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Publication Date

2020-03-01

DOI

10.1016/j.ctim.2020.102334

Peer reviewed

HHS Public Access

Author manuscript

Complement Ther Med. Author manuscript; available in PMC 2021 March 01.

Published in final edited form as:

Complement Ther Med. 2020 March ; 49: 102334. doi:10.1016/j.ctim.2020.102334.

Autonomically-mediated decrease in microvascular blood flow due to mental stress and pain in sickle cell disease: A target for neuromodulatory interventions

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Abstract

Pain and vaso-occlusive crises (VOC) are hallmark complications of sickle cell disease (SCD) and result in significant physical and psychosocial impairment. The variability in SCD pain frequency and triggers for the transition from steady state to VOC are not well understood. This paper summarizes the harmful physiological effects of pain and emotional stressors on autonomically-mediated vascular function in individuals with SCD and the effects of a cognitive, neuromodulatory intervention (i.e. hypnosis) on microvascular blood flow. We reviewed recent studies from the authors' vascular physiology laboratory that assessed microvascular responses to laboratory stressors in individuals with SCD. Results indicate that participants with SCD exhibit marked neurally mediated vascular reactivity in response to pain, pain-related fear, and mental stress. Further, pilot study results show that engagement in hypnosis may attenuate harmful microvascular responses to pain. The collective results demonstrate that autonomically-mediated vascular responses to pain and mental stress represent an important SCD intervention target. This ongoing work provides physiological justification for the inclusion of cognitive, neuromodulatory

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CRediT authorship contribution statement

Sarah R. Martin: Writing - original draft, Writing - review & editing, Conceptualization, Investigation, Visualization. **Payal Shah:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing - original draft, Writing - review & editing, Project administration, Visualization, Data curation. **Christopher Denton:** Investigation, Writing - review & editing, Visualization, Data curation. **Lonnie K. Zeltzer:** Conceptualization, Investigation, Writing - review & editing, Supervision, Funding acquisition, Project administration. **Saranya Veluswamy:** Conceptualization, Methodology, Investigation, Writing - review & editing, Project administration, Formal analysis, Visualization, Data curation. **Michael C.K. Khoo:** Conceptualization, Methodology, Investigation, Writing - review & editing, Supervision, Funding acquisition, Project administration. **Thomas D. Coates:** Conceptualization, Methodology, Investigation, Writing - review & editing, Supervision, Funding acquisition, Project administration.

and complementary treatments in SCD disease management and may inform the development of targeted, integrative interventions that prevent the enhancement of autonomic vascular dysfunction in SCD.

Keywords

Anxiety; Autonomic nervous system; Hypnosis; Neuromodulatory treatment; Pain; Sickle cell disease; Stress; Vasoconstriction; Vaso-occlusive crises

1. Introduction

Sickle cell disease (SCD) is an inherited blood disorder due to a point mutation in the β-globin gene resulting in abnormal sickle hemoglobin (HbS) which polymerizes upon deoxygenation, transforming the red blood cell (RBC) from flexible to the rigid, characteristic sickle shape. Sickled RBC can occlude the microvasculature causing vaso-occlusive crisis (VOC), which is the hallmark of SCD and manifests as sudden onset of musculoskeletal pain. There is significant variability in VOC severity even among patients with the same SCD genotypes. Many SCD patients have relatively low VOC frequency, while a small subset of SCD patients have more frequent and more severe VOC, accounting for most hospitalizations for pain.[1,2] This limited understanding of variability in SCD pain frequency and severity plays a role in the inadequate management of VOC pain, provider suspicion of patients' pain reports, and an under appreciation for the potential harmful physiological effects.[3,4]

Cold temperature, pain and emotional stress are stated triggers for VOC, but mechanisms by which these events trigger the transition from steady state to SCD-related pain and VOC are not yet well understood. Recent studies have suggested that autonomic nervous system (ANS) modulation of vascular function may play an important role in triggering the onset of VOC from steady state.[5,6] Psychological and behavioral pain responses (e.g., coping, pain interference and catastrophizing) have been shown to be associated with SCD clinical pain outcomes and markers of central sensitization,[7–10] but further examination of psychophysiological responses is needed to improve pain outcomes in SCD.

The inclusion of nonpharmacological interventions is often recommended in SCD management [11–13] and cognitive neuromodulatory interventions may represent a promising option to target stress and pain-related autonomic central processes.[14,15] The primary objective of this article is to demonstrate 1) how the connection between ANS-mediated microvascular reactivity triggered by pain, pain-related fear, and mental stress plays a role in VOC physiology in SCD, and 2) the effects of a cognitive, neuromodulatory intervention (i.e. hypnosis) on ANS-mediated microvascular reactivity (Fig. 1).

1.1. Mechanism of ANS-mediated triggers and effect on microvascular blood flow

SCD is essentially a disease of blood flow with VOC pain resulting from occlusion of capillaries with sickled RBC. Pain often originates in a specific area of the body and then migrates to other areas and progresses to a VOC. Sickling occurs continuously in steady

state but without clinically significant vaso-occlusion. Eaton and Hofrichter[16] proposed that the relation between the delay time from deoxygenation to polymerization of HbS and the rate of flow through the microvasculature were the two basic determinates of the transition from steady state to VOC. According to this model (see Fig. 2), regional vaso-occlusion occurs when RBC transit time is slowed such that HbS polymerization occurs in the microvasculature where RBC need to be able to deform in order to pass as opposed to the venule whose diameter is larger than the RBC. Thus, factors that reduce blood flow and prolong microvascular transit time increase the likelihood that the rigid sickled RBC will obstruct peripheral blood flow and trigger vaso-occlusion. Most research examinations of VOC in SCD have focused on cellular adhesion and inflammation in the post-capillary venule,[17] which would decrease flow and increase transit time. Although these factors are associated with the occurrence of painful VOC, the initiation and progression of local symptoms associated with VOC suggest that other factors may serve as triggers of VOC.

1.2. Pain, mental stress and ANS-mediated vasoconstriction in SCD

We propose that the ANS-induced vasoconstriction in the pre-capillary arteriole may be one important target of intervention to reduce the likelihood of VOC. The ANS regulates pulmonary, cardiovascular, and inflammation functions, and specifically affects peripheral vaso-reactivity and subsequent microvascular blood flow. Pain, stress, emotion and temperature all affect ANS activity, and states of distress or fear are often marked by sympathetic nervous system (SNS) activation and parasympathetic nervous system (PNS) withdrawal.[5,18–20] Individuals with SCD exhibit autonomic dysregulation,[21] with enhanced PNS withdrawal stimulated by hypoxia[22] and social, emotional and cognitive stressors.[23] A prolonged state of PNS withdrawal and SNS activation may be especially problematic for individuals with SCD as enhanced SNS activity results in vasoconstriction and reduced peripheral blood flow.

ANS activity is not only implicated in the endogenous modulation of pain, but also the physiological and psychological responses associated with the experience of pain. Behavioral pain responses and pain sensitivity have been examined in individuals with SCD, with some results indicating that individuals with SCD have altered pain perception compared to healthy controls.[24–26] However, limited data exist on ANS-mediated vasoconstriction responses to pain itself in SCD. Our group used signal processing and cross-correlation methodology[27] to capture peripheral blood flow responses to thermal pain and to examine the direct effect of pain on microvascular blood flow. Individuals with SCD, 13 years and older, and healthy race-matched controls were recruited. Individuals with SCD were eligible regardless of receiving chronic transfusion treatment or hydroxyurea. Participants underwent thermal pain testing procedures in a quiet, temperature-controlled autonomic testing laboratory and continuous peripheral blood flow was measured by infrared plethysmography (PPG). The experimental procedures included a 5-minute baseline period, verbal instruction 40 s prior to first pain pulse, and six sequential pain pulses that tested pain threshold and tolerance.[19] Measurements from the TSA-II thermal pain neurosensory analyzer (Medoc Advanced Medical Systems, Ramat Yishai, Israel) and the physiological sensors were synchronized using the BIOPAC system-AcqKnowledge software (BIOPAC Systems Inc., Goleta, CA, USA). Signal processing and cross-correlation

analyses compared the correlation between blood flow and the pain pulses to the correlation during the baseline period to determine whether a significant association, beyond random blood flow variation, existed between the pain pulse and blow flow response.[19,27]

We found that microvascular blood flow decreased following thermal pain stimulation in both healthy controls and in individuals with SCD, but vaso-reactivity was more pronounced and time from pain stimulus to vasoconstriction was shorter in individuals with SCD.[19] Not only was vasoreactivity stronger in SCD, the microvascular response was observed simultaneously in the contralateral hand to the pain stimulus as well as the ipsilateral hand, again pointing to a neural mechanism. There was significant variability in vaso-reactivity among participants and in fact, patterns of responsiveness seemed characteristic of individual participants, a finding that may have implications for the clinical variability seen in SCD VOC. Further analysis of microvascular responses to thermal pain stimulation suggests that endothelial dysfunction in SCD subjects accentuates the vascular component of the response and also introduces a neurogenic interaction that reinforces vasoconstriction.[28]

Closer examination of these data revealed that ‘pain anticipation’ also elicited a significant drop in peripheral blood flow.[19] Prior to delivery of the thermal pain stimuli, participants received a verbal instruction that they would soon receive pain stimulation. Mean microvascular blood flow decreased significantly following this instruction, and then again during pain stimulation in both individuals with SCD and in healthy controls (Fig. 3a). These findings show that the fear of an upcoming pain stimulus, in addition to the pain exposure itself, can induce significant decreases in peripheral blood flow. Although change in blood flow during pain anticipation did not differ between control and SCD groups, vasoconstriction and reduced microvascular blood flow present a risk to individuals with SCD because reduced peripheral blood flow may increase the likelihood for HbS polymerization will occur before the RBC escapes the microvasculature resulting in subsequent vascular occlusion[16] (Fig. 2). Further, given that pain is common in SCD and may result in significant medical consequences, marked vasoreactivity in response to the anxiety of pain or pain-related fear is particularly problematic in this population and likely causes further RBC entrapment. These preliminary results provide objective support for neurally mediated vasoreactivity mechanisms in line with clinical reports of pain and stress-induced VOC.[7,29]

The correlation between daily stressors and VOC pain has been documented in previous daily-diary studies.[7,30] We examined the effects of experimental mental stress and pain anticipation on microvascular blood flow.[20] Experiments were performed in a controlled setting[19,20] and peripheral microvascular blood flow was measured via PPG. Following a 5-minute baseline period, individuals with SCD and matched healthy controls were exposed to a stress induction protocol, which included an N-back memory task[31,32] and the conflict Stroop test.[33,34] After completing the mental stress protocol, participants received a visual instruction that they would receive a pain stimulus, but no pain stimulus was administered. Similar to the results of our previous pain protocol studies, the stress tests caused significant decrease in peripheral blood flow for all subjects (Fig. 3b). However, the largest drop in blood flow was seen following pain instruction[20] (Fig. 3b). Importantly, individuals with SCD who reported higher levels of anxiety also tended to exhibit lower baseline blood flow,

presumably from chronic vasoconstriction, and less change in blood flow during the stress tests. This effect was not observed in healthy controls. Taken together, these data provide direct evidence of the negative physiological effects of stress in individuals with SCD and indicate that mental stress, anxiety and pain-related fear may all have significant effects on microvascular blood flow. While it is not surprising that sympathetic outflow results in vasoconstriction, the immediate and global decrease in blood flow in response to pain, pain-related fear, and mental stress was striking (Fig. 3 a, b). These changes in tissue perfusion may have substantial clinical implications for disease outcome in SCD because of the physiology of HbS.[5,6,16]

1.3. Cognitive, neuromodulatory interventions and the modulation of microvascular blood flow

Despite increased appreciation for the multifaceted neurophysiological processes involved in pain modulation and autonomic function,[5,35,36] reliance on solely pharmacological pain treatments continues to increase even in the context of adverse and limited treatment effects.[37] Cognitive-behavioral neuromodulatory approaches are gaining traction in the field of pain as they target cortical and physiological responses that can influence the experience of pain as well as alter future pain processing.[15,38] Hypnosis is a cognitive neuromodulatory approach that engages individuals in a heightened state of focus and awareness with the purpose of creating a change and reducing or resolving an identified problem.[39] Hypnosis, specifically hypnotic analgesia, has demonstrated significant positive effects on pain in pediatric[39–42] and adult[43] clinical and experimental studies. Hypnotic analgesia activates pain inhibition processes through hypnotic suggestions for pain reduction[44] and affects activity in supraspinal areas involved in pain and autonomic processing.[35,45]

Preliminary findings on the psychophysiological effects of hypnosis in patients with SCD suggest that hypnosis is a promising intervention for this population. Early evidence from a SCD case study demonstrated that vasodilation, as evidenced by erythema of the skin, increased during hypnosis[46] and, in an experimental study, patients with SCD reported less pain during and following a hypnosis intervention.[47] Our laboratory recently conducted a pilot study to examine the effect of one hypnosis session on peripheral microvascular blood flow during thermal pain quantitative sensory testing (QST).[48] Following similar methodological procedures in the thermal pain study,[19] adults with SCD and race-matched healthy controls were exposed to thermal heat pain detection and tolerance pulses before and after hypnosis. Adults with SCD had lower baseline peripheral blood flow, but blood flow during pain testing significantly increased to levels comparable to that of controls following engagement in a single session of hypnosis. These data suggest that engaging in hypnosis may prevent, and possibly improve, the vasoconstrictive response to pain or stress.[19,20] While blood flow improved in SCD subjects, improvement in pain threshold and tolerance following hypnosis was observed only in controls.[48] Thus, a session of hypnosis did not significantly decrease pain sensitivity in adults with SCD, but it did have an effect on neurally mediated microvascular responses. Although a randomized controlled trial is needed to confirm these effects, the significant increase in blood flow during pain stimulation following a single session of hypnosis is no-table. These findings implicate that

a single exposure to hypnosis might offset a harmful microvascular response to acute pain and has potential to prevent subsequent VOC.

2. Conclusion

Individuals with SCD are at risk for having decreased peripheral blood flow secondary to enhanced ANS-mediated vasoconstriction in response to mental and pain triggers.[5,19,20,22] Both pain and stress modulate ANS function and individuals with SCD exhibit autonomic dysfunction marked by significant parasympathetic withdrawal and enhanced sympathetic drive.[5,22] ANS modulation of vascular responses may play an important role in triggering VOC and contribute to the complex pathophysiology of VOC in SCD.[5,6]

We were able to demonstrate microvascular vaso-reactivity in response to pain stimulation, pain-related fear, and mental stress in a vascular physiology laboratory.[19,27] Using signal processing,[27] we now have a measurable physiological variable that can be used as a surrogate for microvascular and autonomic dysfunction as well as an end-point for the effects of cognitive, neuromodulatory treatment modalities. These observable variables of microvascular function not only provide tangible support for the harmful physiological effects of emotional stressors in individuals with SCD, but also validate patients' reports of pain-related triggers, and provide physiological justification for the inclusion of cognitive, neuromodulatory and non-pharmacological complementary treatment in SCD management.

The results and limitations of our current work may help guide future research aimed at identifying effective interventions for individuals with SCD. Our studies revealed significant variability in vaso-reactivity, which may have implications for the common clinical variability seen in SCD symptomatology. In the future, we will identify vaso-reactivity response patterns, associations among vaso-reactivity and SCD symptom variability, and effects of vaso-reactivity and symptom variability on neuromodulatory intervention outcomes. Previous research suggests that hypnotizability or hypnotic suggestibility may affect patterns of autonomic function and hypnosis intervention outcomes.[49–51] Results from our hypnosis pilot study were encouraging, and suggest that a more formal, randomized controlled trial of this modality that includes an assessment of hypnotizability on microvascular blood flow would be interesting and important. In addition, future work should examine effects of microvascular reactivity on clinical outcomes and consider how other treatments (e.g., chronic transfusions and hydroxyurea) may affect microvascular responses. Collectively, this work may help clinicians develop more tailored treatment recommendations.

Armed with an objective way to assess the stress response ensuing vasoconstriction propensity, we can explore the effects of a hypnosis session, and potentially moderating effects of social stressors, on microvascular and autonomic pain responses in individuals with SCD. In addition, we can examine associations between patterns of microvascular responsiveness across individuals with SCD and clinical outcomes to identify mechanisms underlying VOC variability. The results from this ongoing work will inform the development of targeted psychological and integrative interventions that affect key psychophysiological processes to alleviate the effects of autonomic vascular dysfunction and subsequent SCD

pathophysiology. Perhaps equally importantly, these responses to experimental stress are clearly visible in the data and can be shown to medical practitioners and students so they can appreciate that these psychological and non-pharmacological approaches have real physiologic consequences in humans.

Acknowledgments

Funding

This work was supported by the National Institutes of Health National Heart, Lung, and Blood Institute [U01 HL117718, PIs: Coates, Khoo, Wood, Zeltzer]; National Institutes of Health National Heart, Lung, and Blood Institute [5F32HL139114, PI: Martin].

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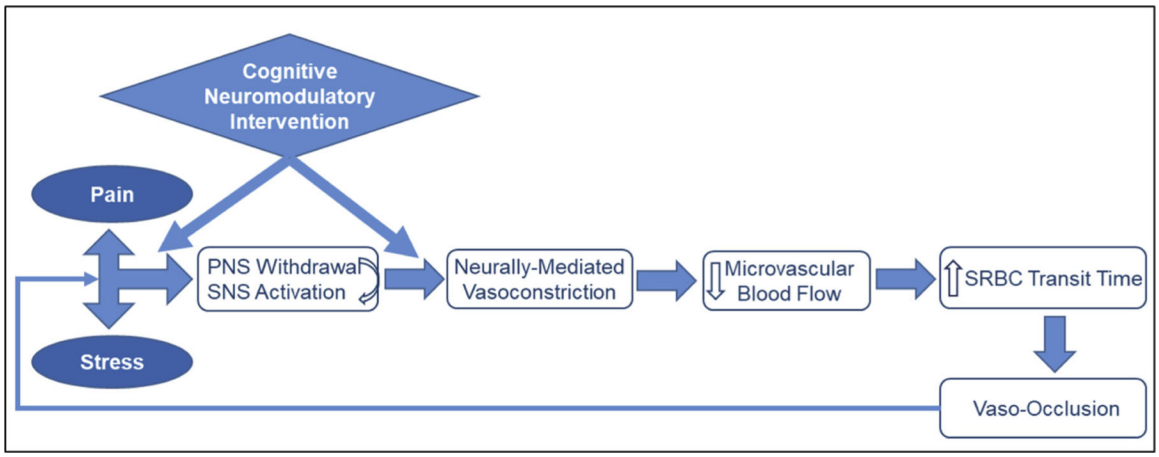

Fig. 1.

Conceptual model depicting that enhanced ANS-mediated vasoconstriction in response to mental stress and pain reduce blood flow, prolong microvasculature transit time, and increase the likelihood that rigid sickled red blood cells (SRBC) will obstruct peripheral blood flow and trigger vaso-occlusion. Cognitive, neuromodulatory interventions may attenuate harmful autonomic-mediated microvascular responses to pain and stress.

Notes: ANS = autonomic nervous system; PNS = parasympathetic nervous system; SNS = sympathetic nervous system; SRBC = sickle red blood cell.

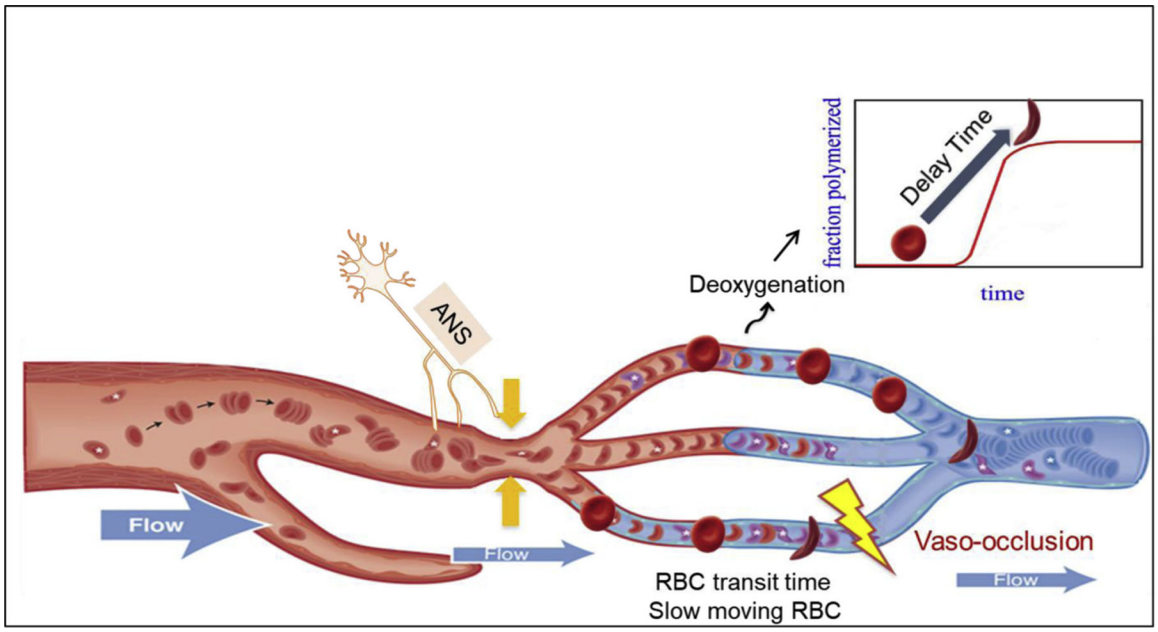

Fig. 2.

Based on a model by Eaton, Hofrichter & Ross (1976) that proposes the relation between the delay time from deoxygenation to polymerization of HbS and the rate of microvasculature are determinates of the transition from steady state to VOC.

Note: ANS = autonomic nervous system; RBC = red blood cell; VOC = vaso-occlusive crisis.

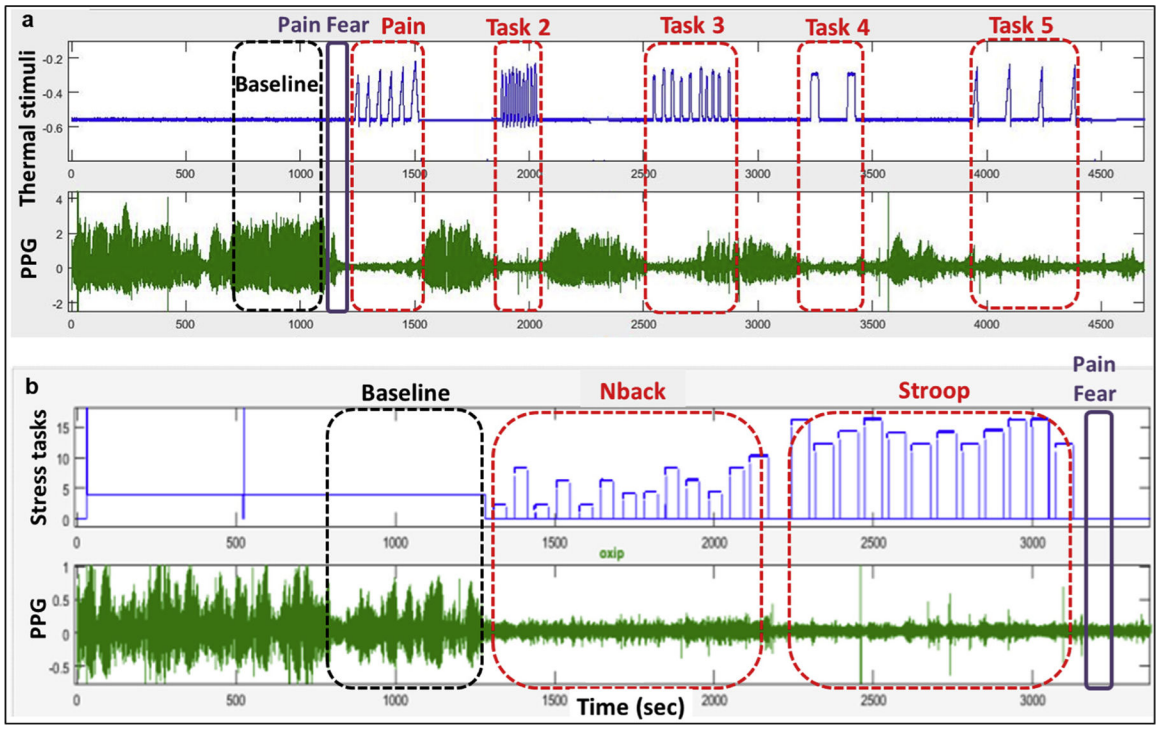

Fig. 3.

a and b The raw photo plethysmography (PPG) waveform signal output during pain (Figure a) and mental stress (Figure b) experiments. The top panels of Figure a and b represent the task output. The height of the peaks or bars represent the pain temperature (a) or difficulty of the task (b), respectively. The second panels are the raw PPG waveform.