Ultraviolet-induced inflammation: Validation of the PI-MED erythema measure and its associations with anhedonia

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Abstract

Affective immunology of the skin is a growing area; however, investigations are limited by the lack of an established protocol for measuring individual differences in cutaneous inflammation. To address this gap, we present a preliminary validation of Precision Implementation of Minimal Erythema Dose (PI-MED) testing as a method for measuring cutaneous inflammation. PI-MED is a recently adapted protocol, optimized for reproducibility and individual differences research, that uses ultraviolet (UV) light to evoke cutaneous erythema, or inflammatory skin reddening. PI-MED's novel UV dosage schedule produced reasonably standardized erythema responses across different skin pigmentation types, showed strong internal consistency within person, and good test-retest reliability across 8–10 weeks. In line with predictions, increased PI-MED erythema was associated with heightened anhedonia, across several anhedonia measures, beyond the influence of non-affective covariates. While future work should further refine the PI-MED dosage schedule for the lightest and darkest skin types, overall, evidence supports PI-MED as a protocol for inducing and measuring individual differences in cutaneous inflammation and PI-MED evoked erythema shows potential for expanding psychoneuroimmunology research to better understand immunological and affective processes in the skin. Further, this work adds to a growing body of evidence demonstrating a distinct relationship between inflammation and anhedonia.

Introduction

Affective immunology of the skin is a growing area (França, et al., 2017; Mostaghimi, Jafferany & Tausk, 2020). The affective and immune systems engage in co-regulation of each other (D'Acquisto, 2017; Kiecolt-Glaser, Derry & Fagundes, 2015) and the skin has been referred to as a 'neuroimmunoendocrine interface', serving as a central site for interactions between the nervous, immune, cutaneous, and endocrine systems (Brazzini, et al., 2003; França & Lotti, 2017; Konstantinou & Konstantinou, 2020; O'Sullivan, Lipper & Lerner, 1998; Scholzen, et al., 1999; Vidal Yucha, Tamamoto & Kaplan, 2019). Inflammation, a process of coordinated delivery of blood components to defend against pathogens, is thought to be a mechanism through which affective processes influence health, including multiple psychiatric conditions (Kiecolt-Glaser, Derry & Fagundes, 2015; Réus, et al., 2015; Segerstrom & Miller, 2004). Affective processes also interact with skin specifically (França, et al., 2017; Konstantinou & Konstantinou, 2020), and inflammation putatively serves an important function in neuro-immuno-cutaneous communication (Chen, et al., 2016; França & Lotti, 2017). While substantial work has examined relationships between affect and inflammation markers sampled from peripheral fluids (Graham-Engeland, et al., 2018; La Fratta, et al., 2018; Medeiros, et al., 2020; Szabo, Slavish & Graham-Engeland, 2020), surprisingly little is known about affect and cutaneous inflammation.

While established protocols and best practices exist for measuring inflammatory parameters from blood and saliva (e.g., Engeland, Bosch & Rohleder, 2019; O'Connor, et al., 2009; Mac Giollabhui, et al., 2020a; Szabo & Slavish, 2021), protocols for measuring inflammation in skin are not widely established. However, there is a need for improved measurement and/or additional approaches to understand psycho-neuro-inflammatory processes in humans. For example, inflammation markers often show inconsistent or

weak associations across blood-based and salivary measures (Engeland, Bosch & Rohleder, 2019; Szabo & Slavish, 2021), suggesting additional measurement modalities may elucidate complex inflammatory processes. Investigation of cutaneous inflammation is a relatively novel and promising avenue for psychoneuroimmunology research. Indeed, immune dysfunction in epithelial tissue (e.g., skin, gut) is thought to play an important precipitating role in broader systemic inflammation (Scrivo, et al., 2011; Uluçkan & Wagner, 2017); however, little is known about how cutaneous inflammation is associated with systemic inflammation and/or inflammatory parameters from peripheral fluids. The emerging field of psychoneurocutaneous medicine considers affect and skin intimately connected (França, et al., 2017; Mostaghimi, Jafferany & Tausk, 2020), yet there is a lack of research jointly investigating affect and inflammatory processes in human skin.

Precision Implementation of Minimal Erythema Dose (PI-MED) testing (Richey, et al., 2019) is a minimally invasive procedure for the precise measurement of inflammatory response to ultraviolet (UV) light exposure, optimized for investigating individual differences in cutaneous erythema (inflammatory reddening of skin). UV-induced inflammation is relevant for psychoneuroimmunology as UV exposure activates pro-inflammatory cytokines IL-6, TNF-α, and IL-1β (Bernard, et al., 2012; Brink, et al., 2000; Park, et al., 2019; Scholzen, et al., 1999), cytokines linked to depression, to positively and negatively valenced depressive symptoms, and to neuroinflammation (Haapakoski, et al., 2015; Kiecolt-Glaser, Derry & Fagundes, 2015; Mac Giollabhui, et al., 2020b; Medeiros, et al., 2020; Réus, et al., 2015).

Extensive evidence highlights interactions between affect and peripheral inflammation. Inflammatory markers extracted from peripheral fluids show associations with both positive and negative emotion (Graham-Engeland, et al., 2018; La Fratta, et al., 2018; Medeiros, et al., 2020; Miyamoto, et al., 2013; Steptoe, et al., 2008), stress (La Fratta, et al., 2018; Steptoe, Hamer & Chida, 2007; Sin et al., 2015; Sturgeon, et al., 2016; Szabo, Slavish & Graham-Engeland, 2020), and depression (Kiecolt-Glaser, Derry & Fagundes, 2015; Mac Giollabhui, et al., 2020b; Medeiros, et al., 2020). Previous MED research suggests factors beyond skin type influence erythema response (Dornelles, Goldim & Cestari, 2004); however, these factors are not well characterized, and relationships between cutaneous inflammation and core dimensions of affect remain incompletely understood.

In particular, research points to a strong relationship between inflammatory activation and anhedonia-related symptoms (Dutcher, et al., 2021; Felger & Treadway, 2017; Friedman, et al., 2007; Medeiros, et al., 2020; Rossetti, et al., 2016; Stellar et al., 2015; Swardfager, et al., 2016; Treadway, 2015), distinct from associations with negative affect (Marsland, et al., 2006; Ong et al., 2018; Prather, et al., 2007; Slavish, et al., 2020) or depression (Fancourt & Steptoe, 2020; Steptoe, et al., 2008). Thus, inflammation's association with anhedonia may be stronger than with other affective correlates. Further, social anhedonia may be dissociable from other types of anhedonia (Case, et al., 2022; Gandhi, Mote & Fulford, 2022; Gooding & Pflum, 2022), with evidence suggesting nuanced associations between social hedonic processes and inflammation (Eisenberger & Moieni, 2020; Eisenberger, et al., 2017). However, research examining cutaneous inflammation in relation to anhedonia/social anhedonia is lacking.

Here, we present a preliminary validation of PI-MED testing (Richey, et al., 2019) as a method for precisely inducing and measuring cutaneous inflammation and present evidence for PI-MED's relevance to psychoneuroimmunology research. Our first aim examined evidence for the precision of the PI-MED procedure. Specifically, we examined evidence for the standardization of the PI-MED erythema response across different skin pigmentations as well as evidence for the internal reliability and test-retest reliability of the PI-MED erythema measure. Our second aim explored PI-MED's relevance for psychoneuroimmunology research by examining associations between PI-MED-evoked erythema and covariates previously associated with other measures of peripheral inflammation. Given research suggesting a pronounced relationship between inflammation and anhedonia, we specifically hypothesized that baseline anhedonia measures would show associations with PI-MED erythema, beyond effects of non-affective covariates.

Method

Participants and Study Overview

Participants provided written informed consent in accordance with the Declaration of Helsinki. Participants were drawn from a randomized controlled trial examining effects of an 8-week Mindfulness Based Stress Reduction (MBSR) intervention (compared to a waitlist control condition) in adults aged 18 to 60 reporting chronic psychological stress. Participants were recruited from a university campus and surrounding community in a rural region of the southern United States. A full description of the clinical trial and affective outcomes have been reported elsewhere (Carlton, et al., 2021). The current manuscript reports only the methods and results pertinent to (1) the standardization of the PI-MED erythema response across skin pigmentations and PI-MED erythema reliability and (2) associations between PI-MED erythema and covariates. Exclusion criteria for the clinical trial were: extensive previous meditation experience, current daily practice with mind-body techniques such as yoga, any medical conditions or current use of medications linked to disruptions in inflammatory response (e.g., diabetes, use of steroids or corticosteroids), or a self-reported problem with drugs or alcohol. Additionally, individuals taking psychotropic medications were excluded if they reported any changes to their medication in the previous three months, and any participants already taking psychotropic medication were discontinued in the study if they altered their medication during the study. While recruitment materials targeted stressed adults, there were no inclusion/exclusion criteria related to stress levels.

To assess erythema response, PI-MED testing was conducted at baseline (prior to randomization into either the mindfulness intervention or waitlist condition) and at study end-point (approximately 8—10 weeks after baseline assessments and after completion of the intervention/waitlist period). Potential covariates of inflammation were collected at baseline including non-affective covariates (e.g., age, body mass index) and self-report measures of affect. At baseline, sixty-one participants completed PI-MED, however PI-MED data were not collected from 18 participants at end-point (end-point n = 43) for the

following reasons: 7 participants withdrew from the study; 5 participants had scheduling conflicts that interfered with end-point data collection; and, out of an abundance of caution, the PI-MED procedure was not conducted on 6 participants due to residual discoloration from PI-MED implemented at baseline (approximately 8-10 weeks prior), or because the participant opted out. See Table 1 for participant demographics.

Measures

PI-MED Erythema

Precision Implementation of Minimal Erythema Dose (PI-MED). Cutaneous erythema was induced and measured using PI-MED testing, a procedure recently adapted by Richey and colleagues (2019) to precisely measure individual differences in erythema response to ultraviolet (UV) light exposure. The PI-MED procedure is an adaptation of Minimal Erythema Dose (MED) testing (Heckman, et al. 2013) intended to optimize the procedure for reproducibility and investigating individual differences in cutaneous inflammation. See Supplemental Method for a extended rationale for the PI-MED procedure compared to typical MED testing.

Details of PI-MED Standardization of UV-Irradiation. In accordance with procedures described in detail by Richey and colleagues (2019), six small portions of skin on the non-dominant inner forearm were exposed, in sequence, to different timed amounts of UV light, utilizing a novel dosage schedule (Richey, et al., 2019). The novel PI-MED dosage schedule provided by Richey and colleagues (2019) is calibrated to individual differences in skin pigmentation (as described below) to reliably produce erythema across the Fitzpatrick Skin Types (Fitzpatrick, 1988). Specifically, the dosage schedule provides a method for standardizing UV dosage under a constant assumption of UVB energy at 270 $\mu W/cm^2$, which is monitored via handheld radiometer. Based on published median dosages (Gambichler, et al., 2006) required to produce a minimal erythema response for skin types II, III, and IV, the PI-MED dosage schedule was extrapolated to capture the minimal erythema response at the mid-point of a given dosage schedule for each skin type by assuming a linear relationship between skin type and dosage needed to produce a minimal erythema response (see Richey, et al., 2019 for further details). This calculated dosage schedule, in combination with measurement of erythema via instrumentation (handheld spectrophotometer, as below) was intended to provide a closed loop measurement environment via temporal and energetic standardization of UV-irradiation across different skin types.

The PI-MED Procedure. Participants wore a six-aperture dose testing patch (purchased from The Daavlin Company, 2020) to allow different dosages of UV exposure across six sites on the skin. Aperture coverings were removed at timed intervals according to the published dosage schedule (Richey, et al., 2019). As UV-exposure is temporally reduced for each subsequently exposed site, PI-MED produces a gradated erythema response across the six exposure sites, such that the greatest erythema occurs in exposure site one and the least erythema response occurs in exposure site six. See Richey, and colleagues (2019) for additional details regarding materials and equipment.

Composite Erythema. Erythema, or skin redness was measured via instrumentation both prior to UV-exposure and at follow-up 24 to 48 hours subsequent to the PI-MED procedure. In accordance with prior work (Heckman et al., 2013), a handheld spectrophotometer (purchased from Konica Minolta, 2020) was used to assess erythema by measuring skin redness. Specifically, the a* scale reading from each exposure site was used as an objective measure of both pre-exposure skin color and variation in skin color induced by UV radiation 24 to 48 hours post-exposure. UV-induced erythema was computed by subtracting each exposure site's pre-exposure a* scale reading from its post-exposure a* scale reading (Δa*). As detailed further in the section entitled 'Assessment of PI-MED Reliability', the Δa* measure was averaged across the six exposure sites to create a *Composite Erythema* measure at study baseline and at study end-point, and internal consistency of the Composite Erythemameasure was estimated across the six exposure sites' Δa* measures. To examine changes in Composite Erythema across the study, *Studywise Composite Erythema* was computed by subtracting *Baseline Composite Erythema* from *End-Point Composite Erythema*.

Characterizing Skin Pigmentation.Degree of skin pigmentation is an important determinant of UV-induced erythema (Coelho, et al., 2013; Dornelles, Goldim & Cestari, 2004). The Fitzpatrick Skin Type schema (Fitzpatrick, 1988) has been used extensively to classify human skin coloration on a scale of 0—40 points, which map onto six categories of skin pigmentation from lightest (I) to darkest (VI). In the context of MED testing, this schema has been used to determine the duration of UV exposure required to produce a minimal erythema response in an individual, based on their skin type (e.g., Heckman, et al., 2013). Broadly based on the Fitzpatrick schema, the skin-typing system developed by the National Tanning Training Institute (NTTI, 2004) classifies skin coloration on a continuous scale of 0—86 points (*NTTI Skin Spectrum)*, which map onto six primary skin type categories (*NTTI Skin Type:* I—VI). Previous research has validated NTTI schema (Miller, et al., 2012), and compared to the Fitzpatrick system, the NTTI system offers a more fine-grained scale, assessing skin type based on: the color of untanned skin, hair and eye color, number of freckles, ethnic background, and sunburn and tan potential.

Calibration of PI-MED to Skin Type. The current study used the six primary NTTI Skin Type categories to determine UV dosage administration in accordance with the procedures and dosage schedule developed by Richey and colleagues (2019). Following recommendations of the NTTI instrument (NTTI, 2004) and protocols reported by Richey and colleagues (2019), PI-MED testing was not conducted on individuals with Type I skin, due to the potential for UV over-dosage. Calibrating the PI-MED dosage schedule to skin pigmentation based on categorical NTTI Skin Type (II-VI) is intended to attenuate differences in erythema response that would otherwise occur if different skin types were exposed to the same amount of UV.

Accounting for Variation in PI-MED Erythema Not Fully Standardized by Calibration to Skin Type. Although the PI-MED dosage schedule is calibrated to categorical NTTI Skin Type, there remains considerable between-individual variation in erythema response, possibly due to variation in the continuous NTTI Skin Spectrum score that is collapsed when using the categorical NTTI Skin Type. In other words, the continuous NTTI Skin Spectrum variable should more precisely approximate the skin's intrinsic sensitivity to UV radiation beyond what is accounted for by the PI-MED dosage schedule. To

assess the degree to which the continuous NTTI Skin Spectrum score affected PI-MED erythema response despite the calibration for categorical NTTI Skin Type (II-VI), the continuous 0—86 NTTI Skin Spectrum score was used as an additional covariate in analyses assessing associations between PI-MED erythema and other known inflammation covariates.

Self-Report Measures of Affect

Self-report measures of affect included: (A) two anhedonia measures: Snaith–Hamilton Pleasure Scale (SHAPS; Snaith, et al., 1995) and the Dimensional Anhedonia Rating Scale (DARS; Rizvi et al., 2015), which includes an overall anhedonia measure as well as a social anhedonia subscale; (B) measures of positive and negative affect from the Positive and Negative Affect Schedule (PANAS; Watson & Clark, 1999); (C) the Perceived Stress Scale (PSS; Cohen, 1988) and (D) the Beck Depression Inventory (BDI-II; Beck, et al., 1996). All measures and relevant subscales along with sample-specific internal consistency measures are detailed in the Supplemental Method.

Non-Affective Covariates

Several non-affective measures collected at baseline previously associated with other measures of inflammation were also examined as covariates of PI-MED erythema including age, sex, minority status, and body mass index (for review of inflammation covariates see O'Connor, 2009). It should be noted that previous research has not found age to be associated with MED and has inconsistently found MED to vary by sex (Gambichler, et al., 2006; Tan, et al., 2020). Body mass index (BMI) was only collected for 77% of the sample (n = 47) at baseline, and analyses are presented both with and without this covariate to preserve power. As previously noted, we used the continuous NTTI Skin Spectrum score as a covariate to capture additional variance in erythema response beyond that induced by PI-MED dosage based on categorical Skin Type.

Analytic Approach

To examine preliminary validation of PI-MED testing for psychoneuroimmunology research, we examined (1) the standardization of PI-MED Composite Erythema across skin pigmentation types and the reliability of the PI-MED Composite Erythema measure and (2) associations between Composite Erythema and non-affective and affective covariates.

Assessment of PI-MED Composite Erythema Standardization and Reliability. As the specific dosage schedule implemented within PI-MED is novel to MED testing (Richey, et al., 2019) and was intended to standardize erythema response across different skin pigmentation types, we (1a) used examined Composite Erythema across NTTI Skin Type using an ANOVA and follow-up t-tests, with the expectation that successful standardization of PI-MED erythema response would result in attenuated differences (ideally no differences) in Composite Erythema between the skin types. As there were only three subjects in the NTTI Skin Type IV group, this skin type was excluded from statistical analyses. Reliability of the PI-MED erythema measure was assessed by examining (1b) internal consistency across

the six exposure sites (that were averaged to create the Composite Erythema measure), both at baseline and at study end-point. Specifically, Chronbach's alpha was computed across the six Δa* values (spectrophotometer measures of pre-to-post UV exposure change in skin redness). PI-MED erythema reliability was also assessed in terms of (1c) the test-retest reliability of the Composite Erythema measures collected at baseline and at study end-point, approximately 8-10 weeks later. The test-retest reliability of Composite Erythema was examined in the whole sample, collapsing across the mindfulness and waitlist groups. Additionally, Composite Erythema test-retest reliability was also examined separately within the mindfulness and waitlist groups, as mindfulness interventions have previously been shown to lower inflammation (Dutcher, et al., 2021; Sanada, et al., 2020; Villalba, et al., 2019), suggesting that participation in the mindfulness intervention may alter test-retest associations.

Affective Correlates of PI-MED Composite Erythema. As preliminary validation of the relevance of PI-MED testing for psychoneuroimmunology research, we examined zero-order correlations between Composite Erythema and self-report measures of affect previously associated with peripheral inflammation markers, including measures of anhedonia (detailed below), PANAS Positive and Negative Affect, the Perceived Stress Scale, and the Beck Depression Inventory. Given research suggesting that inflammation may be particularly associated with symptoms of anhedonia, we hypothesized that baseline anhedonia measures, specifically, SHAPS Anhedonia, DARS Overall Anhedonia, and DARS Social Anhedonia, would show associations with Composite Erythema, beyond the effects of non-affective covariates. To test this, we estimated hierarchical regressions in which different anhedonia measures were (each separately) added to base prediction models with non-affective covariates that included NTTI Skin Spectrum, Sex, Age, Minority Status, and Body Mass Index.

Results

Participant Characteristics

The baseline sample was comprised of 61 participants (35 female; 22 ethnic minority: 11 Asian, 3 Black/African American, 1 Hispanic, 4 Middle Eastern, 3 other), ranging in age from 18—57 (M = 32.4, SD = 11.4). Following baseline data collection, approximately half of the participants (n = 35) were randomized to the mindfulness intervention while the remaining participants were placed on the waitlist. The average BMI for the sample was 25.9 (SD = 8.9). The sample included NTTI Skin Types II—V, and consistent with self-reported demographics, 64% of participants fell *within the lighter skin tone categories of Type II and III. Baseline self-reported stress levels on the Perceived Stress Scale (M = 22.1, SD = 6.6) were substantially higher than previously reported population norms* (Cohen, 1988), confirming that our sample was, in line with the recruitment strategy for used for the clinical trial, indeed comprised of highly stressed individuals. *See Table 1 for sample demographics and other variables of interest.*

[Insert Table 1]

Table 1. Summary statistics for sample demographics and other variables of interest.

Baseline Participants (n = 61)	Mean (SD) or Total	Percentage of sample with data available
Age	32.4 (11.4)	100%
Gender (Female)	35	100%
Minority	22	98%
Body Mass Index (n = 47)	25.9 (8.9)	77%
NTTI Skin Spectrum (continuous)	36.6 (16.7)	100%
NTTI Skin Type (categorical)		100%
Type I	*excluded from PI-MED testing*	
Type II	17	
Type III	22	
Type IV	19	
Type V	3	
Type VI	0	
Composite Erythema (non-transformed)		
Baseline Composite Erythema	2.13 (2.3)	100%
End-Point Composite Erythema (n = 43)	2.04 (2.0)	70%
Randomized to Mindfulness after Baseline	35	100%
Baseline SHAPS Anhedonia	2.11 (2.8)	100%
Baseline DARS Overall Anhedonia	48.1 (9.8)	100%
Baseline DARS Social Anhedonia	10.5 (3.2)	100%
Baseline PANAS Positive Affect	27.9 (7.6)	100%
Baseline PANAS Negative Affect	23.0 (7.2)	100%
Baseline Perceived Stress	22.1 (6.6)	100%
Baseline Beck Depression Inventory II	15.7 (10.3)	100%

† Composite Erythema means and standard deviations were computed on untransformed variables

Standardization of PI-MED Erythema

The means and distributions for Baseline Composite Erythema across the NTTI Skin Types are depicted in Figure 1. The effect of NTTI Skin Type (excluding Type V) on Composite Erythema was not significant [F(2,55)=.83, p = .44]. Follow-up t-tests, conducted for robustness, did not reveal any significant differences in Composite Erythema between either NTTI Skin Type II (M = .55, SD = .30) and Type III (M = .50, SD = .24; $t(37) = .68$, $p = .50$), or between NTTI Skin Type II and Type IV (M = .44, SD = .25; $t(34) = 1.23$, $p = .23$), or between NTTI Skin Type III and Type IV ($t(39) = .71$, $p = .48$). A lack of significant differences here is consistent with the PI-MED dosage schedule standardizing the erythema response across skin types II–IV. While formal statistical analysis could not include NTTI Skin Type V due to the small number of individuals in the group, the mean Composite Erythema for this group was substantially lower (M = .20, SD = .32) than that of the other skin types.

To assess the degree to which the continuous NTTI Skin Spectrum score affected PI-MED erythema response despite the PI-MED dosage calibration to categorical NTTI Skin Type, associations between NTTI Skin Spectrum and Composite Erythema were estimated across the whole sample and were found to be moderate at both baseline ($r = -.26$, 95% CI = [-.48, -.01]) and at end-point ($r = -.35$, 95% CI = [-.59, -.05]; see Table 2).

[Insert Figure 1: Color Figure]

Reliability of PI-MED Erythema

Internal Consistency of Composite Erythema

All six Δa* values were available for each subject who completed the PI-MED procedure at a given time point (i.e., within the PI-MED sessions, there was no missing data across the six exposure sites). The Composite Erythema measure demonstrated excellent internal consistency across the six exposure sites for both the Baseline Composite Erythema (α = .94, n = 61) and the End-Point Composite Erythema (α = .94, n = 43) measures.

Test-Retest Reliability of Composite Erythema

The Composite Erythema measures were highly skewed both at baseline (skew = 1.1) and at end-point (skew = 1.55), and thus both variables were log-transformed for subsequent analyses. The Composite Erythema measure showed good test-retest reliability between the baseline and end-point assessments (n = 43; $r = .72$, 95% CI = [.53, .84]; see Figure 2). Further, the four skin types represented in the current sample appeared to be well distributed within the association between the baseline and end-point measures of Composite Erythema (see Figure 2). In the mindfulness group, Composite Erythema test-retest was excellent (n = 23; $r = .79$, 95% CI = [.56, .91]), and in the waitlist group, Composite Erythema test-retest was relatively attenuated (n = 20; $r = .58$, 95% CI = [.19, .82]).

PI-MED Erythema Covariates

Zero-order correlations between baseline covariates and Composite Erythema and between-group differences in both Baseline Composite Erythema and Studywise Composite Erythema are presented in Table 2. As hypothesized, anhedonia measures showed significant moderate associations with Composite Erythema, with SHAPS Anhedonia showing a positive association (r = .27, 95% CI = [.02, .49]) and DARS Social Anhedonia showing a negative association (r = -.29, 95% CI = [-.50, -.04]). As the SHAPS and DARS measures were coded in opposite directions (higher vales representing greater anhedonia and lesser anhedonia, respectively), the correlations showed a consistent pattern of increased anhedonia associated with a greater erythema response. Neither the DARS Overall Anhedonia measure nor any of the other affective or non-affective covariates showed significant associations with Composite Erythema, and there were no significant between-group differences in either the Baseline Composite Erythema nor the Studywise Composite Erythema measure for sex, minority status, or randomization to the mindfulness intervention.

[Insert Table 2]

Table 2 Relationships between Composite Erythema and covariates

Correlations between Baseline Erythema and Known Inflammation Covariates

	Baseline Composite Erythema		
	r	95% CI	df
NTTI Skin Spectrum	**-.26**	**[-.48, -.01]**	59
Age	-.16	[-.39, .10]	59
Body Mass Index	-.09	[-.37, .20]	45
Baseline SHAPS Anhedonia	**.27**	**[.02, .49]**	59
Baseline DARS Overall Anhedonia	-.23	[-.46, .02]	59
Baseline DARS Social Anhedonia	**-.29**	**[-.50, -.04]**	59
Baseline PANAS Positive Affect	-.14	[-.38, .11]	59
Baseline PANAS Negative Affect	-.05	[-.30, .20]	59
Baseline Perceived Stress	.15	[-.11, .39]	59
Baseline Beck Depression Inventory II	.13	[-.13, .37]	59

Between-Group Differences in Baseline Composite Erythema

	Baseline Composite Erythema				
	mean diff	*t*	95% CI	Cohen's d	df
Female vs. Male	-.03	-.48	[-.17, .11]	-.13	59
Minority vs. White	-.14	-1.90	[-.28, .00]	-.52	58
Mindfulness Intervention vs Waitlist	.02	.35	[-.12, .16]	.09	59

Between-Group Differences in Studywise Change in Erythema Response

	End-Point Composite Erythema - Baseline Composite Erythema				
	mean diff	*t*	95% CI	Cohen's d	df
Female vs. Male	.04	.66	[-.07, .15]	.20	41
Minority vs. White	-.02	-.41	[-.15, .10]	-.14	40
Mindfulness Intervention vs Waitlist	.05	.90	[-.06, .16]	.27	41

Concurrent Associations between Anhedonia and PI-MED Erythema

Models examining concurrent associations between Baseline Composite Erythema and baseline predictors including demographic predictors and NTTI Skin Spectrum are presented in Table 3. A base model including all covariates accounted for 9% of the variance and was not significant, possibly due to the smaller sample (n = 46) produced from including the BMI variable (which was available for only 77% of the sample). A base model excluding BMI (n = 60) was nearly significant (p = .06), accounted for 15% of the variance, and was determined to be the Final Base Model. In this model, only age was a significant predictor of Baseline Composite Erythema (β = -.29, p = .03).

To examine concurrent associations between anhedonia measures and Composite Erythema above and beyond non-affective covariates, a hierarchical model was estimated for each of the three anhedonia measures, adding each to the Final Base Model. The model that added Baseline SHAPS Anhedonia significantly improved upon the Final Base Model (p= .03) and accounted for an additional 7%

of the variance (R2= .22), with Baseline SHAPS Anhedonia as a significant positive predictor of Baseline Composite Erythema (β = .28, *p* = .03). The model that added Baseline DARS Overall Anhedonia was a near-significant improvement upon the Final Base Model (*p*= .06), accounting for an additional 6% of the variance (R2= .21) compared to the Final Base Model. The model that added Baseline DARS Social Anhedonia significantly improved upon the Final Base Model (*p*= .01) and accounted for an additional 9% of the variance (R2= .24), with Baseline DARS Social Anhedonia as a significant negative predictor of Baseline Composite Erythema (β = -.32, *p* = .01). Prospective associations between anhedonia and PI-MED erythema are presented in the Supplement; only SHAPS Anhedonia was a significant improvement upon a base model in prospective prediction of PI-MED erythema; however, the direction of the association was reversed with greater anhedonia predicting lower erythema at study endpoint. These results likely reflect regression to the mean and are discussed further in the Supplement.

[Insert Table 3]

Table 3 Concurrent associations between anhedonia measures and PI-MED erythema

	β Coef	B Coef	SE	*t*	*p*	95% CI
Base Model with All Covariates (n = 46)	**F(5,40)= .80, *p*= .56, R2= .09, Adj-R2= -.02, SE of Estimate= .27**					
****Constant**		.85	.22	3.86	< .001	[.41, 1.30]
NTTI Skin Spectrum	-.19	.00	.00	-.67	.51	[-.01, .01]
Sex	-.11	-.06	.08	-.71	.48	[-.23, .11]
Age	-.20	-.01	.00	-1.16	.25	[-.01, .00]
Minority	-.10	-.05	.16	-.32	.75	[-.38, .27]
Body Mass Index	-.05	.00	.00	-.31	.76	[-.01, .01]
~*Final Base Model (n = 60)	**F(4,55)= 2.40, *p*= .06, R2= .15, Adj-R2=.09, SE of Estimate= .26**					
****Constant**		.89	.16	5.47	< .001	[.56, 1.21]
NTTI Skin Spectrum	-.23	.00	.00	-1.02	.31	[-.01, .00]
Sex	-.07	-.04	.07	-.52	.61	[-.17, .10]
***Age**	-.29	-.01	.00	-2.16	.03	[-.01, -.00]
Minority	-.16	-.09	.12	-.72	.47	[-.34, .16]
***Hierarchical Model: Final Base + SHAPS (n = 60)**	**ΔF(1,54)= 4.78, *p*= .03, R2= .22, Adj-R2=.15, ΔR2= .07, SE of Estimate= .25**					
****Constant**		.84	.16	5.30	< .001	[.52, 1.16]
NTTI Skin Spectrum	-.36	-.01	.00	-1.61	.11	[-.01, .00]
Sex	-.05	-.03	.07	-.40	.69	[-.16, .11]
~*Age	-.24	-.01	.00	-1.87	.07	[-.01, .00]
Minority	-.01	.00	.13	-.03	.97	[-.26, .25]
***Baseline SHAPS Anhedonia**	.28	.03	.01	2.19	.03	[.00, .05]
~*Hierarchical Model: Final Base + DARS Overall (n = 60)	**ΔF(1,54)= 3.84, *p*=.06, R2=.21, Adj-R2=.13, ΔR2= .06, SE of Estimate= .25**					
****Constant**		1.34	.28	4.79	< .001	[.78, 1.91]
NTTI Skin Spectrum	-.25	.00	.00	-1.17	.25	[-.01, .00]
Sex	-.03	-.02	.07	-.24	.81	[-.15, .12]
***Age**	-.29	-.01	.00	-2.23	.03	[-.01, -.00]
Minority	-.13	-.07	.12	-.58	.57	[-.32, .17]
~*Baseline DARS Overall Anhedonia	-.24	-.01	.00	-1.96	.06	[-.01, .00]
***Hierarchical Model: Final Base + DARS Social (n = 60)**	**ΔF(1,54)= 6.75, *p*= .01, R2= .24, Adj-R2=.17, ΔR2= .09, SE of Estimate= .25**					
****Constant**		1.21	.20	6.11	< .001	[.81, 1.61]
NTTI Skin Spectrum	-.33	-.01	.00	-1.55	.13	[-.01, .00]
Sex	-.04	-.02	.07	-.30	.76	[-.15, .11]
***Age**	-.29	-.01	.00	-2.27	.03	[-.01, -.00]
Minority	-.05	-.03	.12	-.23	.82	[-.27, .22]
***Baseline DARS Social Anhedonia**	-.32	-.03	.01	-2.60	.01	[-.05, -.01]

** $p < .01$
* $p < .05$
~* $p \leq .07$

Discussion

Psychoneurocutaneous research is a burgeoning area, but understanding relationships between affect and skin inflammation is limited by the lack of an established protocol for measuring cutaneous inflammation that is suitable for individual differences research. To address this gap, we present a preliminary validation of Precision Implementation of Minimal Erythema Dose, or PI-MED testing (Richey, et al., 2019) as a method for measuring cutaneous inflammation and further demonstrate its relevance for psychoneuroimmunology research. Specifically, we demonstrate that PI-MED's novel UV dosage

schedule produces a reasonably standardized erythema response across NTTI Skin Types II–IV and that PI-MED erythema shows strong internal consistency and good test-retest reliability across 8–10 weeks. Together, this evidence supports the use of PI-MED as a protocol for inducing and measuring individual differences in cutaneous inflammation. Additionally, we examined associations between PI-MED erythema and known covariates of other measures of peripheral inflammation and, unexpectedly, found that most non-affective and affective covariates showed only weak and/or non-significant associations. However, as predicted, cutaneous erythema response demonstrated a specific relationship with anhedonia, beyond non-affective covariates.

The novel contribution of PI-MED is the focus on reproducibility, achieved through the application of a uniform level of UV energy, temporal standardization of UV dosage across different skin types, and objective measurement of cutaneous response via spectrophotometer. The lack of a significant effect of NTTI Skin Type (for Types II–IV) on PI-MED erythema can be considered preliminary evidence of PI-MED having a standardizing effect on cutaneous erythema response across different skin pigmentation types. However, as PI-MED is a recently adapted procedure that yielded a novel measure of inflammation, we did not conduct a power analysis, and thus, null findings can only provide limited evidence for erythema standardization. Further, evidence for erythema standardization is limited to Skin Types II–IV (discussed further below). Despite evidence of standardization across skin types, NTTI Skin Spectrum scores still showed a moderate correlation with PI-MED erythema, likely due to additional variation not accounted for by calibrating PI-MED dosage to skin type categories. PI-MED erythema showed good internal consistency within person across six exposure sites at both baseline and study end-point. Further, PI-MED erythema showed good test-retest reliability across an 8-10-week interval. Importantly, the four different skin types appeared to be well distributed within the association between the baseline and end-point erythema measures, suggesting erythema was reliably induced across skin types within the sample.

Across three anhedonia measures, higher baseline anhedonia levels showed consistent concurrent associations with increased baseline erythema, controlling for non-affective predictors. Interestingly, concurrent associations between anhedonia and PI-MED erythema were of a similar magnitude to associations between erythema and NTTI Skin Spectrum score, suggesting that the relationship between anhedonia and cutaneous erythema is not trivial, in line with other research suggesting a particularly strong relationship between inflammation and anhedonia (Felger & Treadway, 2017; Friedman, et al., 2007; Medeiros, et al., 2020; Rossetti, et al., 2016; Stellar et al., 2015; Swardfager, et al., 2016). Further, given the relatively weak associations with perceived stress, depression, and positive and negative affect, it appears that UV-induced erythema may show a discriminate association with anhedonia.

Limitations

The current study has some important limitations that constrain generalization of findings and should guide future work. First, associations between PI-MED erythema and most potential covariates were only weak and non-significant, raising questions about how PI-MED erythema relates to peripheral inflammation markers, which do typically show associations with such covariates. Second, evidence of

PI-MED's standardization of erythema is limited to Skin Types II–IV, due to excluding Skin Type I from the procedure, and under-sampling or no sampling, respectively, of Types V and VI. Further, as Skin Type V showed a much lower erythema response compared to other skin types, it suggests the current PI-MED dosage schedule may be inappropriately calibrated for the darkest skin types. This is consistent with previous research using the MED measure that found large differences in erythema sensitivity between Skin Types V and VI and lighter skin types (Carretero-Mangolis & Lim, 2001; Dornelles, Goldim & Cestari, 2004). Thus, future work should continue to refine the PI-MED dosage schedule to produce a similar erythema response across different skin types, with particular attention to calibrating the dosage for the darkest (Types V and VI) and lightest (Type 1) skin types. Together with research suggesting that assessment of skin type via self-report is biased by Eurocentric White norms (Eilers, et al., 2013), future work should particularly focus on refining both skin type assessment and UV dosage schedules to ensure procedures are appropriate for dark-skinned people. Further, the PI-MED dosage schedule assumed a linear erythema response across skin types, based on an extrapolation of previously published median MED results for lighter skin types; however, future work might consider using a dosage schedule based on a cubic function (or other functional forms) for the association between skin type and time used to produce erythema, with relatively lower dosages for Type I and relatively higher dosages for Types V and VI.

Conclusions

While further refinement for broader skin types is needed, PI-MED offers a promising method for inducing and measuring individual differences in cutaneous inflammation. Further, PI-MED offers opportunity to study relationships between cutaneous inflammation and inflammation markers sampled from fluids and between cutaneous inflammation and affect, particularly anhedonia. Overall, PI-MED has potential to expand psychoneuroimmunology research for better understanding immunological and affective processes in relation to the skin.

Declarations

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Open Data: Open data is available at https://osf.io/yh458/?view_only=8889f012ed694675868fca263a8039f7

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Figures

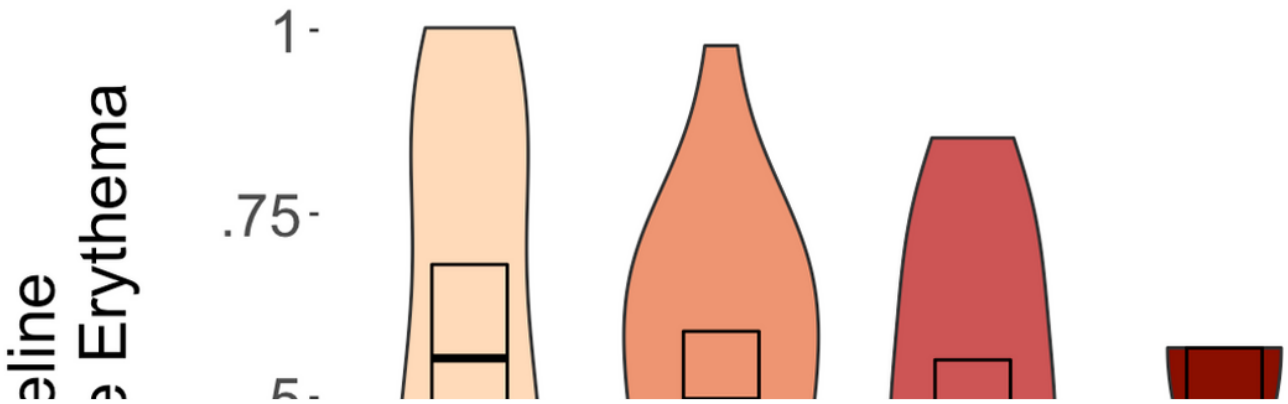

Figure 1

Violin plots summarizing means, 95% CIs, and distributions for Baseline Composite Erythema across NTTI Skin Types included in PI-MED procedure In line with PI-MED's intended standardization of UV dosage across skin types, differences in Composite Erythema between NTTI Skin Types II, III, and IV appeared to be relatively minimal and were non-significant. However, average Composite Erythema for NTTI Skin Type V was substantially lower than that of the other skin types.

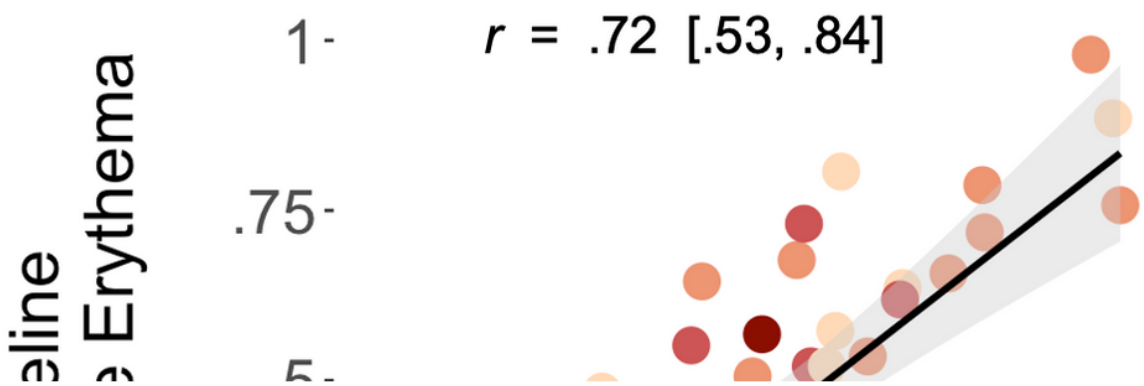

Figure 2

Scatterplot depicting the re-test reliability for Composite Erythema Composite Erythema, derived from PI-MED testing, showed good test-retest reliability between the baseline and end-point measurements (*r* = .72, 95% CI = [.53, .84]). The four skin types included in the sample appeared well-distributed, suggesting the PI-MED procedure reliably induced erythema across a spectrum of skin pigmentations.

Supplementary Files

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- Erythema2022430supplement.docx