. Single-trial baseline corrections were performed with an interval of –500 ms to 0 ms as the baseline.

We further assessed the relationship between power changes and pain relief between conditions. Specifically, power changes were calculated as the difference between no-holding and either close other or stranger conditions. A sliding window method was also adopted for the heart rate analysis, to capture the dynamic relationship between power changes and pain reduction.

Source Localization (Standardized Low Resolution Electromagnetic Tomography Algorithm)

Source localization was further performed to explore the possible generators of neuronal oscillations for which we observed significant differences across conditions. The standardized low resolution electromagnetic tomography

algorithm (sLORETA) is frequently used to estimate possible generators of neuronal oscillations or evoked potentials.[47] It finds a unique inverse solution for the cortical source of scalp EEGs. Results of sLORETA have been validated using combined EEG-positron emission tomography and EEG-functional magnetic resonance imaging (fMRI) data.[44,48]

In the current study, time-varying cross-spectra were calculated for single-trial data including baseline (–500 to 0 ms) and test intervals.[29,42] Here we first limited the test intervals to the time periods in which differences in theta activity were observed between conditions (see the Results section). These steps were further supplemented by analyses in which the test intervals were extended to the entire presentation of countdown numbers (0–6,000 ms). Current source density of theta activity was estimated for cortical voxels. To align the source localization with the time–frequency analysis, event-related changes of the current source density for each time frame within the test interval were calculated as log event-locked deviations from baseline mean.

Statistical Analyses

Repeated measures 2-way analysis of variance (ANOVA) calculations were first performed with SPSS (version 22; IBM Corp, Armonk, NY) on pain intensity and pain unpleasantness to examine the habituation to the noxious stimuli. Pain intensity and pain unpleasantness were split to the first and second half, respectively (15 trials in each half), and condition (close other, stranger, no-holding), and time (first half, second half) were specified as the repeated measure factors. Post hoc t-tests were conducted with a Bonferroni correction with the α level set to .05.

Further, repeated measures 1-way ANOVAs were performed to examine the condition difference in current calibration, pain intensity, pain unpleasantness, and AUC of heart rate change, respectively. Condition (close other, stranger, no-holding) was specified as the repeated measure factor. Post hoc t-tests were conducted with a Bonferroni correction to further explore the significant main effects of condition, and the α level was set to .05.

For time–frequency data, differences between conditions were evaluated using a nonparametric cluster-based permutation test. This method can be used to compare conditions for significant spatiotemporal differences, which provides a straightforward way to solve the multiple comparisons problem.[38] In other words, this analysis identifies time periods and electrode clusters in which a given frequency bin differs across conditions. This method was applied to the time window of interest (0–6,000 ms) in all scalp channels. An observed test statistics value was considered in the cluster permutation if it was below the threshold of .05 in at least 2 of the neighboring channels.[45] Further, 5,000 iterations of trial randomization were carried out for generating the permutation distribution at a given frequency band. A threshold of .025 (2-tailed) was used for evaluating the electrodes that exhibit a significant difference in power. As our a priori hypothesis related to theta activity, statistical analysis was first carried out in theta band (4–8 Hz). Additional analyses were performed separately in other frequency bands (delta = 1–3 Hz, alpha = 9–12 Hz, beta = 13–30 Hz, gamma = 31–100 Hz).

For sLORETA statistical differences between conditions were calculated as images of voxel-by-voxel t values. The localization of differences in cortical activity was on the basis of the standardized electrical current density and resulted to 3-D t score images. In these images, cortical voxels of significant difference were identified using a nonparametric approach thresholded at .05 determined by 5,000 randomizations.[47]

Results

Behavioral Results

Habituation Analysis

Two-way repeated measure ANOVA revealed a main effect of condition in pain intensity ($F_{2,34} = 6.19$, $P < .05$, partial eta squared $[\eta_p^2] = .27$). There was no main effect of time ($F_{1,17} = .16$, $P = .69$, $\eta_p^2 = .01$), or an interaction effect of Condition × Time ($F_{2,34} = 2.03$, $P = .15$, $\eta_p^2 = .11$). Similarly, we found a main effect of condition in pain unpleasantness ($F_{2,34} = 5.00$, $P < .05$, $\eta_p^2 = .23$). There was no main effect of time ($F_{1,17} = .14$, $P = .71$, $\eta_p^2 = .01$), or the interaction effect of Condition × Time ($F_{2,34} = 2.33$, $P = .11$, $\eta_p^2 = .12$). These data together confirmed the absence of habituation. Specific comparisons between conditions are detailed in 1-way ANOVA.

Current Calibration

A repeated measure ANOVA revealed that the main effect of condition was not significant in the current calibration ($F_{2,34} = .43$, $P = .65$, $\eta_p^2 = .03$), confirming that the participants received noxious stimuli of the same current level across 3 conditions (mean = 4.71 mA, SD = 1.56 across conditions).

Pain Intensity

A main effect of condition was found in pain intensity ($F_{2,34} = 6.24$, $P < .05$, $\eta_p^2 = .27$), with post hoc tests showing that pain intensity was lower in close other (95% confidence interval [CI] = –1.75 to –.13, $P < .05$) and stranger condition (95% CI = –1.26 to –.04, $P < .05$) relative to no-holding condition (Fig 2A). Close other and stranger condition revealed no differences in pain intensity (95% CI = –1.02 to .44, $P = .92$).

Pain Unpleasantness

Similarly, we found a main effect of condition in pain unpleasantness ($F_{2,34} = 4.96$, $P < .05$, $\eta_p^2 = .23$). Post hoc tests showed that pain unpleasantness was lower in the close other relative to the no-holding condition (95% CI = –1.51 to –.02, $P < .05$; Fig 2B), but no difference was found in the stranger versus no-holding condition (95% CI = –1.23

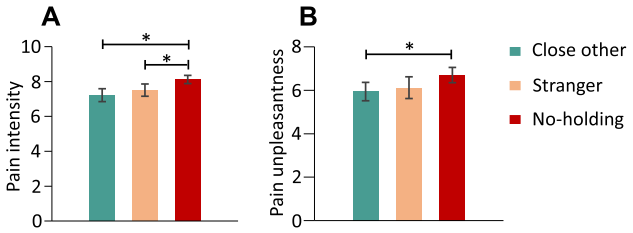

Figure 2. Influence of social support on pain perception. Subjective ratings of (**A**) pain intensity and (**B**) pain unpleasantness (mean ± standard error of the mean). The asterisk represents statistical significance ($P < .05$).

to .06, $P = .10$), or the close other versus stranger condition (95% CI = –.81 to .44, $P = .99$).

Heart Rate Response and Relationship With Pain

Heart rate increased with the progression of countdown numbers in all conditions, although it appeared to taper off between 4,500 to 6,000 ms (Fig 3A). A main effect of condition was found in the AUC of heart rate change ($F_{2,28} = 3.19$, $P < .05$, $\eta_p^2 = .19$). Post hoc tests showed that close other condition produced less AUC than no-holding condition (95% CI = –7.88 to –.21, $P < .05$; Fig 3B), whereas other comparisons did not reach significance. One outlier was detected using GraphPad Prism (https://www.graphpad.com) thresholded at $P < .05$ and consequently removed.

Results also showed that heart rate decrease induced by close other hand-holding was associated with greater pain relief. Pearson correlation revealed that this relationship only reached significance in the late stage of countdown numbers presentation (3,500–6,000 ms; Fig 3C). The results remained consistent when absolute, rather than relative, heart rate measures were used for statistical analysis (see Supplementary Fig 1). In terms of the stranger condition, there was no significant correlation between heart rate reduction and pain relief.

Event-Related Time–Frequency Results and Relation to Pain

The whole-scalp cluster analysis on theta frequency revealed a period (3,300–4,310 ms) during which theta power was significantly decreased in the close other relative to no-holding condition (Fig 4A). The topography of this power decrease had a frontal, slightly right lateralized distribution (significant at AF4, F2, FZ, and FC2). A supplementary analysis showed that there was no difference in any other frequency bands between the close other and no-holding condition.

In terms of the relationship to pain relief (Fig 4B), modulation of theta power was associated with greater pain relief in the late stage of countdown numbers presentation (3,000–5,500 ms).

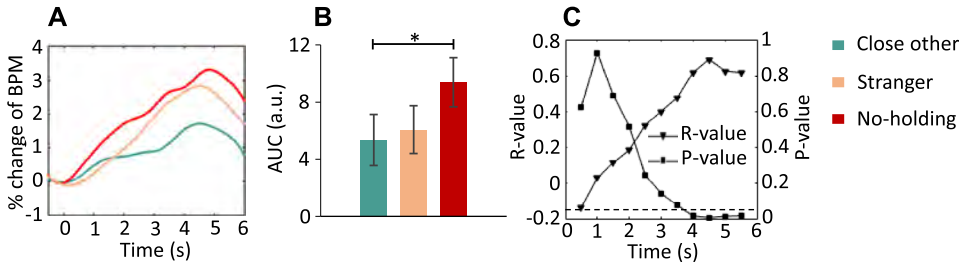

Figure 3. Heart rate change and relationship with pain relief. (**A**) Shows the event-related dynamic changes of heart rate with the progression of countdown numbers. (**B**) Shows the AUC of heart rate changes across conditions. Each column and error bar represent the mean and the standard error of the mean. The asterisk represents statistical significance ($P < .05$). (**C**) Shows the correlation between heart rate (HR) reduction (HR [no-holding condition] – HR [close other condition]) and pain relief (pain intensity [no-holding condition] – pain intensity [close other condition]). a.u., arbitrary unit.

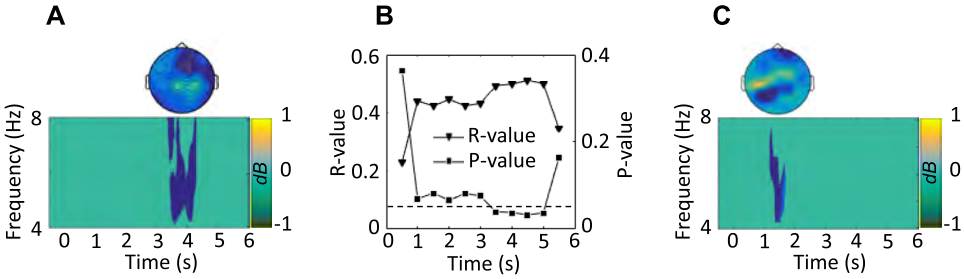

Figure 4. Social support modulates EEG theta activity during threat of pain phase. (**A**) Time frequency plot showing the reduction in theta power in the close other relative to no-holding condition. Cluster analysis showed that this reduction in theta power reached significance at electrodes AF4, FZ, F2, and FC2 during 3,300 to 4,310 ms after the start of the threat phase. Areas with no significant differences were zeroed out. (**B**) There was a significant correlation (below the line; $P < .05$) between the reduction in theta power and subjective rating of pain relief in the same close other compared with no-holding condition. (**C**) Time frequency plot showing the electrodes (P1, P3, P5, PO3) and earlier time period (1,100–1,780 ms) in which theta power was significantly reduced in the stranger relative to no-holding condition.

The nonparametric cluster-based permutation also identified an early period (1,100–1,780 ms) in which theta power was significantly decreased in the stranger relative to no-holding conditions. This power decrease was located over left parieto-occipital regions (P1, P3, P5, and PO3; Fig 4C). No other significant differences were observed in any other frequency bands between the stranger and no-holding condition. Moreover, this spatiotemporal modulation of theta power was not associated with pain relief.

Source Localization

Periods identified by the nonparametric cluster-based permutation as differing significantly between conditions were subjected to source localization procedures. In the time window that theta power difference was observed (3,300–4,310 ms), decreased source localized theta activity was found in the left pregenual anterior cingulate cortex (pgACC; Brodmann area [BA] 24, Montreal Neurological Institute [MNI] coordinates: $X = -5$, $Y = 23$, $Z = 14$, $t = -3.47$, $P < .05$), the bilateral subgenual anterior cingulate cortex (sgACC; BA 25, MNI coordinates: $X = 0$, $Y = 1$, $Z = -5$, $t = -3.55$, $P < .05$), and the right insula (BA 13, MNI coordinates: $X = 45$, $Y = 10$, $Z = -5$, $t = -3.44$, $P < .05$), in the close other relative to no-holding condition (Fig 5).

When the test interval was extended to the whole stage of countdown numbers presentation (0–6,000 ms), decreased activity of the left pgACC (BA 32, MNI coordinates: $X = -5$, $Y = 35$, $Z = 15$, $t = -4.37$) was observed in the close other relative to no-holding condition (see Supplementary Fig 2).

In another time window (1,110–1,780 ms), no brain activation was found at $P < .05$, corrected for multiple comparisons, in the stranger relative to no-holding condition. No brain activation was found when we extended the test interval to the entire presentation of countdown numbers (0–6,000 ms).

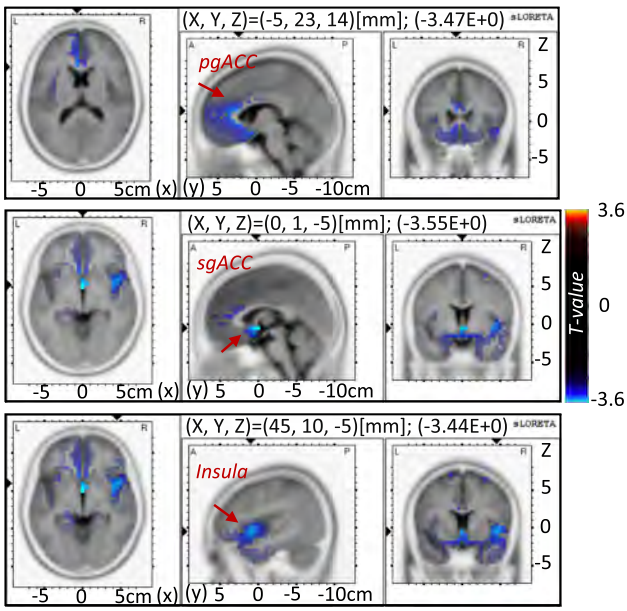

Figure 5. Source localization of EEG theta oscillation in the time window of 3,300 to 4,310 ms in close other versus no-holding condition. Results were shown at $P < .05$, multiple comparison corrected.

Discussion

Preliminary evidence has indicated a buffering process that may link social support to pain reduction.[25,59,60] In the current study, we used a novel design to manipulate the threat of pain and characterize the autonomic and neurophysiological changes within the proposed buffering effect. Consistent with most of the literature, our results show that social support alleviated the experience of pain. In addition, our data provide novel evidence of the buffering effect in which social support reduced heart rate and fontal theta oscillations during the threat of pain (ie, before noxious stimulation), and that the magnitude of these changes were related to greater pain reduction. These findings provide evidence that the analgesic influence of social support may be driven by its role in the modulation of the threat of pain.

Previous studies have shown that social support is able to attenuate pain and physiological responses to painful stimuli, including heart rate,[21,51] blood pressure,[21,51] skin conductance,[28,49] and cortisol levels.[51] Building on these findings, our data show that hand-holding with a close acquaintance reduced pain perception (Figs 2A and 2B), and heart rate preceding delivery of painful stimuli that was seen in other conditions (Figs 3A and 3B). We further found that decreased autonomic response to the threat of pain was associated with greater pain reduction in the presence of social support. Therefore, by assessing the threat of pain before painful stimulation our results directly show the social-buffering effect through attenuated autonomic arousal to pain. Moreover, this was only observed in the close other but not in the stranger condition, which further suggests a modulatory influence of relationship quality in the buffering effect.

In addition, an interesting dynamic relationship was observed between the reduction in autonomic and subjective metrics of pain experience by social support (Fig 3C). Specifically, this relationship only reached significance in the late stage of presentation of countdown numbers (approximately 3.3–6 seconds) preceding the delivery of noxious stimuli. A well controlled methodology was used in the pain calibration to determine the intensity of painful stimulation. Countdown numbers were adopted to dynamically manipulate the threat of painful stimuli with the intention that individuals may experience accumulated stress with the impending threat of pain. This is supported by our results, which showed a dynamic increase in heart rate in anticipation of painful stimuli (Fig 3A). Unique to our study design, the buffering influence of social support on the autonomic response could be tracked in the lead up to the delivery of noxious stimuli. Furthermore, the data suggest that this change was not simply due to somatosensory distraction (as suggested by Eisenberger et al[19]), because stranger hand-holding did not decrease heart rate, which also created somatosensory distraction. Together, these findings

suggest that the buffering influence of social support on pain experience may actually increase in value as pain threat increases. Thus, the analgesic effect of social support is associated with downregulating the threatening quality of painful stimuli.

We also showed decreased frontal theta activity during the threat of pain in the presence of close other hand-holding, which provides, to our knowledge, for the first time, the neurophysiological evidence of the social buffering effect in the context of pain. Previous studies have suggested that social support may prime safety or reward-related brain activation (eg, ventromedial prefrontal cortex) in the reduction of pain.[18,19,62] One EEG study reported that frontal theta is related to the expression of fear,[43] whereas other studies suggested that this is associated with the experience of social distress (eg, social exclusion).[13,58] Therefore, decreased frontal theta in our protocol may represent a lower level of stress aroused by impending painful stimuli. Importantly, decreased frontal theta in the close other condition selectively predicted greater pain reduction when the painful stimulation becomes more threatening (approximately 3–5.5 seconds; Fig 4B). This finding builds upon the behavioral and fMRI evidence in this area, by providing direct evidence for the social buffering hypothesis in which decreased frontal theta activity to the threat of pain is able to predict greater pain reduction.

However, there are other potential, although perhaps inter-related, interpretations. Beyond threat processing, frontal theta oscillation is also implicated in top-down control[8,23,34] and behavioral adjustment to uncertain or aversive outcomes.[9,16] In the context of the present results, an alternative explanation is therefore that frontal theta oscillations may also reflect the effort required to regulate the experienced distress. This may explain why heart rate tapers off in the end of stress manipulation when it is otherwise expected to be at its highest.

Finally we provide source localization analysis performed in the theta range to examine the potential neurological mediators generating the buffering effect. This procedure identified event-related changes of the current source density in the theta range that are presumed to account for the effects of social support observed as described previously. Specifically, decreased neural activity was found in the pgACC, sgACC, and insular cortex (anterior as well as posterior parts) in the close other compared with no-holding condition (Fig 5). Although EEG has the advantage of high temporal resolution, the results of EEG source localization are limited in terms of spatial resolution, especially compared with fMRI studies. Nonetheless, the results of EEG beam-forming were highly congruent with regions of neural activity identified in related fMRI works.[9,19,62]

It is acknowledged that the threat of pain may be highly connected to pain experience.[50] The current study induced threat of pain before painful stimulation, which was designed to directly examine the social buffering effect. However, this does not mean that they are independent of each other. Our data support this idea by showing high correlations between decreased neurophysiological threat response and pain reduction in the context of social support. Moreover, it was not our intention to show that heart rate and neural (EEG) activity are fully independent, because they are likely to be at least partially related via the hypothalamic–pituitary–adrenal axis. Instead, the present methodology allowed us to measure each independently and together they tell a story of closely inter-related autonomic and regionally specific neural changes associated with the social modulation of pain.

Close other hand-holding did not show any advantage over stranger hand-holding in decreasing pain or suppressing neurophysiological stress systems. This is different from the literature, which shows the effects of spousal hand-holding on pain reduction compared with stranger hand-holding.[9,39] This finding could be interpreted to support the evidence that the quality of a relationship modulates the analgesic effects of social support.[31] Indeed, several studies in this area manipulate social support through romantic relationships, whereas our participants' "close other" included not only romantic partners, but also friends and family members. This was done to be more reflective of the broad levels of social support in daily life, however, these types of relationships may not have the same salience as a romantic partner and may therefore have less of an effect on buffering the threat of pain.

Consistent with the literature,[9,39] stranger hand-holding did not reduce pain unpleasantness (Fig 2B) or modulate the autonomic response in anticipation of painful stimuli (Fig 3B). However, pain intensity ratings were decreased in the stranger relative to no-holding condition (Fig 2A). This discrepancy in terms of the reduction in pain intensity but not unpleasantness underscores the multidimensional definition of pain experience (ie, somatosensory and affective–motivational dimension[40]), and further research is warranted to explore the modulation of specific dimensions of pain by social support. Our findings suggest that stranger hand-holding does not necessarily provide social support to individuals in distress as it is not able to decrease the unpleasant feelings or physiological arousal. Nonetheless, the data indicate that some qualities of pain experience are reduced by stranger hand-holding and that a different mechanistic basis might underlie this effect.

To further explore this possibility, EEG oscillation was contrasted in the stranger with no hand-holding condition and significantly lower posterior theta was observed (eg, parietal, occipital regions) in the early presentation of countdown numbers (Fig 4C). A number of studies have shown the involvement of posterior theta in the processing of stimuli of high emotional arousal (eg, emotional faces), especially in the early stage of stimulus presentation.[2,23] Further studies have reported an early increase in posterior theta power during selective processing of threatening cues.[15,55,63] These studies suggest the critical role of posterior theta in selective attention for emotionally arousing and especially threatening cues. The reduction in posterior theta power in the present study may therefore reflect reduced processing of threatening stimuli, perhaps due to distraction or attentional processes associated with stranger hand-holding.

Beyond the theoretical implications, our findings may also help understand and improve the role of social support in chronic pain patients. Our data may provide evidence in favor of support-assisted pain management therapies, in which the caregiver could help pain patients reappraise pain and related conditions as less stressful.[1,24,27] Our results further emphasize the significance of relationship quality as well as the quality of social support in pain management. Factors influencing the quality of social support, such as frequent changes in caregivers in a pain management facility, could affect patient's pain outcomes. Moreover, although pain may not always be continuous, the threat of pain may continue between pain flares, and our data suggest that social support is likely to have a more prolonged and meaningful effect on patients' pain experience through modifying the threat of pain. However, it may be the case that our findings using a paradigm of acute pain in healthy participants do not generalize to chronic pain populations. In studies of people with chronic pain, cognitive responses to pain have been reported to be altered in chronic pain conditions compared with healthy individuals (ie, pain is perceived as more painful and threatening).[14,22] It may be that there is a ceiling effect beyond which social support can cope. Moreover, although our behavioral outcomes assessed the effect of social support on perceived pain, social support may act on other aspects of the chronic pain experience such as functional disability and depression.[5,61] Further research is therefore required to investigate the relationship and effect of social support in chronic pain patients.

There are several limitations in the study. Despite the significant results reported in this investigation, they are on the basis of a relatively small sample size. The extent to which the findings might therefore generalize to a larger and potentially more diverse sample is not clear and should be investigated in future studies. In addition, hand-holding was used to convey social support in this study. However, social support is a multidimensional construct that goes beyond physical contact. Indeed, a recent meta-analysis has shown that the influence of social support on pain is modulated by the subject's perception of the intention and capacity of the social partner to provide assistance, as well as the preexisting relationship between them.[31] Further studies are therefore warranted to investigate the possible effects of social support across different contexts (ie, beyond hand-holding), as well as factors that may affect the influence of social support such as relationship quality. Finally, although we present analysis suggesting that the neural source of EEG activity in our data was congruent with brain regions involved in the processing of threat and pain,[9,20,41,54] EEG source localization is limited in spatial resolution, particularly in the localization of deeper brain regions.[47] Future studies could consider examining this protocol with concurrent fMRI and EEG recording.

Overall, this study extends the work of previous studies suggesting that social support may be able to reduce pain through modifying perceived threat of pain.[19,25,59,60] In this study, we provided a novel manipulation to induce a threat phase before the painful stimulation to directly examine the social buffering effect and the dynamics within this effect. Our findings show that social support decreased threat-related changes in heart rate and reduced frontal theta activity, with the magnitude of these changes associated with greater pain reduction. Furthermore, the social buffering effect was generally stronger and did not subside as the threat of pain increased. Our results thus provide evidence in support of the social buffering effect by showing the neural and physiological dimensions of this effect. Together, this study provides novel insights of the dynamics of the buffering effect of social support on pain.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2017.12.007.

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