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Authors
Roemer, Ryan
Martinez, Ariana
Torres, Tara
et al.

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Emotion Regulation and Positive Affect in the Context of Salivary Alpha-Amylase Response to Pain in Children with Cancer

Brooke N. Jenkins, PhD[1,2], **Douglas A. Granger, PhD**[3], **Ryan J. Roemer, PsyD**[4], **Ariana Martinez, BS**[2,5], **Tara K. Torres, BA**[2,3], **Michelle A. Fortier, PhD**[2,4,5,*]

[1]Department of Psychology, Chapman University

[2]UCI Center on Stress and Health, School of Medicine, University of California-Irvine

[3]Department of Psychology and Social Behavior, University of California-Irvine

[4]Department of Pediatric Psychology, CHOC Children's Hospital, Orange, CA

[5]Department of Anesthesiology & Perioperative Care, University of California-Irvine

Abstract

Background: Children with cancer routinely undergo painful medical procedures invoking strong physiological stress responses. Resilience to this pain may be conferred through resources such as emotion regulation strategies and positive affect.

Procedure: This study measured dispositional positive affect in children with cancer (N = 73) and randomly assigned participants to one of three emotion regulation strategy conditions (distraction, reappraisal, or reassurance). Children applied their assigned strategy during an experimental pain procedure (the cold pressor task [CPT]) and provided saliva samples before, immediately after, and 15 minutes after the CPT. Saliva samples were later assayed for alpha amylase (sAA) – a surrogate marker for autonomic/sympathetic nervous system activity and regulation.

Results: Children in the reassurance group had sAA levels that continued to rise after completion of the CPT compared to children in the distraction ($b = -1.68$, $p = .021$) and reappraisal conditions ($b = -1.24$, $p = .084$). Further, dispositional positive affect moderated the effect of condition such that children in the reassurance group with lower levels of positive affect had sAA levels that continued to rise after completion of the CPT (dy/dx = 1.56, $p = .027$) whereas children in the reassurance condition with higher levels of positive affect did not exhibit this rise ($p > .05$).

Conclusions: Specific emotion regulation strategies, such as distraction and reappraisal, may attenuate the stress response to pain in pediatric patients with cancer, and positive affect may

*Corresponding to: Michelle A. Fortier, PhD (mfortier@uci.edu); 505 S. Main St. Orange, CA, United States 92697; Tel: 714-456-2833; Fax: 714-480-0733.

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Conflict of Interest Statement

In the interest of full disclosure, DAG is the founder and chief scientific and strategy advisor at Salimetrics LLC and Salivabio LLC and these relationships are managed by the policies of the committees on conflict of Interest at the John Hopkins University School of Medicine and the University of California at Irvine.

confer resilience in response to pain even with use of less effective coping strategies such as reassurance.

Keywords

cancer; emotion regulation strategies; oncology; pain; positive affect; salivary alpha amylase

Introduction

Pediatric patients with cancer routinely undergo painful medical procedures[1], invoking sometimes intense physiological responses. The magnitude of these responses are important to understand because acute physiological stress has the potential to impede healing, is linked to increased negative affect and problem behavior, and can have deleterious effects on downstream physiological systems [2–4]. In the context of certain pediatric illnesses, exposure to painful invasive procedures is unavoidable. However, the expression of individual differences in the biobehavioral response to painful medical procedures can be moderated by learned emotion regulation strategies and by intrinsic factors such as positive affect [5].

The stress response to pain is often assessed by autonomic nervous system (ANS)/ sympathetic nervous system (SNS) reactivity to and recovery from a painful stimulus [6]. Recently, salivary alpha amylase (sAA) has emerged as a minimally invasive surrogate marker of the ANS/SNS component of the psychobiology of the stress response[7–9]. Measuring sAA levels has proven useful in estimating individual differences in children's stress-related reactivity and recovery to pain tasks [10]. This is important as high stress reactivity and slower stress recovery have been independently tied to future negative health outcomes [11]. In terms of the pain stimulus, the use of experimental induction of pain enables an ethical and safe method of studying biobehavioral responses while ensuring methodological standardization across participants. The cold pressor task (CPT), in which individuals submerge their hand into near freezing water, is one experimental pain task that has been widely used with children [10,12] and has been shown to reliably increase sympathetic activity [13,14].

Pain management techniques often include emotion regulation strategies such as distraction and reappraisal. With children, distraction may include watching a video, playing a game, or talking with others [15]. Distraction techniques have been utilized in numerous pediatric pain settings, including oncology, and have beneficial effects on self-reported pain [16,17]. Reappraisal is a related, but distinct, cognitive emotion regulation strategy that has also been used to manage pain. Often, reappraisal is used during a painful experience to reframe the experience of pain in a positive manner [18], for example, by acknowledging the benefits of the pain (e.g., a painful treatment will help the individual become healthy). Many interventions have used reappraisal techniques, including thinking about pain from a third person perspective and reframing pain experiences as less threatening to effectively manage pain [18,19].

A third emotion regulation technique that is less commonly used in interventions is reassurance. Reassurance includes statements that seek to improve the emotional state of the child (e.g., "you're ok," "it's going to be fine")[20] and tends to occur naturally and frequently

in the context of pediatric pain by adults and healthcare providers in an effort to soothe children [15]. However, evidence suggests that reassurance may actually have detrimental effects on pain because it draws attention towards the pain [15]. Unlike mindfulness techniques that also draw attention towards a child's pain but then decrease the perception of pain through certain strategies (e.g., acceptance, an open attitude [21]), reassurance not only draws attention towards the pain but can also invalidate the pain experience. Children are told that they are "ok" when indeed they are not feeling okay. Therefore, we hypothesized that reassurance would lead to higher sAA reactivity and slower recovery (i.e., a less steep decline in sAA post CPT) compared to distraction and reappraisal.

When studying physiological stress responses, it is important to understand how the naturally occurring affective context plays a role. Specifically, dispositional positive affect arises as a variable of interest given the large body of research demonstrating that positive affect has health and pain reducing benefits (for review see [5]). For example, positive affect has been shown to decrease pain [22,23] and buffer responses to stress [24], and individuals high in positive affect have better overall physiological functioning [25]. Positive affect may have a direct association with physiological functioning [26] and changes to physiological functioning during times of stress reduce the experience of pain [22]. Additionally, positive affect is thought to have indirect effects on physiological functioning during times of stress through its association with better sleep [27,28], social support [29], and other coping resources [30]. Therefore, we hypothesized that high dispositional positive affect would lead to lower sAA reactivity to and faster sAA recovery from the CPT and buffer the detrimental effects (high reactivity, slow recovery) of reassurance.

Materials and Methods

Participants

Participants included 73 children undergoing treatment for cancer at the Children's Hospital of Orange County (CHOC Children's), CA. Children were 6 to 18 years old (M_{age} = 11.67, SD_{age} = 3.79) and the majority (62%) were male. Sixty-seven percent of participants were Hispanic/Latino, 25% were non-Hispanic White, and 8% were other or more than one race. The majority of children were diagnosed with leukemia. Parents provided written informed consent and children provided assent/consent as appropriate. All study procedures were approved by CHOC Children's Institutional Review Board (see Supplemental Participants Material for more information).

Procedures Overview

Upon arriving to the lab, parents completed questionnaires assessing demographic variables and children completed a measure of dispositional positive affect. Then, children were taken to a separate room to complete the CPT with a research assistant and without their parent present. Before starting the CPT, participants were randomly assigned to one of three emotion regulation conditions: distraction, reappraisal, or reassurance (see Supplemental Figure S1 and Supplemental Procedures Material). Children provided saliva samples 15 minutes before, immediately after, and 15 minutes after the CPT. Upon removing their hand from the cold water, children rated their pain.

Measures

Dispositional positive affect.—Dispositional positive affect was assessed using the Positive and Negative Affect Schedule for Children (PANAS-C[31]). The PANAS-C asked children to indicate to what extent they felt a list of 12 positive emotions (e.g., joyful, happy) in the past few weeks rated on a scale from 1 (very slightly or not at all) to 5 (very much). Items were summed together to create an overall positive affect score (Cronbach's alpha = 0.86). The PANAS-C has been validated in healthy children and children with emotional/behavioral disorders[26] and used extensively in pediatric cancer populations [32,33]. Children in our sample on average scored a 37.18 (SD = 10.02, range = 12 to 53). In previous literature [26], healthy children on average score a 43.40 (SD = 9.81) reflecting a slightly higher average as compared to our sample.

Pain ratings.—Children were asked to report their pain when they removed their hand from the water using a numeric rating scale, a reliable and valid measure with developmentally appropriate anchors [34–36]. Children ages 6 through 11 were asked "How much is it hurting right now?" on a scale of "Not hurting" = 0 to "Hurting a whole lot" = 10. Children 12 to 18 were asked "How much pain are you in right now?" on a scale of "No Pain at All" = 0 to "A Lot of Pain" = 10.

Emotion Regulation Strategies

Children in the distraction condition were shown a non-emotional educational documentary. Children were told to focus on the video and every 30 seconds were reminded to focus. Children in the reappraisal condition were asked to think about how their participation was going to help kids like them with cancer with reminders to do so every 30 seconds. Children in the reassurance condition were told: "Look, I'm really sorry that you have to do this. I know how it feels. The cold can be painful, but don't be nervous. I've been through this and it's alright, you're going to be okay." Every 30 seconds, children in this condition were told "Remember, it's going to be ok."

Cold Pressor Task (CPT)

Children first placed their non-dominant hand in room temperature water (36° Celsius) to familiarize themselves with the procedure. Then, they placed that same hand in 7° Celsius water. Children were asked to remove their hand from the water when they could no longer stand the pain. Time of hand removal was recorded and used to operationally define pain tolerance with longer durations reflecting greater pain tolerance. A four-minute ceiling was used such that children were instructed to remove their hand from the water after four-minutes if they had not already done so (see Supplemental Procedures Material).

Collection and Assay

Following Granger and colleagues, whole unstimulated saliva samples were collected by passive drool 15 minutes before (Pre-task), immediately after (Post-task1), and then 15 minutes after the CPT (Post-task2). On average, sampling times of day were between 11:15am and 5:51pm. Samples were frozen and stored at −20° Celsius until the day of assay. On the day of assay, samples were thawed and mucins removed by centrifugation at 2,080 x

g. Following Granger and colleagues (2007), sAA was assayed using a commercially available enzyme kinetic assay without modification to the manufacturer's recommended protocol (Salimetrics, Carlsbad, CA). Test volume was 10 ul of saliva (then 8 ul of a x200 dilution). Intra- and inter-assay coefficients of variation were on average less than 10% and 15%. All sAA values throughout the CPT were between 3 and 519 u/mL which are within common sAA ranges during a CPT [8,37].

Statistical Analysis

Spline growth curve modeling was used to assess the trajectories of sAA over the course of the pain task [38]. In these analyses, the knot was set at Post-task1 using the mkspline command in Stata. Placing the knot here estimates the linear sAA trajectory from Pre-task to Post-task1 (i.e., reactivity) and then the linear trajectory from Post-task1 to Post-task2 (i.e., recovery) all within the same model. The nature of our data was multilevel with time as a level 1 variable grouped within participants. Condition (distraction, reappraisal, and reassurance) and positive affect (treated as continuous in the analysis but divided using a median split for graphical purposes) were both between subjects variables and thus were used as level 2 variables in the analyses. The main effects as well as the interaction between condition and positive affect were tested. In all analyses, sAA was the dependent variable of interest. sAA was right skewed and was therefore transformed using a square root transformation. This transformation alleviated the problem of skewness. After this transformation, all values were within three standard deviations of the mean.

To determine whether emotion regulation condition influenced pain tolerance, a Cox hazard regression model was used with pain tolerance as the dependent variable and emotion regulation condition as the independent variable. Cox hazard regression does not assume a normal distribution for the dependent variable [39] (in this case time until hand removal). Furthermore, because some children did not remove their hand until they were instructed to do so, we right-censored their data as it is unknown when they would have taken their hand out had they not been instructed to do so. This same model was used with positive affect as the independent variable to assess the association between positive affect and pain tolerance. Differences in self-reported pain between the three conditions were assessed with ordered logistic regression due to the ordinal nature of the dependent variable of self-reported pain. This same model was used with positive affect as the independent variable to assess the association between self-reported pain and positive affect.

In all analyses we adjusted for time since diagnosis given the importance of this variable on distress in children with cancer [40]. We also controlled for age, sex, and race when they were associated with our dependent variable of interest.

Results

Descriptive Statistics

sAA values across the CPT were 112.47 u/mL (SD = 105.22; range = 2.76 to 519.29), 110.00 u/mL (SD = 90.39; range = 4.07 to 442.11), and 110.44 (SD = 92.02; range = 6.82 to 398.35) for Pre-task, Post-task1, and Post-task2, respectively. The average dispositional

positive affect score was 37.18 (SD = 10.02; Range = 12 to 53). On average, children kept their hand in the cold water for 118.34 seconds (SD = 98.24; Range = 3.00 to 240.00 seconds) and reported pain as 5.24 (SD = 3.63; Range = 0 to 10). Thirty seven percent of children kept their hand in the cold water for the entire 4-minute ceiling.

sAA Response

There was a significant interaction between emotion regulation condition and time on sAA such that all conditions had similar Pre-task to Post-task1 trajectories (i.e., reactivity) but that Post-task1 to Post-task2 trajectories (i.e., recovery) varied by condition (see Figure 1). Specifically, during recovery, children in the distraction condition had a significantly greater decrease in sAA compared to individuals in the reassurance condition ($b = -1.68$, $SE = 0.73$, $z = -2.30$, $p = .021$, 95% CI [−3.11, −0.25]). Additionally, children in the reappraisal condition had a marginally significantly greater decrease in sAA during recovery compared to individuals in the reassurance condition ($b = -1.24$, $SE = 0.72$, $z = -1.72$, $p = .085$, 95% CI [−2.65, 0.17]). Reappraisal and distraction were not significantly different from one another ($b = 0.44$, $SE = 0.73$, $z = 0.60$, $p = .545$, 95% CI [−0.98, 1.86]).

Next, the effect of positive affect on sAA was assessed. Positive affect benefitted recovery such that children who reported higher levels of positive affect had greater declines in sAA during recovery compared to children lower in positive affect ($b = -0.07$, $SE = 0.03$, $z = -2.13$, $p = .033$, 95% CI [−0.13, −0.01]; see Figure 2).

When positive affect was added to the model with group and time, there was a three-way interaction between recovery, group, and positive affect on sAA (see Figure 3). Specifically, during recovery, positive affect had a marginally different effect on sAA for the reappraisal compared to the distraction group ($b = -0.16$, $SE = 0.08$, $z = -1.95$, $p = .051$; 95% CI [−0.32, 0.00]) and a marginally different effect for the reappraisal compared to the reassurance group ($b = -0.13$, $SE = 0.07$, $z = -1.81$, $p = .071$; 95% CI [−0.26, 0.01]). Follow up analyses were used to describe these differences. For distraction, higher positive affect actually increased the effect of the distraction condition with those higher in positive affect having greater decreases in sAA (dy/dx = −2.29, $SE = 0.81$, $z = -2.83$, $p = .005$, 95% CI [−3.87, −0.70) compared to those lower in positive affect (dy/dx = 0.51, $SE = 0.91$, $z = 0.56$, $p = 0.574$). In contrast, positive affect did not influence the effect of reappraisal on sAA response, ps > 0.20. Finally, in the reassurance condition children with lower positive affect had an increase in sAA during recovery (dy/dx = 1.56, $SE = 0.71$, $z = 2.21$, $p = .027$, 95% CI [0.18, 2.95]). In contrast, children higher in positive affect in the reassurance condition did not have this upward trajectory (dy/dx = −0.56, $SE = 0.74$, $z = -0.75$, $p = .451$, 95% CI [−2.02, 0.90]).

Pain Tolerance and Self-Reported Pain

There were no differences in pain tolerance (reassurance vs. distraction: $\beta = 0.70$, $SE = 0.42$, $Wald\ \chi^2(1) = 2.84$, $p = 0.092$, $HR = 2.02$, 95% CI [0.89, 4.58]; reassurance vs. reappraisal: $\beta = 0.24$, $SE = 0.41$, $Wald\ \chi^2(1) = 0.35$, $p = 0.553$, $HR = 1.28$, 95% CI [0.57, 2.85]; distraction vs. reappraisal: $\beta = 0.46$, $SE = 0.41$, $Wald\ \chi^2(1) = 1.24$, $p = 0.266$, $HR = 1.58$, 95% CI [0.70, 3.56]) or self-reported pain among the conditions ($\chi^2(4) = 6.94$, $p = .139$).

Similarly, positive affect did not influence pain tolerance ($\beta = 0.01$, $SE = 0.02$, $Wald\ \chi^2(1) = 0.07$, $p = 0.792$, $HR = 1.01$, 95% CI [0.97, 1.04]) or self-reported pain ($\chi^2(3) = 3.93$, $p = .269$).

Discussion

Children in the reassurance group had sAA levels that continued to rise after completion of the CPT compared to children in the distraction and reappraisal conditions. Further, dispositional positive affect interacted with condition such that children in the reassurance group with lower levels of positive affect had sAA levels that continued to rise (past baseline levels) after completion of the CPT. Conversely, children in the reassurance condition with higher levels of positive affect did not exhibit this rise (see Figure 3). Specific emotion regulation strategies, such as distraction and reappraisal, may attenuate the stress response to pain in pediatric patients with cancer, and positive affect may confer resilience in response to pain even with use of less effective coping strategies such as reassurance. These findings have several noteworthy implications and are discussed in terms of how they may impact clinical intervention research.

Contrary to our predictions, there were no condition differences in stress reactivity. However, research regularly finds that it is the recovery period that is of most importance in response to stress [11]. In other words, it is not how an individual responds during stress but how he or she feels once the stressor is complete. Previous literature has also demonstrated that strategies, such as distraction and reappraisal, may only have differential effects in the long term [41,42]. Nevertheless, we did find substantial variation in sAA reactivity to the CPT which allowed us to examine recovery differences. Altogether, the reactivity period may not be the best reflection of when these strategies are beneficial, and future research should continue to look at both the reactivity and recovery phases.

Emotion regulation strategy differentially predicted sAA recovery in response to the CPT. As hypothesized, reassurance resulted in delayed-prolonged recovery of sAA activity relative to the distraction and reappraisal conditions. Further, there were no differences in recovery between the distraction and reappraisal conditions. These findings suggest that distraction and reappraisal may be more helpful in reducing the physiological stress response due to pain compared to reassurance but that they are no different from one another. Given that reassuring statements redirect a child's attention towards the pain (the opposite of distraction), without providing a way for the pain to be reinterpreted (reappraisal) it is not surprising that reassurance would have dissimilar effects compared to distraction and reappraisal. Further, this corroborates the findings that reassurance may increase distress in the context of acute pain[15].

Dispositional positive affect was also found to influence the stress response. On average, children with higher levels of positive affect had sAA levels that dropped more quickly after the pain task was completed compared with children who had lower levels of positive affect. Further, there was a significant interaction between positive affect, emotion regulation condition, and time such that children with lower levels of positive affect in the reassurance condition had sAA levels that continued to rise *even after* completion of the pain task,

whereas children with higher levels of positive affect did not experience this increase in ANS/SNS activity. These findings suggest that positive affect may buffer the stress response to pain when using potentially unhelpful emotion regulation techniques. This buffering effect of positive affect may have occurred for a variety of reasons. For example, positive affect has been tied to better sleep [27,43], stronger social support networks [44], and increased exercise [45], all of which allow individuals to cope better under stress. In addition, although positive affect did not influence the effect of reappraisal, it did benefit the distraction condition such that children with higher positive affect in the distraction group experienced an even greater decline in ANS/SNS activity compared to other children in this group with lower positive affect. This may suggest that positive affect could be one factor in determining the efficacy of distraction. A next step in future research is to manipulate positive affect to determine whether state positive affect has similar effects.

Surprisingly, emotion regulation and positive affect had no effect on pain tolerance or self-reported pain. This provides further evidence that behavioral and subjective pain reports may not always match the physiological response demonstrating that it is important to assess all three outcomes [18,46]. The mismatch in this study may have occurred because of the nature of this population. Specifically, children with cancer routinely experience painful procedures and in comparison to painful clinical procedures, the cold pressor task may not have been as distressing. Indeed, the average pain rating on a scale of 0 to 10 was 5.42. Therefore, the biological component adds important information that the self-ratings and behavior do not reveal. Although self-report pain ratings are clinically relevant, the underlying biological response here demonstrates that even though the perception of pain may have “habituated” there are still individual differences in the physiological consequences at play.

There are likely several differences between experimental pain tasks and painful medical procedures that should be considered in relation to our findings. First, during a naturalistic stressor such as a venipuncture or bone marrow aspiration there may be differences in pain due to procedural and physician differences in technique. Using emotion regulation strategies in this setting may come with challenges related to delivery. For example, distraction may be relatively easy to use if an electronic device or activity such as bubble blowing are accessible. In contrast, reminding a child to use reappraisal during a venipuncture may be challenging due to the need for personnel to coach a child to implement reappraisal effectively.

There are several limitations to this work which future research could address. First, our sample was relatively small and heterogeneous which could contribute to a lack of findings in the self-report and behavioral data. Second, we did not have access to data regarding children’s medication use that may have impacted pain response (e.g., analgesic use). Third, there is still more to learn about the use of sAA as a surrogate marker of ANS/SNS activity. Although a majority of research has demonstrated the association between sAA and SNS activity[7–9], research by Nagy and colleagues [47] found that sAA may be under control of both SNS and parasympathetic nervous system (PNS) functioning. Thus, it may be more difficult to determine whether increases in sAA are reflecting SNS and/or PNS activity. Nagy and colleagues also demonstrated that sAA may increase immediately after, but not during stress, which implies that sAA measurements should be collected during as well as after the

stress task. Collecting such data may have allowed us to examine more detailed changes in sAA over the course of the stressor. Nevertheless, although we did not assess sAA during the stressor (i.e., while the child had his or her hand in the cold water), our results are still important given that it was recovery from the stress that was altered by emotion regulation condition and positive affect.

Despite these limitations, our findings may have clinical implications in the health care of pediatric oncology patients and guide future research. First, this study provides evidence that distraction and reappraisal might be useful techniques for decreasing physiological distress in children with cancer during painful treatments as compared to reassurance which may enact physiological tolls on the body, although no self-reported differences in pain between the conditions were found. Second, dispositional positive affect may provide resilience to the harmful effects of reassuring statements. These findings pave the way for future intervention research in clinical settings. In conclusion, better understanding the physiological stress response to pain and methods for decreasing this stress response can improve the quality of life in children with cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

sAA	Salivary Alpha Amylase
ANS	Autonomic Nervous System
SNS	Sympathetic Nervous System
CPT	Cold Pressor Task
PANAS-C	Positive and Negative Affect Schedule for Children
PNS	Parasympathetic Nervous System

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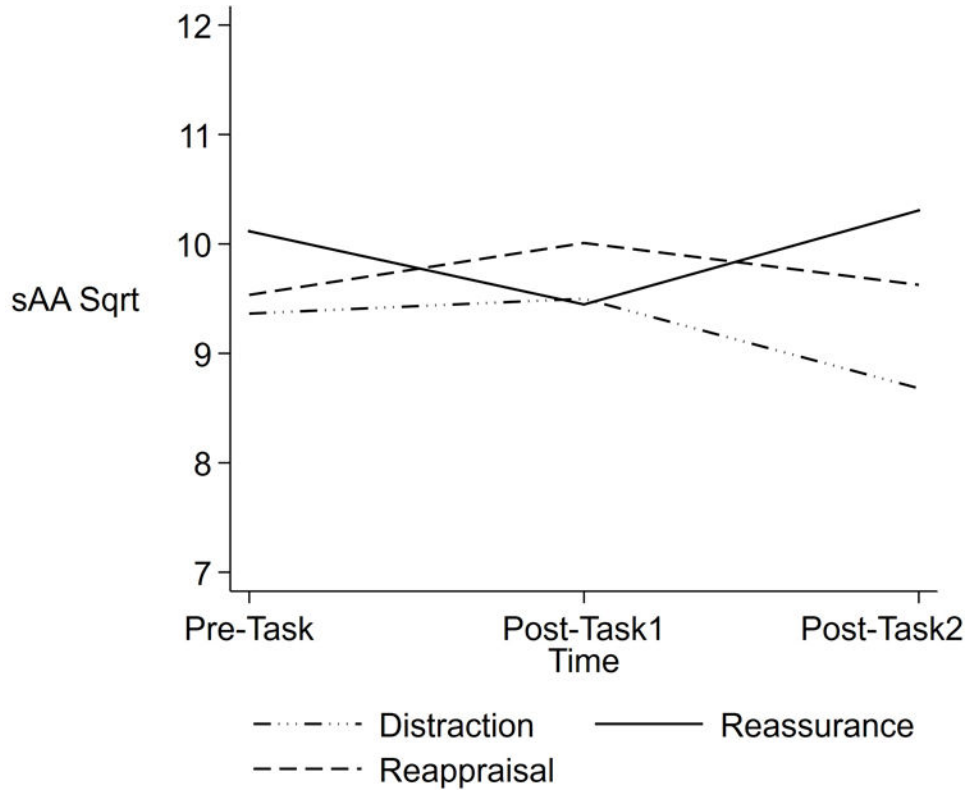

Figure 1.
Effect of Emotion Regulation Condition on Salivary Alpha-Amylase Response

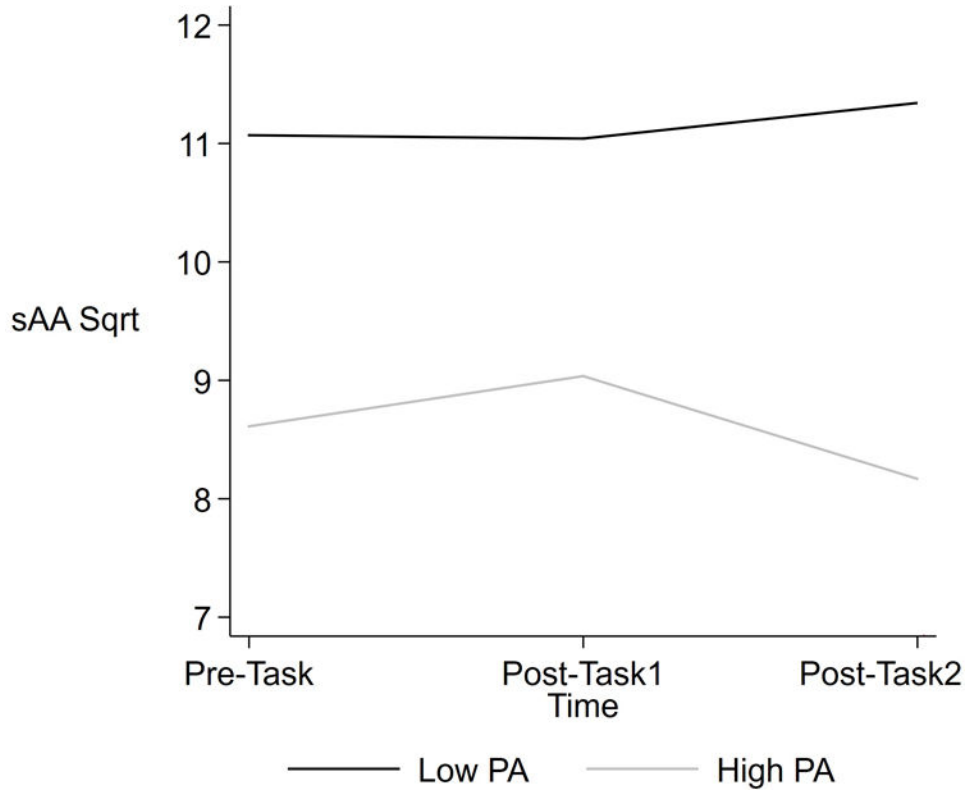

Figure 2.
Effect of Positive Affect on Salivary Alpha-Amylase Response

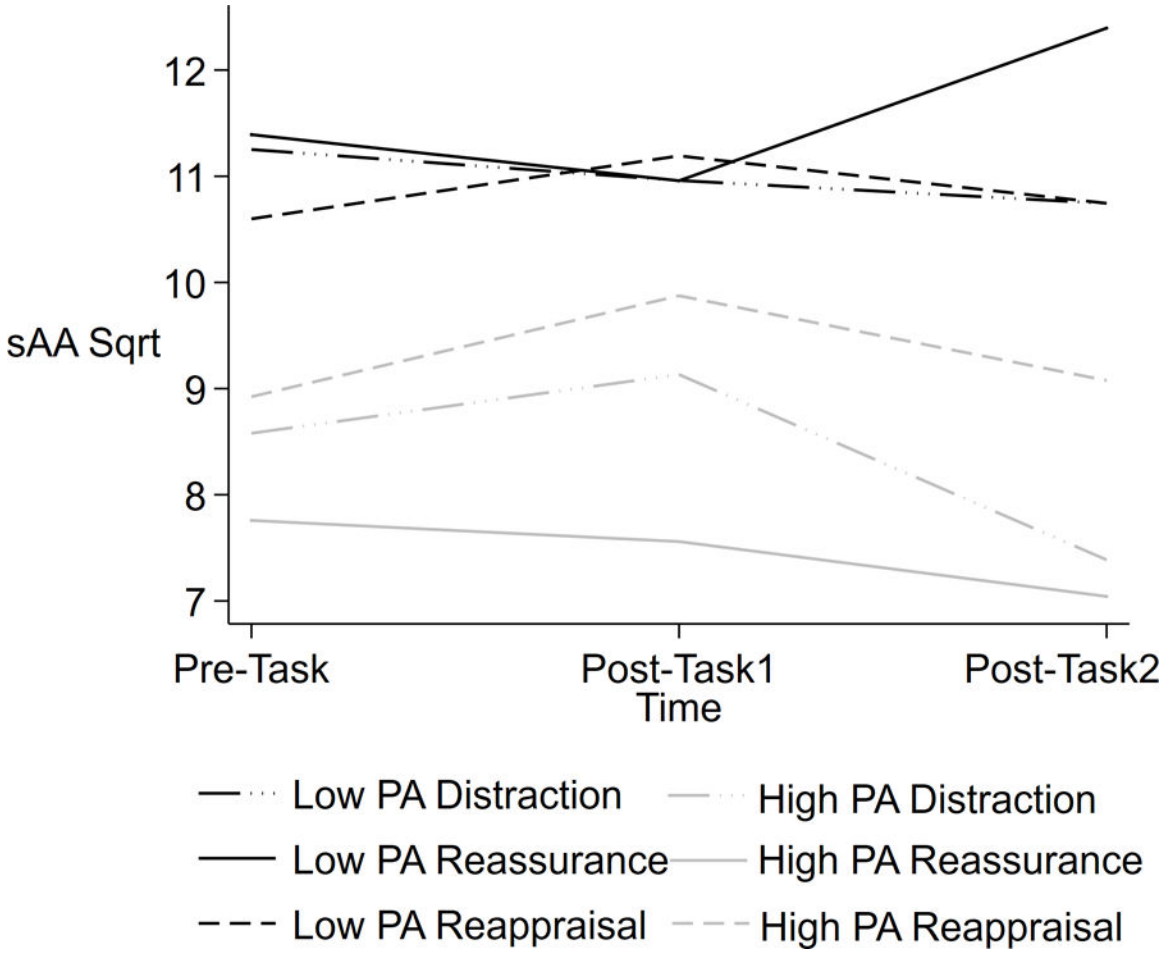

Figure 3.
Effect of Emotion Regulation Condition and Positive Affect on Salivary Alpha-Amylase Response