Understanding Context-Dependent Attentional Bias to Threat in Posttraumatic Stress Symptoms

BY

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B.A., University of Pennsylvania, 2016

THESIS

Submitted as partial fulfillment of the requirements
for the degree of Master of Arts in Psychology
in the Graduate College of the
University of Illinois at Chicago, 2020

Chicago, Illinois

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LIST OF ABBREVIATIONS

AB	Attentional Bias
DSM-5	Diagnostic and Statistical Manual of Mental Disorders- Fifth Edition
ABM	Attention Bias Modification
RDOC	A Research Domain Criteria
SCID	Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders 5
PTSD	Posttraumatic Stress Disorder
PTSS	Posttraumatic Stress Symptoms
WSAS	Work and Social Adjustment Scale
WHODAS	World Health Organization Disability Assessment Schedule

SUMMARY

Attentional bias to threat (AB) is a transdiagnostic deficit for many internalizing disorders including posttraumatic stress disorder (PTSD). The relationship between AB and PTS symptoms (PTSS) is robust and consistent throughout the literature, but it is unclear *which* specific AB is associated with PTSS. It is also possible that this relationship could be different when assessing AB during an aversive context and if the threatening stimuli that draw the attention is masked. This study used a masked dot-probe task to measure AB to angry faces in two independent samples—50 treatment-seeking participants, and a second independent sample of 98 trauma-exposed participants. Linear mixed effects models yielded an increased orienting AB in an aversive (relative to safe) context in both samples; however, PTSS did not moderate these effects in either sample. These results highlight the importance of assessing AB in varying contexts and in multiple samples of differing severity. Given prior research, these null results suggest that AB deficits in PTSD are likely due to later threat processing rather than early threat detection.

I. INTRODUCTION

Epidemiological studies have shown that approximately 90% of adults in the U.S. have experienced a Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 defined traumatic event in their lifetime, and yet only about 10% of these individuals will meet full criteria for a categorical diagnosis of PTSD (Kilpatrick et al., 2013). Therefore, exposure to trauma is a necessary but insufficient causal mechanism for PTSD, suggesting that it is important to identify other etiological factors of the disorder or of posttraumatic stress symptoms (PTSS) more broadly. Information processing biases are one set of etiological factors that might contribute to the onset and maintenance of PTSS (Buckley, Blanchard, & Neill, 2000).

One specific information processing bias that may be particularly relevant for PTSS is attentional bias (AB) to threat—or the tendency for an individual's focus to be disproportionately centered on negative or threatening stimuli (R J McNally, Kaspi, Riemann, & Zeitlin, 1990). Research has shown AB to be a transdiagnostic deficit for many psychological and physical disorders, including depression (Mogg & Bradley, 2005), panic disorder (McNally, Riemann, & Kim, 1990), substance use (Field et al., 2016; Sinclair et al., 2016), disordered eating (Deluchi, Costa, Friedman, Gonçalves, & Bizarro, 2017; Shafran, Lee, Cooper, Palmer, & Fairburn, 2007), insomnia (Jansson-Fröjmark, Bermås, & Kjellén, 2013), obesity (Field et al., 2016), and general levels of stress (McHugh, Behar, Gutner, Geem, & Otto, 2010); however, it is perhaps best known for its contribution to anxiety disorders (see Bar-Haim et al., 2007 for a review; Markela-Lerenc et al., 2011; Mogg & Bradley, 2005). Studies of AB in anxiety have led to Attention Bias Modification (ABM)—a computerized intervention designed specifically to improve AB—and interestingly, ABM has been shown to reduce both anxious (De Voogd, Wiers, Prins, & Salemink, 2014) and depressive symptoms (Browning, Holmes, Charles, Cowen, & Harmer, 2012).

AB may be particularly relevant to posttraumatic stress disorder (PTSD) as well as those experiencing trauma more broadly. A 2007 meta-analysis by Bar-Haim et al. looked at 22 studies in 502 individuals and found a moderate and stable effect size of .36 (confidence interval [CI] = .27, .46) for the relationship between PTSD and AB. However, this meta-analysis only examined categorically defined PTSD even though taxometric studies support the idea of PTSD as a dimensional construct rather than a categorical diagnosis (Ruscio, Ruscio, & Keane, 2002), and studies have shown that individuals with subthreshold PTSD (i.e., PTSS) still experience distress and impairment (Marshall et al., 2001). Importantly, when PTSD was defined dimensionally, studies have continued to find associations between PTSD symptom severity and AB, especially when presenting participants with trauma-specific cues (e.g., bomb sirens, sexual stimuli; Bar-Haim et al., 2010; Cisler et al., 2011; Joyal et al., 2019; Latack, Moyer, Simon, & Davila, 2017; Todd et al., 2015).

While numerous studies have examined the relationship between PTSD and AB, it is unclear which aspect of AB is driving the association with PTSD. One explanation for this gap in knowledge could be due to inconsistencies in how AB is measured as well as which metrics are elicited from the task. The dot-probe task is the gold standard measure of assessing AB (MacLeod, Mathews, & Tata, 1986) and involves participants being presented with faces displaying either neutral or emotional (e.g., threatening) expressions. Although researchers use different versions and scoring of the task, traditionally, the dot-probe yields three types of AB variables, all calculated from the participant's reaction time: *total AB*, representing the participant's average attentional bias, *disengagement,* representing the participant's difficulty disengaging from threatening stimuli, and *orientation,* representing the participant's heightened orientation towards threatening stimuli. Studies of AB in PTSD have been inconsistent with findings highlighting deficits in disengaging from threat (Khoury-Malhame et al., 2011; Pineles, Shipherd, Mostoufi, Abramovitz, & Yovel, 2009), orientation towards threat (Briggs-Gowan et al., 2016) or avoidance of threat (Bar-Haim et al., 2010).

Furthermore, Bar-Haim et al. (2007) argues that anxious individuals automatically and rapidly detect threat, but the use of longer presentations of stimuli (e.g., longer than 500 ms) in the dot-probe confound automatic/rapid threat detection with a more elaborate (i.e., later occuring) processing of threat. It is unclear whether the AB deficits in PTSD represent an early or later threat-detection. One way to isolate automatic and early AB is to use briefly presented aversive stimuli followed immediately by positive stimuli, essentially “masking” the threatening face (Lavie, 1995). Masked dot-probe tasks have been associated with triggering the amygdala’s fear response (Whalen et al., 1998), and a meta-analysis of 28 dot-probe studies found that attention is biased to pre-consciously presented threat stimuli (relative to neutral stimuli) (Hedger, Gray, Garner, & Adams, 2016) indicating that even when using briefly presented emotionally evocative stimuli, AB can be elicited. Few studies have examined AB to masked faces in individuals with PTSS/PTSD, but limited research has shown an increase in amygdala reactivity to orientation to masked faces (Khoury-Malhame et al., 2011) and an increased early ERP component in earthquake survivors with PTSD (Zhang, Kong, Han, Najam Ul Hasan, & Chen, 2014).

It is also possible that individual differences in AB could be related to the environmental context of the task. Studies have shown that negative mood induction alters cognitive processes such as memory for affective words or facial expression recognition (Cavanagh, Urry, & Shin, 2011; Chepenik, Cornew, & Farah, 2007). Research into the dot-probe task under differing contexts is limited but suggests that attention can be modulated by the environmental context in which it is assessed. One small study found that in a threatening context (threat of electric shock), participants averted their attention away from danger cues (Shechner, Pelc, Pine, Fox, & Bar-Haim, 2012). Thus, certain negative contexts may exacerbate AB in individuals with PTSS. However, this research was conducted with longer presented stimuli, thus, it is unclear whether it extends to masked faces.

Additionally, PTSD is a heterogeneous syndrome, characterized by intrusive symptoms, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity following a traumatic event. From DSM-IV to DSM-5, the symptom profile increased from three to four clusters of symptoms (American Psychiatric Association, 2000, 2013). In collapsing across all PTSD phenotypes, key variability in symptom presentation is lost, preventing the understanding of *which* component(s) of PTSD drive the association between AB and PTSD – an important question in order to pinpoint which feature of the disorder might benefit the most from interventions.

Lastly, psychology is facing a replication crisis with less than one-third to one-half of original findings replicating across different labs and populations ("Estimating the reproducibility of psychological science," 2015). In clinical psychology, in particular, researchers have argued that many studies do not contain the appropriate sample size to detect small effect sizes (Tackett, Brandes, King, & Markon, 2019). To address this, the present study will test the generalization of the findings by examining whether the results from a treatment-seeking sample of trauma-exposed individuals are also found in a larger, community sample of trauma-exposed individuals.

A. Study Aims

In sum, the first aim of this study sought to test whether AB to a masked threat is different when assessed in a "safe" vs. "threatening" context (specifically, when there is a threat of an unpredictable aversive noise). We hypothesized that attention bias will be higher in the threatening environment than the safe. The second aim of the study was to establish whether the literature showing an association between PTSS and AB replicates to early-threat detection with the masked dot-probe, hypothesizing that (a) individuals higher in severity and number of PTSS have greater attentional bias, and (b) assess whether the association between PTSS and AB is stronger when AB is assessed in a threatening context. Finally, an exploratory aim of the study (aim 3) was to investigate whether separate DSM-5 clusters—intrusions [B], avoidance [C], negative alterations in cognition and mood [D], and alterations in arousal and reactivity [E] (American Psychiatric Association, 2013)— might differentially relate to different ABs (general AB, orientation, and disengagement), given the heterogeneity of PTSS (Zoellner, Pruitt, Farach, & Jun, 2013). Throughout these aims, generalizability was addressed by first running analyses in a sample of treatment-seeking trauma-exposed individuals, and then by running the same analyses in a larger, community sample of trauma-exposed individuals.

II. METHODS

A. Study 1

a. Participants

This study uses a subset of 50 participants of an ongoing NIMH-funded treatment study. Participants from the greater Chicago area with a significant childhood trauma history were recruited from clinics, as well as through advertisements and community organizations. They ranged in age from 20 – 74 (M = 43.46, SD = 15.58) and 44% met full criteria for current PTSD at the time of assessment (see Table 1 for participant demographics and clinical characteristics). Participants were included if they were over 18 years old, had a significant history of childhood trauma, as well as at least mild current distress as assessed by the Depression Anxiety Stress Scale-21 (DASS-21; Lovibond & Lovibond, 1995). Participants were excluded if they had experienced a DSM-5 defined traumatic event one month prior to recruitment, had colorblindness, a lifetime psychotic or bipolar disorder, or were currently undergoing psychotherapy related to their trauma (as this was an intervention study). All participants underwent the PTSD Checklist for DSM-5 (PCL-5; Blevins, Weathers, Davis, Witte, & Domino, 2015) to obtain dimensional levels of PTSD symptoms, as well as the Work and Social Adjustment Scale (WSAS; Zahra et al., 2014) to ascertain their broad degree of functional impairment.

Table I.
Participant Demographics and Characteristics

	Study 1 (N = 50)		Study 2 (N = 97)	
	Mean (SD)			
Age (Mean(SD))	43.64 (15.58)		22.57 (3.04)	
	Race/Ethnicity/Gender			
White/Caucasian	48% (N = 24)		39.2% (N = 38)	
Black or African American	42% (N = 21)		29% (N = 28)	
Asian	4% (N = 2)		5.2% (N = 5)	
Other or Declined to Answer	6% (N = 3)		8.2% (N = 8)	
Hispanic/Latino	8% (N = 4)		18.6% (N = 18)	
Female identifying	74% (N = 37)		80% (N = 78)	
	Psychopathology Status			
	Current	Past	Current	Past
Post-traumatic Stress Disorder	44% (N = 22)	54% (N = 27)	6.2% (N = 6)	32% (N = 31)
Major Depressive Disorder	16% (N = 8)	70% (N = 35)	12.4% (N = 12)	57.7% (N = 56)
Generalized Anxiety Disorder	8% (N = 4)	18% (N = 9)	9.3% (N = 9)	21.6% (N = 21)
Panic Disorder	4% (N = 2)	16% (N = 8)	6.2% (N = 6)	16.5% (N = 16)
Social Anxiety Disorder	24% (N = 12)	28% (N = 14)	21.6% (N = 21)	33% (N = 32)
Obsessive-Compulsive Disorder	10% (N = 5)	12% (N = 6)	10.3% (N = 10)	11.3% (N = 11)
Specific Phobia	8% (N = 4)	18% (N = 9)	21.6% (N = 21)	27.8% (N = 27)
Substance Use Disorder	52% (N = 26)	94% (N = 47)	10.3% (N = 10)	35.1% (N = 34)

b. <u>**Questionnaires and Interviews**</u>

The PCL-5 (Blevins et al., 2015). is a 20-item self-report measure assessing the 20 PTSD symptoms in DSM-5, and yields a variety of metrics, including a total PTSD symptom severity measure, DSM-5 cluster severity scores (for clusters B, C, D, and E), and a provisional PTSD diagnosis It has been shown to have high internal consistency (α = .96) and test-retest reliability (*r* = .84), as well as both discriminant and convergent validity (2015). Both the total PTSD dimensional score, as well as the dimensional, cluster-level scores were elicited for this study. The correlation matrix for the various cluster-level PTSD scores indicated no evidence of multicollinearity concerns (see Table 2).

Table II.

Study 1 Correlation Matrix for PCL-5 Cluster-Level Variables

	Cluster B	Cluster C	Cluster D	Cluster E
Cluster B	1.0	.40	.51	.62
Cluster C	.40	1.0	.50	.42
Cluster D	.51	.50	1.0	.67
Cluster E	.62	.42	.67	1.0

The WSAS (Zahra et al., 2014) is a five-item self-report scale measuring functional impairment attributed to a specific problem. Cronbach's alpha showed high internal consistency in individuals with depressive and anxiety disorders (Mundt, Marks, Shear, & Greist, 2002). The WSAS has also been shown to have strong convergence with perceived improvement at follow-up when compared to clinical interviews (2002). The total functioning score was incorporated as a covariate for models in Aims 2 and 3 as a proxy for physical and psychiatric comorbidities impacting overall functioning (see Data Analysis section below).

B. Study 2

a. Participants

This study uses a subset of participants drawn from a NIMH-funded family study (see; Katz, Hee, Hooker, & Shankman, 2018; Weinberg, Liu, Hajcak, & Shankman, 2015). Advertisements (fliers, internet postings, etc.) were used to recruit participants, aged 18-30, from the community and from mental health clinics in the greater Chicago area with a wide range of psychopathologies. A Research Domain Criteria (RDoC; Insel et al., 2010) approach was taken to participant recruitment such that recruitment screening was agnostic to DSM diagnostic categories (beyond the exclusion criteria listed below). However, participants with severe internalizing psychopathology were oversampled to ensure that the sample was clinically relevant. Inclusion criteria for the larger study required participants to have at least one full biological sibling also willing to participate in the study. Individuals were excluded if they presented with a personal or family history of psychosis or mania at the time of the interview, an inability to read or write in English, a history of serious head trauma, or left-handedness (Correa, Liu, & Shankman, 2019).

For this study, we selected the 97 trauma-exposed participants who exhibited at least one DSM-5 symptom of PTSD (to ensure that the participant, at least in part, continued to have some post-trauma symptoms at the time of the assessment of AB). Participants were 18 to 30 years old (M = 22.6, SD = 3.0) and nested within 82 families, including 16 sibling pairs (see Table 1 for participant demographics and clinical characteristics). All participants underwent a Structured Clinical Interview for DSM-5 (SCID-5; First, Williams, Karg, & Spitzer, 2015) to ascertain dimensional levels of PTSD symptoms, as well as the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0; Üstün et al., 2010) to assess their overall level of functional impairment.

b. Questionnaires and Interviews

The SCID (First, Williams, Karg, & Spitzer, 2015) is a semi-structured clinical interview designed to assess whether an individual meets criteria for diagnoses defined in DSM-5. Although participants were assessed on the following modules—MDD, AUD, Substance Use Disorder (SUD), PTSD, Panic Disorder, Agoraphobia, SAD, Specific Phobia, OCD, GAD, Anorexia, Bulimia, Binge Eating Disorder, and the bipolar and psychotic screening modules—the current study only focuses on the PTSD component. SCID interviewers included trained doctoral students and bachelor's level research assistants supervised by a licensed clinical psychologist. The SCID has been shown to have substantial internal consistency (Cronbach's alpha > .80), good test-retest reliability, and concurrent and predictive validity, particularly for symptom severity over and above DSM categorical diagnoses. Interrater reliability for lifetime diagnoses was fair to substantial (k's = .46 - .87) and was fair to moderate (k's = .54 - .74) for current diagnoses (Shankman et al., 2018). After a participant met Criteria A (i.e., experienced a trauma), all other symptoms were assessed on a 1-3 scale, allowing us to generate dimensional levels of PTSD clusters by summing the 20 symptoms assessed in the PTSD module. Exploratory analyses were conducted with the total PTSD cluster severity (i.e., cluster B, C, D, and E). The correlation matrix for the various cluster-level PTSD scores indicated no evidence of multicollinearity concerns (see Table 3).

Table III.

Study 2 Correlation Matrix for PCL-5 Cluster-Level Variables

	Cluster B	Cluster C	Cluster D	Cluster E
Cluster B	1.0	.23	.35	.41
Cluster C	.23	1.0	.37	.44
Cluster D	.35	.37	1.0	.58
Cluster E	.41	.44	.58	1.0

The WHODAS 2.0 is a 36-item interview designed to assess health and disability globally (Üstün et al., 2010). Similar to the SCID, it has demonstrated high internal consistency (Cronbach's alpha, α: 0.86), as well as a stable factor structure in prior studies (Ustun et al., 2010) and a Cronbach's alpha of .85 in the present sample. The primary factor, General Disability, comprises six sub-factors including cognitive, mobility, self-care, getting along, life activities, and participation. Individual differences in the General Disability factor relates to the presence of both psychotic and non-psychotic psychiatric symptoms (Hernández-Orduña et al., 2017) and was included as a covariate in this study as a proxy for overall psychiatric severity/comorbidity (see data analysis section below).

C. Dot-Probe Task

For the dot-probe task, each trial began with a 1-s, centered fixation cross, followed by two faces (either both neutral, or one threatening (i.e., angry) and one neutral face) of the same person presented simultaneously and briefly (33-ms) to the left and right of the fixation cross. The threatening/neutral faces then disappeared and were replaced with a mask (100-ms) of two images of the same person making a happy face (see Egloff & Hock, 2003; Mathews, Ridgeway, & Williamson, 1996 for details about masked presentation of emotional stimuli). After the happy face mask, a dot was immediately presented in either the left or right quadrant, and the reaction time (RT) of participant's detection of the dot's location was recorded (see Figure 1). Participants were instructed to press a button corresponding to the side of the screen on which the dot appeared as quickly and accurately as possible. The dot-probe procedure was identical to that in *Study 1* and *Study 2*, apart from one discrepancy. In *Study 2*, due to a computer processing error, the number of safe and threat trials was not equivalent across the two conditions. To ensure an equal number of trials included per conditions, 19 trials of each condition were randomly selected for inclusion in the following analyses, resulting in 114 total trials (a total 79% of trials maintained). The accuracy for dot-probe in the parent sample for *Study 2* (i.e., correctly clicking on the side of the screen as the dot) was 97.7% at the trial level. Accuracy data was unavailable for *Study 2*; however, no participants were excluded for missing dot-probe data.

There were three types of trials for the brief threatening/neutral faces – congruent, incongruent, and neutral. In congruent, there is one neutral and one threatening face with the dot replacing the threatening face. In incongruent, there is one neutral and one threatening face with the dot replacing the neutral face. In neutral trials, there were two neutral faces with the dot replacing one of the neutral faces. The location of the threatening face was counterbalanced. In neutral trials, both faces were of the same person displaying a neutral expression. There were equal numbers of male and female faces and faces with open and closed mouths. Faces were from the NimStim databank (see Tottenham et al., 2009). Twenty-four trials of each condition were presented across two blocks, resulting in a total of 72 trials.

As per aim 1, participants completed the dot-probe task under ‘aversive’ and ‘safe’ contexts (the order of the two contexts were counterbalanced between participants). During the aversive context, participants heard random presentations of a woman screaming or metal garden fork scraping on a chalkboard (stimuli were those used by Lissek et al., 2005 and Neumann & Waters, 2006, respectively, who used these sounds as unconditioned stimuli in Pavlovian conditioning). During the safe context, no sounds were presented.

Figure 1.

Dot-probe congruent trial example (pictures from Tottenham et al., 2009)

D. Data Analysis

As per standard practice (Price et al., 2015), all incorrect trials (i.e., when the subject pressed the button on the wrong side of where the dot was) were discarded. To account for outliers in dot-probe, RT values outside 2.5 standard deviations--or beyond the 25th or 75th percentiles--for each trail type were Winsorized to the nearest value (see Price et al., 2015 for a similar approach). Average condition scores were calculated for the three conditions—incongruent, congruent and neutral. As data were skewed after Winsorizing, reaction time averages were also natural log transformed. Using these values, the following traditional AB scores (Cisler & Koster, 2010; MacLeod et al., 1986) were calculated: (1) *Attention Bias* (incongruent RT - congruent RT), reflecting attentional vigilance toward (positive scores) and attentional avoidance away (negative scores) from the emotional face; (2) *Disengagement* (incongruent RT - neutral RT), reflecting disengagement from threat; and (3) *Orientation* (neutral RT - congruent RT), reflecting orientation to threat.

Given limited sample sizes, all missing data was replaced with the sample mean for that variable. In *Study 1*, this included (a) one participant who was missing the incongruent and neutral trials in the threatening condition (and consequently also missing for the corresponding AB metrics—AB_{threat}, $Orientation_{threat}$, and $Disengagement_{threat}$), (b) one participant who did not respond to PCL-5 question 10, and (c) 8 participants who did not complete the WSAS. In *Study 2*, this included one participant who did not complete the dot-probe in the safe condition, and 8 participants who did not complete the WHODAS 2.0.

All three aims were addressed with mixed effects models to account for the repeated measures design within participants—Condition (*Safe* vs. *Threat*) nested within Trial Type, (*Incongruent*, *Congruent*, and *Neutral*), or AB metric (total *AB*, *Orientation*, and *Disengagement*), nested within participants. To test Aim 1 (i.e., whether condition [safe vs. threat] impacts different AB), a 2 (Condition) x3 (Trial Type) Mixed Effects Model was run. Mixed models follow-up tests examined the difference of *Safe* and *Threat* dot-probe values for each of the three AB metrics. To test aim 2 (i.e., whether PTSD severity impacts the effects tested in aim 1), mixed effects models examined the interaction of dimensional PTSD and environmental context (i.e., safe vs threat) to predict traditional AB metrics. To further examine generalizability, all analyses will be run in both separate *Study 1* and *Study 2*.

Regarding covariates for aim 2, in *Study* 1, to be inclusive of all participants, there were separate models covarying for sex assigned at birth (hereafter referred to as sex) and affirmed gender (hereafter referred to as gender). Separate variables for sex and gender were not assessed in *Study 2*.

Additionally, given the prevalence of current and lifetime psychopathology in both samples (see Table 1), models included a global functioning covariate to act as a proxy for these comorbidities. Simply including all categorical diagnoses is inappropriate given the large number of possible variables (e.g., current and lifetime, MDD, GAD, OCD, etc.). Moreover, including a single variable measuring whether a participant has an additional diagnosis removes the potential impact of subjects with multiple comorbidities, and including a count of the total number of diagnoses assumes that each diagnosis is of comparable severity (e.g., someone with simple phobia and GAD has two diagnoses, but might not be more severe than someone who just has a diagnosis of MDD). Thus, to account for the complexities of comorbidity, in *Study 1* the WSAS, a measure of global functioning, and in *Study 2* the general disability metric from the WHODAS were included as covariates.

Finally, for exploratory Aim 3, the same mixed effects models as Aim 2 explored individual clusters covarying for all remaining symptom clusters (i.e. examining Cluster B while covarying for Clusters C, D and E). This allowed the for exploration of whether one particular cluster of symptoms was driving the relationship between PTSS and AB.

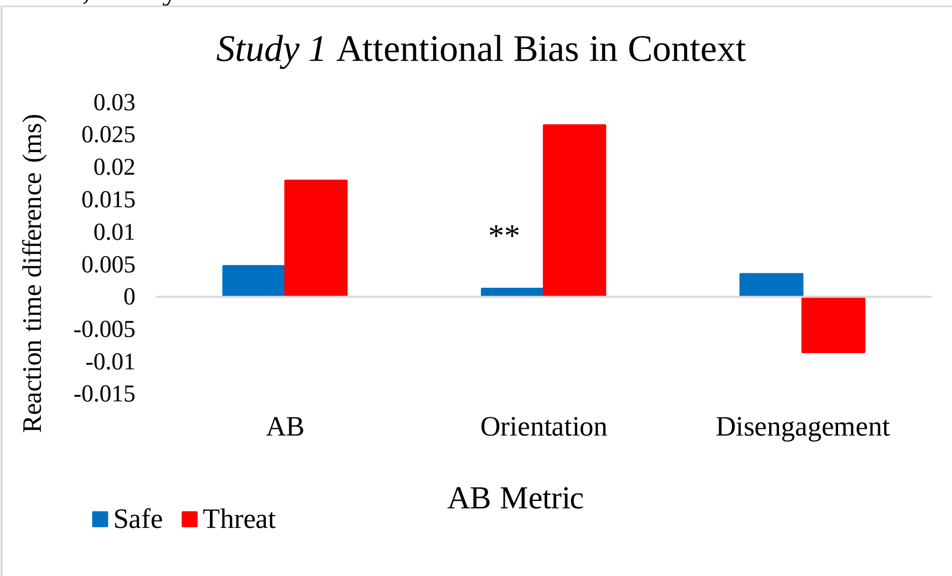
All analyses were run in R (Version 1.1.456, R Core Team, 2018) using the following packages: *moments* (Version 0.14, Komsta & Novomestky, 2015), *rcompanion* (Version 2.0.3, Mangiafico, 2018), *lmerTest* (Kuznetsova & Brockhoff, 2017), *lme4* (Bates, Maechler, Bolker & Walker, 2015), *tidyr* (Version 0.8.2, Wickham & Henry, 2018), *dplyr* (Version 0.8.0.1, Wickham, Fraçois, Henry, 2019), *effects* (Fox & Weisberg, 2018), *ggplot2* (Wickham, 2016) and *afex* (Version 0.21-2, Singman, Bolker, Westfall & Aust, 2018).

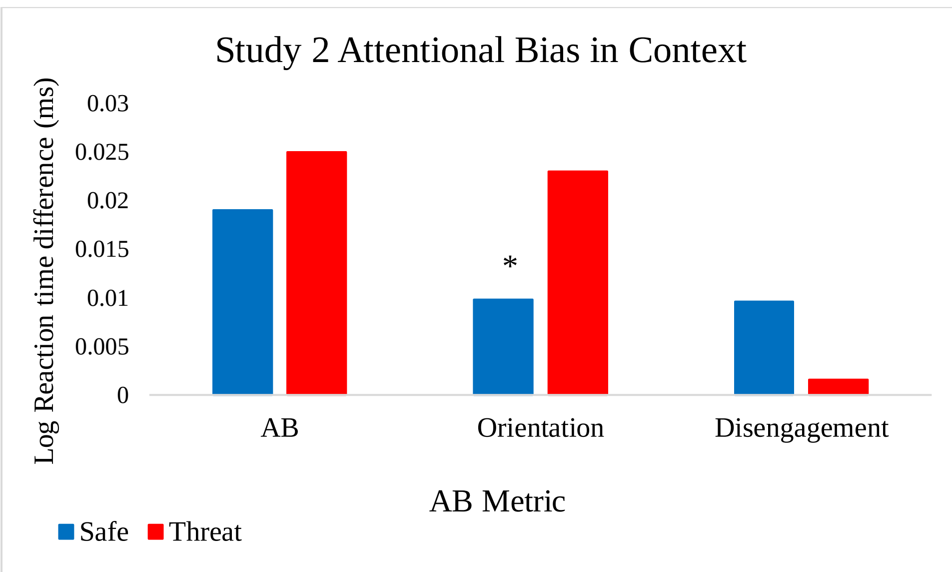
III. RESULTS

A. Aim 1: Is masked AB different under safe and aversive context?

In *Study 1*, the results from the omnibus model in Aim 1 yielded a significant condition x trial type interaction ($F(2, 149.97) = 4.37$, $p < .05$), as well as a significant main effect of condition ($F(1, 50) = 5.25$, $p < .05$) and a significant main effect of trial type ($F(2, 72.61) = 5.05$, $p < .01$, see Figure 2). Follow up models showed a significant impact of condition on the Orientation bias ($t(49) = 2.87$, $p < .01$) but not overall AB ($t(98) = 1.35$, $p = .18$) nor disengagement ($t(49) = -1.58$, $p = 0.12$), indicating that there was significantly heightened orientation bias in the threat context compared to the safe context ($b = .025$). In *Study 2*, there was not a significant condition x trial type interaction in the omnibus model ($F(2, 405.25) = 1.10$, $p = 0.33$; see Figure 2) or a significant main effect of condition ($F(1, 74.25) = .41$, $p = .53$); however, there was a marginal main effect of trial type ($F(2, 405.25) = 2.87$, $p = .058$). To parallel the analyses to *Study 1*, this model was also followed up. These analyses yielded a marginally significant effect of condition on the Orientation bias ($t(192) = 1.98$, $p = .062$) but not for overall AB ($t(71.37) = 0.62$, $p = .54$) nor disengagement ($t(84.12) = -0.75$, $p = 0.45$), again indicating a trend of increased orientation bias in the threat context ($b = .013$) compared to the safe context. Importantly, the results for study 2 should be interpreted with caution given the lack of a significant interaction in the omnibus model.

Figure 2.
Aim 1, 2-way RM ANOVA of attentional bias in safe and threat context





* $p < .05$, ** $p < .01$

B. Aim 2 and 3: Does total (or cluster-level) PTSS moderate the relationship between masked AB and context?

Results for Aim 2 were not significant in either *Study 1* or *Study 2*, regardless of whether the models covaried for sex or gender and/or global functioning (all p's > .12). Results for interactions are presented in Table 4 and main effects are presented in Table 5.

The exploratory aim 3 examining the impact of specific PTSD symptom clusters did yield some significant results. In *Study 1*, there were no significant interactions or main effects for any of the 4 PTSD symptom clusters predicting any of three AB metrics. In *Study 2*, there was a significant main effect of cluster E symptoms on Orientation bias (see Table 5), indicating that after adjusting for other clusters, more cluster E symptoms were related to a lower orientation bias across both safe and threat conditions (b = -.010, p < .05; see Figure 3).

Table IV.
Beta values for interaction of Environment (i.e., Safe vs. Threat) and PTSS

	AB		Orientation		Disengagement	
	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
PTSS total	-.013	.0099	-.0013	.0065	-.012	.0017
Cluster B	-.0086	.0080	.0023	-.0035	-.011	.012
Cluster C	-.0090	-.0020	-.0044	-.0049	-.0046	.0021
Cluster D	-.011	.0058	.00091	.033	-.012	-.0098
Cluster E	-.014	.013	-.0049	.0077	-.0087	.0038

Note: In *Study 1*, results remained whether or not models included a covariate of WHODAS general disability and/or sex; and in *Study 2*, results remained whether or not models covaried for sex and/or gender and/or WSAS. Beta values presented do not include any combination of covariates, and PTSS scores from both studies have been z-scored for ease of comparison.

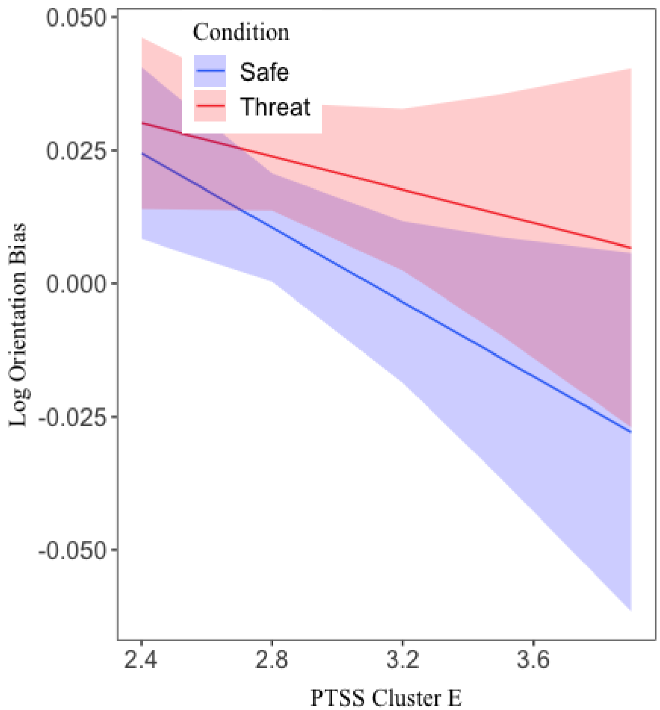
Table V.
Beta values for main effect of PTSS on dot-probe

	AB		Orientation		Disengagement	
	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
PTSS total	-.00011	-.00064	.0047	-.0039	-.0047	.0016
Cluster B	.0011	.0013	.0013	.0012	-.00029	.00015
Cluster C	-.0022	-.0033	-.0018	-.0036	-.00030	-.00011
Cluster D	.0016	-.0047	.0012	.0074	.00034	-.013
Cluster E	-.0022	.0052	-.00082	**-.010***	-.0013	.014

* $p < .05$

Note: In *Study 1*, results remained whether or not models included a covariate of WHODAS general disability and/or sex; and in *Study 2*, results remained whether or not models covaried for sex and/or gender and/or WSAS. Beta values presented do not include any combination of covariates, and PTSS scores from both studies have been z-scored for ease of comparison.

Figure 3.
Main effect of PTSS cluster E symptoms on Orientation Bias in *Study 2*



IV. DISCUSSION

The results from Aim 1 highlight that AB to masked stimuli in trauma-exposed populations is altered when measured in an aversive context but that severity of current PTSS did not impact AB. The omnibus model testing for the moderating effect of context was significant for the treatment-seeking sample in *Study 1* but not for the community sample in *Study 2*; however, follow up models in both samples revealed that the same type of bias was especially impacted by the aversive environment. Specifically, orientation bias (i.e., heightened orientation to threatening stimuli) was increased in both samples during the aversive context relative to the safe context, whereas the other two AB metrics were not affected by the environmental stressor. The tests for Aim 2 did not yield any association between PTS symptoms and masked AB in any of the metrics; although, in Aim 3, models in *Study 2* indicated that those higher in cluster E symptoms displayed lower overall orientation bias, or avoidance, regardless of context.

These results emphasize the importance of examining the separable types of AB—overall AB, and its specific components (Orientation and Disengagement)—as the mechanism of AB is often thought of as having both bottom-up (e.g., threat detection) and top-down (e.g., attentional control) components (Cisler et al., 2011). However, the overall AB metric makes it difficult to disambiguate the different aspects of AB, as any true bias may be potentially masked due to the nature of how it is calculated (Incongruent – Congruent). Looking at Orientation (Congruent – Neutral) and Disengagement (Neutral – Incongruent) metrics allows AB to be examined in its component parts. In the treatment-seeking sample in *Study 1*, AB was moderated by the aversive environment resulting in heightened Orientation towards the threatening stimuli (and this effect on Orientation was trending in *Study 2*). Importantly, the aversive context did not impact participants' abilities to Disengage from the threatening image; although, given the brevity in which the threatening image was presented, participants may not have had the time to fully "engage and then disengage." That is, if the masked dot-probe elicits individual differences in early threat detection, it stands to reason that effects would be stronger for orientation bias rather than a longer process like disengagement (2011). Taken together, this suggests that while in an aversive context, trauma-exposed participants were immediately more hypervigilant towards the threatening image, but they reallocated their attention back towards the probe without any concerning difficulty (i.e., no difficulty disengaging). However, the latter may have simply been a function of this specific, masked, dot-probe task.

To our knowledge, no study has examined AB to *masked* threatening stimuli under an aversive vs. safe context. However, several studies have examined unmasked context-dependent AB. Using shock anticipation to create an aversive context (a manipulation most similar to the present study), one study showed that participants exhibit an avoidance of threatening words (Shechner, Pelc, Pine, Fox, & Bar-Haim, 2012a). Other studies examining attention more broadly highlight that, in an aversive context, participants have difficulty disengaging from a cognitive task (Choi, Padmala, & Pessoa, 2012), and using an electrophysiological indicator of attention, Mercado, Carretié, Tapia, and Gómez-Jarabo found that some people show heightened attention when they're primed with a threatening stimulus (2006). Importantly, apart from the study by Shechner et al. (2012), this work has evaluated attention broadly, rather than breaking down AB into its component parts, does not evaluate AB using the dot-probe task, and, for all above studies (including Shechner et al.), sample sizes are less than 50 participants. Ultimately, Mercado et al. suggests the aversive context might activate an early attentional component (2006); however, Choi et al., on the other hand, suggested it might be a later process of difficulty disengaging (2012). Despite these flaws, it appears from the literature that AB *can* be altered in an aversive context, and these results from Aim 1 suggest that, with a masked dot-probe paradigm, the nature of this deficit is that participants are hypervigilant and exhibit greater threat detection.

It remains unclear, however, why the results from Aim 1 did not fully generalize from *Study 1* to *Study 2.* One reason may be that treatment seeking samples, as opposed to community samples, exhibit different intensities of AB. That is, the overall effects may have been stronger for *Study 1* as these participants were experiencing psychopathology for which they were seeking treatment, and thus were generally more impaired. Another possible reason is because of the age difference between the two samples - *Study 1* was primarily middle adults while *Study 2* was primarily young adults. A prominent developmental theory, Socioemotional Selectivity Theory (SST), postulates that as the perception of time decreases, older adults tend to prefer positive stimuli and avoid negative stimuli, in a desire to purposefully experience a more positive environment (Carstensen, Isaacowitz, & Charles, 1999). Research into age differences of unmasked AB in healthy adults has seen this effect of AB to positive stimuli comparing younger (18-30) and older (60+) adults (Bi & Han, 2015; Namaky et al., 2017), and another study by Lu et al. using eye-tracking, found age effects for positive AB among patients with MDD (i.e., middle adults (31-50) had less positive AB than young adults (18-30)), but not for negative AB compared to healthy controls (2017)). Although it does seem that there is an impact of age on AB in some circumstances, it is unclear whether this theory applies to middle-aged adults (such as those in *Study 1*), how this might extend to a dot-probe paradigm, or how the effect of trauma impacts SST.

In addition to the Null results from Aim 2, the results from Aim 3 were largely nonsignificant apart from one model in *Study 2* which did not generalize between samples. In the community sample (*Study 2*), after adjusting for the other clusters, higher cluster E symptoms were associated with lower orientation bias, suggesting that those who, clinically, presented with more symptoms in the hypervigilance PTSS cluster tended to avoid the threatening stimuli regardless of context. Although these results did not generalize across samples, they were specific to that particular cluster and suggest that examining specific components of PTSS may uncover specific relationships that are clouded by examining PTSS overall (or the categorical diagnosis of PTSD). While it is possible that the results for these specific clusters in *Study 2* are Type I Error (given their lack of generalization to *Study 1*), the null results for *Study 1* may have been due to the sample's higher overall symptoms. That is, *Study 1*'s higher overall PTS symptoms may have led to reduced variability in specific cluster-level profiles. It is also noteworthy that the effects observed for specific PTSS clusters were for orientation bias which (as alluded to earlier) is the expected form of bias with this type of masked paradigm.

On the one hand, it is puzzling why the present study did not replicate prior research showing a strong relationship between PTSS and AB (Bar-Haim et al., 2010; Cisler et al., 2011; Joyal et al., 2019; Latack et al., 2017; Todd et al., 2015). Yet, studies examining this association have typically not used masked faces (Bar-Haim et al., 2010; Joyal et al., 2019). One meta-analysis comparing masked to unmasked stimuli found that PTSD was more strongly associated with AB for unmasked methodologies (Cisler et al., 2011), although this meta-analysis evaluated studies that assessed AB using the emotional Stroop task, a paradigm that, unlike the dot-probe task, does not separate AB into its component parts. And yet, in combat-related PTSD, findings are mixed with research implicating that individuals in an aversive context both display avoidance of threatening stimuli (Wald, Lubin, et al., 2011) and AB suppression (Constans, Vasterling, McCloskey, Brailey, & Mathews, 2004). In trauma-exposed populations using an unmasked word-based dot-probe paradigm, it appears that with an acute environmental stressor, participants display an avoidant AB (Wald, Shechner, et al., 2011) and that this AB increases as a function of the proximity of the threat (Bar-Haim et al., 2010). However, at a 1-year follow-up Wald and Shechner (2011) found that these bias tendencies are both predictive of increases in PTSS and also manifest as hypervigilance towards threat. However, it is important to acknowledge that these studies are between- not within-subjects designs in the context of the aversive environment, and do not use an image dot-probe task.

Interestingly, much of the literature on AB deficits in anxiety outside of trauma exposure highlights a vigilant-avoidant theory of AB, in that, typically, individuals with greater anxiety are initially quicker to orient to a threatening stimuli, but when AB is measured in an aversive or stressful context, this bias shifts to avoidance (Garner, Mogg, & Bradley, 2006; Helfinstein, White, Bar-Haim, & Fox, 2008). Overall, this literature might imply that the mechanism for PTSD may be different than anxiety. Moreover, given that vigilance to threat seems to play a key role in both categorical PTSD as well as AB mechanisms, none of these studies examined AB with a masked dot-probe to properly elicit early threat detection. The results from the present study indicate that in a trauma-exposed population (similar to the samples in Wald, Shechner et al., 2011 and Bar-Haim et al., 2010), participants do show this early-threat detection to threatening stimuli, but findings were not moderated by severity of PTSS. Since PTSD is no longer considered an anxiety disorder, it is important to continue this work in identifying mechanisms that separate it from other anxiety phenotypes.

Although the present study did not find a moderating effect of PTSS, results highlight the impact of an aversive context on early threat detection biases in trauma-exposed individuals. This result has important clinical implications for trauma-focused interventions. For example, Prolonged Exposure (PE)—an intervention designed to gradually expose clients to memories of their trauma until they habituate to the experience (Foa, Hembree, & Rothbaum, 2015)—is one of the front-line treatments for PTSD. As the results of this study suggest that AB is sensitive to differing aversive contexts, future studies could explore the potential benefit of assessing AB across varying degrees of aversiveness (i.e., during a session of PE) to test whether changes in AB track with changes in reactivity to exposure. Additionally, although speculative, it is possible that the PTSD clusters in Aim 3 that showed a modest relation with AB may point to which type of PTSD symptom profile would benefit the most from PE over another treatment, such as ABM. That is, it is possible that individuals high in cluster E symptoms may improve with a simpler intervention, targeted specifically at decreasing their avoidance (i.e., decreased orientation) of threatening stimuli.

There are several limitations to this study that are worth noting. First, although the present study attempted to examine whether effects generalized across two independent samples, neither sample size individually was substantially large—and this could have prevented the detection of small effect sizes. Second, participants in *Study 1* and *Study 2* samples had varying types of trauma. In a meta-analysis, Cisler et al. (2011) found that the relation between PTSD and AB (at least as measured by the emotional Stroop task) was greater for individuals who experienced an assaultive rather than non-assaultive trauma. It is therefore possible that the heterogeneity in traumas in these samples contributed to the null results for PTSS tested in Aims 2 and 3. Third, the aversive context with which the dot-probe was presented was not trauma-specific. Individuals with PTSS may show a heightened response to their trauma cue, but not aversive contexts more broadly. Thus, future work should examine trauma-specific, context-dependent AB. Fourth, compared to other methods to test AB such as event-related potentials (Helfinstein et al., 2008) and eye tracking (Garner et al., 2006), a reaction time measure may not be sensitive enough to detect this subtle, automatic AB. Fifth, it is possible that the reliability of the dot-probe metrics may be contributing to the inconsistent results. Evans and Briton (2018) and Price, Brown, and Siegle, (2019) have proposed new, reaction time measures of AB from dot-probe that have better psychometric properties than the traditional scoring of dot-probe reaction time used in the present study. Future studies should examine and compare the traditional dot-probe metrics, with these newer scoring methods to evaluate whether certain populations benefit from this more sensitive analysis. Finally, it is unclear whether the results for cluster E tested in Aim 3 reflect that AB is a result of PTSS or a precursor to developing these symptoms after trauma exposure. Understanding the directionality of this mechanism could have important implications for screening individuals at risk for PTSD (particularly members of the military who are at higher risk of experiencing a trauma), as well as for furthering personalized medicine and treatments in this area

In sum, even though the AB literature is robust, the specifics about which facet of AB is associated with which PTSD symptoms is still unclear. This study contributes to the existing literature by investigating AB under both safe and aversive contexts, by examining AB to masked faces to evaluate threat detection, by separating AB into its component parts, and by attempting to generalize findings across treatment-seeking and community samples. Results highlight that AB appears to be stronger in treatment-seeking samples and this difference is especially pronounced when AB is assessed in a threatening environment. Future studies should continue this work in larger samples with varying intensities of PTSS, as well as comparing masked and unmasked dot-probe under aversive and safe contexts. These results could have important treatment implications for PE and other trauma-related interventions including ABM and help clarify the mechanisms implicated in symptom development of trauma-exposed individuals.

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PUBLICATIONS:

Shankman, S.A., Kaiser, A.J.E., **Shenberger, E.R.** (In press). The importance of examining psychometrics of biomarkers: A commentary on "Intergenerational transmission of frontal alpha asymmetry among mother-infant dyads." *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*

Andrews, K. G., Martin, M. W**., Shenberger, E.,** Pereira, S., Fink, G., McConnell, M. Financial Support to Medicaid-Eligible Mothers Increases Caregiving for Preterm Infants (*Accepted for Submission for Maternal and Child Health Journal)*

Lewis, T. P., Andrews, K. G., **Shenberger, E.,** Betancourt. T. S., Fink, G., Pereira S., McConnell, M. (2019). The Costs of Caregiving: Understanding the NICU Experiences of Mothers with Preterm Infants. *BMC Pregnancy and Childbirth*

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CONFERENCE POSTERS AND PRESENTATIONS:

Low, D. M., **Shenberger, E**., Bentley, K. H., Shankman, S., Ghosh, S. S. (2020). *Automated assessment of mental health from audio and text.* 2020 Harvard Center for Research on Computation and Society Workshop on AI for Social impact, Cambridge, USA.

Shenberger E.R., Funkhouser, C.J, Correa K.A., Kaiser A.J.E., Shankman, S.A. *Using an Actor-Partner Interdependence Model to test the Association Between Sibling Relationship Quality and Depression Severity* Poster presented at: Society for Research in Psychopathology, Annual Meeting; 2019 September 19-22

Kaiser, A., **Shenberger, E.,** Correa,K., Funkhouser, C. J., & Shankman, S.(2019, May). *Familial association between reward anticipation frontal asymmetry and depressive symptoms.* Poster presented at the Society for Research in Psychopathology Annual Convention, Buffalo, NY

Shenberger E.R., Funkhouser, C.J., Meissel, E.E.E., Shankman, S.A. *Do the Four PTSD Symptom Clusters have Differential Associations with Attentional Biases to Threat?* Poster presented at: Society for Biological Psychiatry, Annual Meeting; 2019 May 16-18; Chicago, IL

Andrews, K., Pereira, S., McConnell, M., Fink, G**., Shenberger, E.**, Lewis, T. *Overcoming Financial Barriers to Caring for Preterm Infants: A qualitative study and randomized controlled trial of the impact of financial support on breastfeeding and skin-to-skin care.* Presentation given at the American Public Health Association, Annual Meeting; 2017 November 4-8; Atlanta, GA.

Hunt, M., Rushton, J., **Shenberger, E.,** & Murayama, S. *Just take a deep breath: Positive effects of diaphragmatic breathing on physiological stress reactivity in athletes*. Poster presented at: Anxiety and Depression Association of America, Annual Meeting; 2017 April 6-9; San Francisco, CA.

Shenberger, E., Kuna, S.T., Wang, S., Leinwand, S., Schwab, R. J. *Abdominal fat differences between sexes in lean and obese apneics*. Poster presented at: Center for Sleep and Circadian Neurobiology Research Retreat; 2015 June 17; Philadelphia, PA.