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Stress sensitivity mediates the relationship between traumatic life events and attenuated positive psychotic symptoms differentially by gender in a college population sample

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ABSTRACT

The purpose of this study was to investigate whether stress sensitivity mediates the relationship between traumatic life events and total attenuated positive psychotic symptoms, as well as the relationship between traumatic life events and endorsement of 8 or more attenuated positive psychotic symptoms as distressing (a threshold that has been associated with higher risk for psychosis in clinical groups). Participants ($n = 671$, aged 17–35, 29% male) were college students who were administered the Prodromal Questionnaire, the Perceived Stress Scale and the Life Events Checklist. Bootstrapping results indicated that stress sensitivity significantly mediated the relationships between traumatic life events and the number of attenuated positive psychotic symptoms endorsed and between traumatic life events and those who endorsed 8 or more distressing attenuated positive psychotic symptoms. Stratified gender analyses indicated the findings were specific to females. Results suggest that stress sensitivity may represent a specific vulnerability factor for risk of attenuated psychotic symptoms in those previously exposed to traumatic life events and that this liability appears stronger in females.

1. Introduction

Traumatic life experiences (TLEs) have been repeatedly associated with risk for and severity of psychotic disorders, with clinical high risk for psychosis and with attenuated (i.e., less frequent, severe, distressing or convincing) positive symptoms in nonclinical samples (Spauwen et al., 2006; Gracie et al., 2007; Thompson et al., 2009; Heins et al., 2011; Addington et al., 2013). A recent meta-analysis found that trauma exposure significantly increased the odds of experiencing subclinical psychotic experiences (odds ratios [OR] 2.79–2.99), regardless of demographic factors and comorbid psychopathology (Varese et al., 2012). Despite the repeated link between TLEs and psychotic symptoms, the mechanisms underlying this association remain unclear.

One possibility is that those at risk for psychosis may respond differently to TLEs, such as by demonstrating heightened subjective stress appraisals in response to these events (Collip et al., 2008; Lardinois et al., 2011). Stress sensitivity has been defined as an individual's appraisal of perceived threat to their physical or psychological viability given their assessment of available coping resources (Bruce et al., 2013). While there are various methods for the assessment of stress sensitivity (e.g., physiological measures, experience sampling method [ESM], self-report rating scales), indices of stress sensitivity, including increases in self-reported perceived stress and elevations in baseline cortisol, have been associated with subclinical psychotic experiences, schizotypal personality disorder, concurrent first rank symptoms, longitudinal prediction of heightened positive symptoms and transition to psychotic disorders (Lataster et al., 2009; Tessner et al., 2011; Lataster et al., 2012; Collip et al., 2013; Devylder et al., 2013; Walker et al., 2013). Given these findings, TLEs may exert a higher risk for psychosis among individuals who have elevated stress sensitivity.

Stress sensitivity also has been found to differ by sex, with females appearing to have greater stress sensitivity compared to

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males. Specifically, findings indicate that females are more likely to report higher perceived stress scores compared to males (Myin-Germeys et al., 2004). Similarly, females diagnosed with psychotic disorders report higher levels of stress compared to males, and greater stress sensitivity has been significantly associated with increases in positive symptoms among females (Rector and Seeman, 1992; Navarro et al., 1996; Myin-Germeys et al., 2004; Lardinois et al., 2011; Oldehinkel and Bouma, 2011). Although many results suggest that females may be particularly responsive to TLEs, potentially increasing risk for psychotic disorders, not all studies in clinical high risk or psychotic samples find gender differences in stress sensitivity (Myin-Germeys et al., 2001; Devylder et al., 2013).

To our knowledge, no study has tested whether increased stress sensitivity mediates the relationship between TLEs and attenuated positive psychotic symptoms (APPS). Thus, the present study aimed to determine whether stress sensitivity mediates the relationship between TLEs and APPS in a non-clinical college sample that may be more representative of the general population than treatment-seeking individuals. The importance of assessing psychotic experiences dimensionally is underscored by research supporting the existence of an extended psychosis phenotype, whereby APPS experienced by non-help-seeking individuals have been linked to risk for developing a psychotic disorder, and subclinical and clinical psychosis have been found to have overlapping risk factors (van Os et al., 2009; van Os and Linscott, 2012). We hypothesized that exposure to TLEs would be associated with significant increases in APPS, and that stress sensitivity would mediate this relationship. We also hypothesized that these findings would be more prominent among females. The aforementioned relations were also examined in individuals who might be at higher clinical risk for psychosis by examining those who endorsed 8 or more APPS as distressing compared to those with a lower frequency of APPS. We viewed these analyses as exploratory given that our measure has only been validated in clinical samples.

2. Material and methods

2.1. Participants and procedures

The study was approved by Temple University's Institutional Review Board and all participants provided informed consent. Participants included 671 undergraduate students recruited from an online subject pool across various interdisciplinary courses. All participants filled out a set of online questionnaires on a laboratory computer. To address the possibility of careless test-taking, procedures were carefully explained to participants and examiners were readily available to answer questions.

2.2. Instruments

APPS were evaluated using the positive scale (45 items) of the full length, 92 item Prodromal Questionnaire (Loewy et al., 2007). The timeframe covers the past month and asks individuals to endorse whether they have experienced these symptoms while not under the influence of drugs, alcohol, or other medications and whether endorsed symptoms were experienced as distressing. The dependent variables were the total number of APPS endorsed and endorsement of 8 or more distressing APPS (D-APPS status) compared to endorsement of 3 or fewer distressing APPS (the mean in our sample), which represented the low risk group. Endorsing 8 or more APPS as distressing has been validated against the Structured Interview for Prodromal Syndromes (SIPS) in clinical populations with a 90% sensitivity and 49% specificity rate, and in a non-clinical undergraduate population 2% of the sample met this criterion (Loewy et al., 2005, 2007, 2012).

Stress sensitivity was evaluated with the Perceived Stress Scale (PSS), which measures perceived global stress and coping ability in the past month, with a focus on the predictability and controllability of past events (Cohen et al., 1983). This scale has high concurrent and predictive validity with physical and psychiatric outcomes, moderate internal and test–retest reliability, and significant correlations with physiological measurements of stress (Cohen, 1988; Hewitt et al., 1992; Cohen et al., 1993). This scale has been found to discriminate between clinical risk for psychosis and healthy controls and has been correlated with additional perceived stress measurements, such as the ESM (Palmier-Claus et al., 2012; Tso et al., 2012). PSS sum scores were used (Cohen et al., 1983).

The Life Events Checklist (LEC) assessed traumatic life event exposure (Gray et al., 2004). Respondents were asked to indicate their proximity to each TLE (1 = happened to me, 2 = witnessed it, 3 = learned about it, 4 = not sure, 5 = does not apply). If participants responded with a 3, 4 and 5, they were recoded as not experiencing that particular TLE, as we aimed to assess more severe and proximal exposure, which is consistent with previous measurements and has better test–retest reliability (Gray et al., 2004; Elhai et al., 2007). Responses of "1" for the first 16 TLEs were included as well as responses of "2" for scenarios where "1" was not a viable option, or for items where vicarious exposure has been related to potential posttraumatic stress disorder (PTSD) outcomes, including sudden, violent death; sudden, unexpected death of someone close to you; and serious injury, harm, or death you caused to someone else (APA, 2000). In addition, the question asking the participant to identify "other" TLEs was excluded from the analyses as there was no information about these TLEs types. The LEC has been shown to be adequate when evaluating consistency with the actual occurrence of events, has demonstrated good convergent validity, and has moderate temporal stability (Gray et al., 2004).

A curvilinear relationship was observed between the number of TLEs experienced and the number of APPS endorsed, as well as the number of these symptoms additionally endorsed as distressing. Specifically, Loess graphs (a locally weighted scatterplot regression not constrained to be linear, available upon request) suggested that as the number of TLEs increased, APPS scores increased, but this relationship plateaued after 4 TLEs for both the number of APPS endorsed and the number endorsed as distressing (i.e., no further significant increases in APPS following 4 TLEs). Similarly, the change in the number of APPS endorsed and in the number endorsed as distressing significantly increased for individuals who experienced 4+ TLEs compared to all other possible TLE categories (e.g. approximately a 4 point increase in APPS scores compared to all other possible TLE categories, see Fig. 1). Given these findings, the frequency of TLEs was collapsed into 2 categories: any exposure to a TLE versus no TLE exposure and exposure to 4 or more TLEs versus no TLE exposure (referred to as Any TLE and 4+ TLEs, respectively).

2.3. Statistical analyses

The APPS dependent variable was assessed for normality of distribution by examining skewness and kurtosis values and visually inspecting the data. Age and gender were examined as potential covariates by performing bivariate analyses with the main independent and dependent variables. Specifically, chi-square analyses were conducted to establish if significant differences existed between dichotomous variables (gender and D-APPS status and gender and TLEs) and ANOVAs were conducted to determine if there were significant differences with one dichotomous variable and one continuous variable (gender and APPS scores, gender and stress sensitivity, age and D-APPS status, and age and TLEs). Pearson correlations were conducted to test the association between age and stress sensitivity and between age and APPS. Outliers were

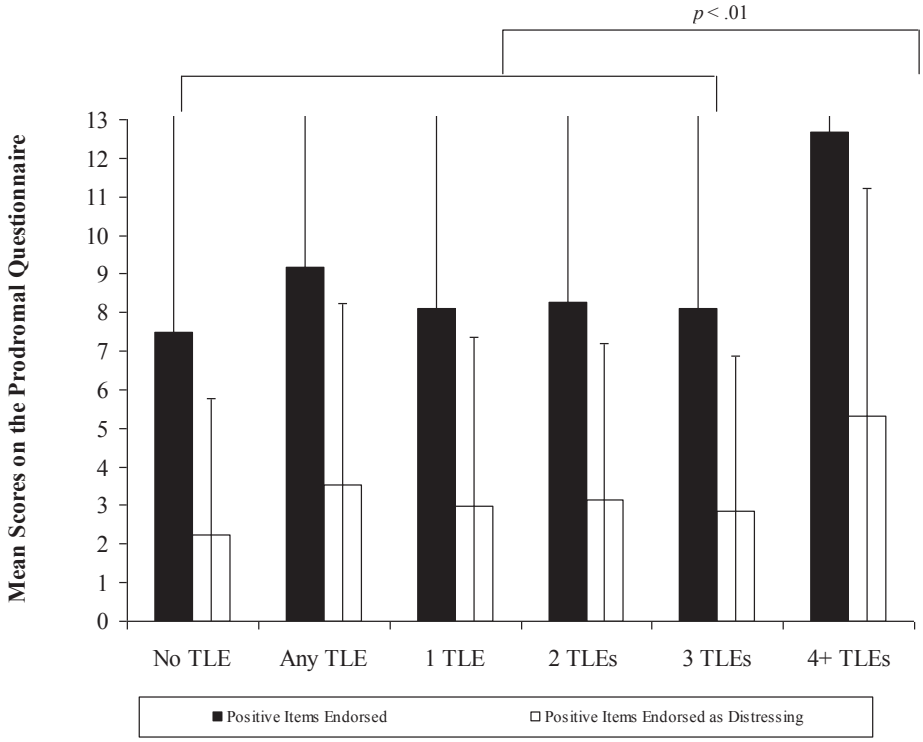

Fig. 1. Attenuated positive psychotic symptoms by traumatic life experience (TLE) category. The maximum number of positive items that participants could endorse was 45 (see Table 1 for mean and range of number endorsed). For descriptive purposes, raw means are presented. Main analyses conducted with log transformed variables. The figure indicates the mean number of attenuated positive symptoms endorsed (in black) and the mean number endorsed as distressing (in white) for each traumatic life experience category. This graph illustrates that participants in the 4+ TLEs category scored significantly higher than the other TLE categories on both Prodromal Questionnaire outcomes.

examined for aberrant responding by examining consistency between questions that overlapped between questionnaires.

In order to test for mediation, the independent, dependent, and mediator variables must be significantly associated with each other. Pearson correlations (stress sensitivity and APPS), ANOVAs (TLEs and APPS), and logistic regressions (to determine if TLEs or increases in stress sensitivity significantly increased the odds of D-APPS) were conducted to determine whether there were significant relations between the main study variables. To test the hypothesis that stress sensitivity mediates the relationship between TLEs and APPS and D-APPS status, the Preacher and Hayes SPSS indirect bootstrapping macro for mediation was used, which has been considered the most appropriate test for mediation with a single mediator (Preacher and Hayes, 2008). A 95% bootstrap confidence interval (CI) for the indirect effects was generated and adjusted for bias in the bootstrap distribution. Although there are no *p*-values associated with this method, significance is established when the CIs do not include zero. All models were conducted separately for Any TLEs and 4+ TLEs. Regression and logistic regression models were conducted to determine the relation between TLE and psychosis outcome variables with gender by PSS interaction terms added to the models. However, due to our a priori hypotheses all mediation analyses also were stratified by gender, regardless of interaction results, given that neglecting to probe insignificant interactions can obscure important findings (Brambor et al., 2006). Statistical significance was based on $p < 0.05$ and all tests were two-tailed.

3. Results

3.1. Demographic and clinical characteristics

Demographics and clinical characteristics, as well as descriptive statistics for the main independent, mediator, and dependent variables, are presented in Table 1. Given the non-normal positively skewed distribution of APPS scores (skewness = 1.30, kurtosis = 1.41), this variable was log transformed (log10 after adding 1). Five participants were removed from analyses given that their ages were greater than 3 standard deviations above the mean age of the sample (greater than 38 years old) and were beyond the typical age of onset for schizophrenia (APA, 2000). Three participants who endorsed 14+ TLEs were treated as outliers and removed from analyses. Age was significantly correlated with PSS scores ($r = 0.10$, $p = 0.02$), but age was not significantly related to the main independent and dependent variables: Any TLE ($F = 0.97$, $df = 1, 669$, $p = 0.33$), 4+ TLEs ($F = 1.04$, $df = 1, 252$, $p = 0.31$), APPS ($r = 0.06$, $p = 0.13$) or D-APPS status ($F = 0.00$, $df = 1, 549$, $p = 0.99$); therefore, age was not used as a covariate in analyses. Females exhibited significantly higher stress sensitivity scores compared to males ($F = 11.18$, $df = 1, 669$, $p = 0.001$). The interaction between gender and stress sensitivity was not significant for all TLE and psychosis outcome models (all ps > 0.1). There were no significant differences between males and females on APPS ($F = 0.03$, $df = 1$, $p = 0.85$), D-APPS status ($\chi^2 = 1.27$, $df = 1$, $p = 0.26$), Any TLE ($\chi^2 = 2.90$, $df = 1$, $p = 0.09$) or 4+ TLEs ($\chi^2 = 3.43$, $df = 1$, $p = 0.06$).

3.2. Main analyses: attenuated positive psychotic symptoms

Fulfilling the criteria for mediation, the independent, dependent, and mediator variables were significantly associated with each other. Significant differences were found between the number of APPS endorsed for Any TLE versus no TLE ($F = 11.13$, $df = 1, 669$, $p = 0.001$) and 4+ TLEs versus no TLE ($F = 31.26$, $df = 1, 252$, $p < 0.0001$). Stress sensitivity scores were significantly correlated with APPS ($r = 0.29$, $p < 0.0001$). ANOVA results indicated significantly higher stress sensitivity scores for those who reported Any versus no TLEs ($F = 9.67$, $df = 1, 669$, $p = 0.002$) and 4+ TLEs versus

Table 1
Demographics and clinical characteristics.

	Overall sample ($n = 671$)[a]
Demographics	
Male, *n* (%)	192 (29)
Age (years), mean (SD) [range]	20.50 (2.3) [17–35]
Race, *n* (%)	
Non-Hispanic White	392 (58)
African-American	84 (13)
Asian/Pacific Islander	95 (14)
Hispanic/Latino	26 (4)
Biracial	34 (5)
Other	40 (6)
Clinical characteristics	
Total number of traumas endorsed, mean (SD) [range]	2.05 (1.8) [0–11]
Any TLE, *n*, %	538 (80.2)
0 TLEs, *n*, %	133 (19.8)
1 TLE, *n*, %	170 (25.3)
2 TLEs, *n*, %	151 (22.5)
3 TLEs, *n*, %	96 (14.3)
4+ TLEs, *n*, %	121 (18.0)
PSS score, mean (SD) [range]	29.0 (4.3) [16–44]
PQ scores, mean (SD) [range]	
Total attenuated positive psychotic symptoms endorsed ($n = 671$)	8.8 (7.4) [0–37]
Low risk[b] ($n = 463$)	0.9 (1.12) [0–3]
D-APS status[c] ($n = 88$)	13.0 (4.6) [8–27]
Receiving or seeking treatment, *n* (%)	
Entire sample ($n = 671$)	85 (12.7)
Low risk[b] ($n = 463$, 30% male)	41 (8.9)
D-APS status[c] ($n = 88$, 24% male)	26 (29.5)

PSS= Perceived Stress Scale, PQ= Prodromal Questionnaire, TLEs = Traumatic Life Events.
Five participants were excluded as the age was >3 standard deviations above the mean (i.e. 38–53 years) and were past the typical age of onset for schizophrenia (17–35 years; APA, 2000).
[a] Three participants were excluded for endorsement of 14+ traumatic life events.
[b] Endorsement of 3 or fewer distressing attenuated positive symptoms.
[c] Endorsement of 8 or more distressing attenuated positive symptoms.

no TLEs ($F = 19.21$, $df = 1, 252$, $p = 0.0002$). Indirect bootstrapping results suggested that stress sensitivity mediated the relation between TLEs and APPS, and when stratifying by gender, the pattern of significant mediation was restricted to females (as indicated by the CIs not including zero for these models, see Table 2). The decrease in the magnitude of TLEs on APPS after incorporating stress sensitivity into each model can be observed in Table 3.

Table 2
Indirect effect[a] of traumatic life experiences (TLEs) on attenuated positive psychotic symptoms (APPS) and distressing APPS status (D-APPS) through stress sensitivity.

		Point estimate	Standard error	Lower CI	Upper CI
Number of attenuated positive psychotic symptoms (APPS) endorsed[b,c]					
Overall model	Any TLE	0.0289	0.0107	0.0096	0.0518
	4+ TLEs	0.0596	0.0107	**0.0315**	**0.0978**
Females	Any TLE	0.0201	0.0105	**0.0022**	**0.0444**
	4+ TLEs	0.0489	0.0189	**0.0182**	**0.0936**
Males	Any TLE	0.0467	0.0282	−0.0062	0.1088
	4+ TLEs	0.0610	0.0376	−0.0080	0.1404
Distressing attenuated positive psychotic symptoms (D-APPS) status					
Overall model	Any TLE	0.2725	0.1197	**0.0666**	**0.5325**
	4+ TLEs	0.5278	0.2054	**0.2173**	**1.0415**
Females	Any TLE	0.1821	0.1243	−0.0449	0.4460
	4+ TLEs	0.4516	0.2308	**0.1232**	**1.0552**
Males	Any TLE	0.3806	0.2580	−0.0094	1.0392
	4+ TLEs	0.5252	0.4723	−0.0139	1.8270

Any TLE = History of any traumatic life event exposure.
4+ TLEs = History of exposure to 4 or more traumatic life events.
Confidence intervals displayed in bold indicate significant mediation.
[a] Mediation tested via the indirect bootstrapping macro (Preacher and Hayes, 2008).
[b] Values reflect log-transformed dependent variable.
[c] Bias-corrected 95% confidence interval; CIs that contain zero are interpreted as not significant.

3.3. Exploratory analyses: distressing attenuated positive psychotic symptom status

The independent, dependent, and mediator variables were significantly associated with one another. Logistic regressions indicated that Any TLE, 4+ TLEs and increases in PSS scores were each associated with significantly increased odds of being classified as D-APPS status. As Table 3 indicates, adding stress sensitivity to the aforementioned logistic regression models significantly reduced the odds of D-APPS status for all TLE models. While the overall model suggested that the association between exposure to TLEs and D-APPS was mediated by stress sensitivity, findings indicated that results were driven by females, specifically those who endorsed 4+ TLEs (as these CIs did not include zero, see Table 2). Exposure to TLEs did not significantly increase the odds of D-APPS status for males; therefore, one criterion of mediation was not met. Similarly, CIs of the mediation results contained zero for males (see Table 2). The magnitude of these mediation relationships can be observed in Table 3.

4. Discussion

To our knowledge, this is the first study to determine that the association between traumatic life events and attenuated positive psychotic symptoms is mediated by increases in stress sensitivity. We found that stress sensitivity also mediated the relation between TLEs and report of 8+ distressing APPS, a threshold which is considered to be more clinically relevant. Mediation was most pronounced for females, as mediation analyses were only significant among females and adding stress sensitivity to the models substantially reduced the magnitude of the relation between TLEs and D-APPS (i.e., from 6.05 to 4.70 for 4+ TLEs and leading to non-significant findings for Any TLEs). The current results are congruent with research that has found independent associations between both TLEs and stress sensitivity and subclinical psychosis (Lataster et al., 2006; Spauwen et al., 2006; Gracie et al., 2007; Collip et al., 2013). Future studies are necessary to determine whether the current findings generalize to clinical high risk, prodromal, and other non-clinical, general population samples.

While the vulnerability–stress model often assumes that liability takes the form of genetic vulnerability, there are multiple possibilities for the origins of altered stress sensitivity among those who experience APPS (Nuechterlein and Dawson, 1984; Mittal et al., 2008; Holtzman et al., 2013). First, stress sensitivity may have a biological basis, as increased concordance rates in subjective stress sensitivity were found between monozygotic twin pairs from the general population who were considered to be at increased risk for psychosis (Lataster et al., 2009). Second, environmental factors associated with risk for psychotic disorders have also been associated with increases in stress sensitivity and/or alterations in brain systems associated with stress responses. Specifically, animal and human models suggest that exposure to stressors early in life may sensitize individuals to later stressors, suggesting that TLEs may increase risk for psychosis through increasing sensitization to future TLEs and stressors (Goel and Bale, 2009; Holtzman et al., 2013). Obstetric complications that have been associated with psychosis outcomes also have been linked to reduced hippocampal volumes, a brain region critical in hypothalamic pituitary adrenal axis regulation (Mittal et al., 2008; Zammit et al., 2009). Collectively, these findings suggest that altered stress sensitivity could potentially precede and/or be a consequence of multiple risk factors for psychosis, which requires a life-course

Table 3
Coefficients and odds ratios for attenuated positive psychotic symptoms (APPS) and distressing APPS status (D-APPS).

	APPS (log transformed)					D-APPS			
	Beta[a]	*B*[a]	Lower CI[b]	Upper CI[b]	*p* Value	OR	Lower CI	Upper CI	*p* Value
Overall model									
Step 1									
Any TLEs	0.128	0.113	0.046	0.179	0.001	2.05	1.05	4.00	0.035
Step 2									
Any TLEs	0.095	0.084	0.019	0.148	0.011	1.78	0.89	3.56	0.103
Stress sensitivity	0.278	0.023	0.017	0.029	<0.0001	1.25	1.17	1.33	<0.0001
Step 1									
4+ TLEs	0.333	0.252	0.163	0.340	<0.0001	5.24	2.50	11.18	<0.0001
Step 2									
4+ TLEs	0.252	0.191	0.103	0.279	<0.0001	4.02	1.83	8.83	0.001
Stress sensitivity	0.301	0.024	0.015	0.033	<0.0001	1.25	1.13	1.38	<0.0001
Females									
Step 1									
Any TLEs	0.152	0.137	0.057	0.216	0.001	2.35	1.03	5.38	0.042
Step 2									
Any TLEs	0.130	0.117	0.039	0.194	0.003	2.08	0.89	4.88	0.093
Stress sensitivity	0.242	0.02	0.013	0.028	<0.0001	1.25	1.15	1.35	<0.0001
Step 1									
4+ TLEs	0.385	0.288	0.185	0.390	<0.0001	6.05	2.42	15.12	0.0001
Step 2									
4+ TLEs	0.319	0.239	0.136	0.342	<0.0001	4.70	1.80	12.29	0.002
Stress sensitivity	0.244	0.021	0.009	0.032	0.001	1.25	1.10	1.42	0.0005
Males									
Step 1									
Any TLEs	0.078	0.067	−0.055	0.190	0.282	1.40	0.44	4.45	0.565
Step 2									
Any TLEs	0.021	0.018	−0.097	0.133	0.759	1.22	0.36	4.06	0.748
Stress sensitivity	0.374	0.031	0.020	0.042	<0.0001	1.24	1.09	1.41	0.001
Step 1									
4+ TLEs	0.208	0.166	−0.016	0.348	0.073	3.18	0.86	11.82	0.084
Step 2									
4+ TLEs	0.115	0.092	−0.078	0.261	0.283	2.53	0.63	10.18	0.191
Stress sensitivity	0.429	0.032	0.016	0.048	<0.0001	1.24	1.04	1.48	0.017

Any TLE = History of any traumatic life event exposure.
4+ TLEs = History of exposure to 4 or more traumatic life events.
[a] Beta (standardized coefficients) and *B* (unstandardized coefficients) reflect the coefficients for regression with the log transformed APS variable as the dependent variable.
[b] Confidence intervals (CIs) for the unstandardized (B) coefficients.

perspective to tease apart the potential genetic and environmental contributing factors.

Our findings support emerging research of differential trajectories in the etiology of psychosis for males and females (Walder et al., 2013). Specifically, the findings from the present study were primarily restricted to females, suggesting that females may represent a particularly vulnerable group when exposed to TLEs, possibly due to increases in stress sensitivity. The differential gender findings seemed most apparent for those exposed to multiple TLEs, which may suggest that gender differences become apparent after repeated exposure to TLEs. While the ORs for 4+ TLEs predicting the likelihood of females endorsing 8+ APPS as distressing dropped substantially from 6.05 to 4.70 after the addition of perceived stress, 4+ TLEs were still independently linked to D-APPS status among females after controlling for perceived stress in the model (see Table 3), which suggests that additional mechanisms beyond perceived stress likely influenced our findings (Fisher et al., 2013; van Winkel et al., 2013). Thus, additional research that assesses multiple mediators in the TLE–APPS model, which incorporates gender differences, is warranted.

A similar differential effect of stress sensitivity across gender has been documented in animal studies, such that male mice have been found to exhibit increased physiological stress sensitivity only during prepubertal periods, while female mice demonstrate increased stress sensitivity independent of age (Romeo et al., 2013). Further, females diagnosed with psychotic disorders and at clinical high risk for psychosis have also been found to have heightened physiological and subjective stress sensitivity (Myin-Germeys et al., 2004; Corcoran et al., 2012). Similarly, a meta-analysis found that males reported significantly more TLEs than females, yet the prevalence rate for PTSD was nearly two times higher in females (Tolin and Foa, 2006). Our stratification results parallel these findings, as the rate of TLEs was similar between genders in our sample, but the manner in which the females reported *reacting* to stressors (i.e. stress sensitivity) was a strong contributing factor for increases in APPS (Myin-Germeys et al., 2004).

While our results for Any and 4+ TLEs exposure were similar, exposure to 4+ TLEs appears to have greater clinical significance for increased risk of psychosis. These findings complement prior dose–response relationships found between the number of TLEs and severity of psychotic symptoms, with one study finding a dose–response association to be uniquely present for females with first episode psychosis (Fisher et al., 2009; Varese et al., 2012). Nevertheless, our findings indicate that the relationship between TLEs and risk of psychosis may be non-linear, as increases in positive symptoms plateaued following 4 TLEs, suggesting that previous interpretations of a dose–response relation between TLEs and psychosis may only hold for lower numbers of TLEs. These findings are consistent with studies that have found threshold effects for number of stressful life events being related to symptom onset or worsening of psychotic symptoms once crossing this threshold, which underscores the importance of examining critical thresholds in future research for the relations between TLEs and the psychosis spectrum (Holtzman et al., 2013).

There are several strengths to highlight in the current study. Our results reinforce findings that the connection between TLEs and

psychosis spans the entire psychosis phenotype of positive symptoms (van Os and Linscott, 2012). Additionally, the nature of our sample was unique in that the sample size was large and participants were non-treatment-seeking, which contrasts with many of the studies investigating the clinical high risk phase of psychosis that have relied on treatment seeking individuals (a sample type that potentially reduces external validity to individuals with incipient psychotic symptomatology who have yet to cross a threshold of severity that might necessitate clinical services) (Fusar-Poli et al., 2013). While there is the possibility that examining an undergraduate population reduces generalizability, our sample was drawn from a university population that is quite large (approximately 38,000 students) and socioeconomically and demographically diverse, making the results more likely to be generalizable to same-aged individuals. Despite the diversity of our sample (e.g., percentage of African Americans is equivalent to the US population), results from the present study are most generalizable to Caucasian females, who comprised the majority of the sample.

An important limitation to consider is the lack of validation of our D-APPS variable in non-clinical populations, and thus, the exploratory nature of these analyses. While substantial research indicates that endorsing symptoms as distressing increases the likelihood of a mental disorder, it is unclear whether participants in the D-APPS group were specifically "at risk" for psychotic disorders (Freeman and Garety, 1999; Garety et al., 2001). The nature of our non-clinical sample limits generalizability to clinical populations and increases the likelihood of false positives above what would be expected in psychosis clinical high risk samples (Cannon et al., 2008). Nonetheless, risk of conversion after one year has been found to be 3.5 times higher in those who experience subthreshold psychotic symptoms in a general, non-help seeking population, suggesting that our results may have relevance to those at risk for psychotic disorders (Kaymaz et al., 2012). Further, although our participants were not recruited as treatment seeking, the D-APPS group was much more likely to endorse seeking or receiving treatment in the past month (although information pertaining to specific treatment type and medication usage were not available), providing additional support that the D-APPS participants may represent a more clinically meaningful group (see Table 1). Conversely, it is possible that a small minority of participants met diagnostic criteria for a psychotic disorder, as the current study did not assess for this. However, the majority of our sample was still within the risk period for psychotic disorders (mean age = 20.5) and our findings were restricted to females, who generally have a later age of onset, increasing the likelihood that many of those in the D-APPS group were still at risk for psychosis (Leung and Chue, 2000; de Girolamo et al., 2012).

Of note is that the D-APPS classification isolated 2% of an undergraduate sample in Loewy et al. (2007), while this criterion isolated 13% of our undergraduate sample. This discrepancy in rates may be predominantly accounted for by differences in demographic characteristics between these undergraduate samples. For example, participants in the original college sample were 38% Asian, 34% Caucasian, and 2% Black while our sample was 58% Caucasian, 14% Asian, and 13% Black (Loewy et al., 2007). Given prior research suggesting increased risk of APPS among Black populations, as well as lower rates of APPS among Asian populations, future research is necessary to determine whether the differences in our sample compared to previous studies contributed to higher rates of APPS in our non-clinical sample (Laurens et al., 2008; Morgan et al., 2009).

Although our findings lend confidence to the significance of stress sensitivity as an explanatory variable in the TLE–psychosis relationship among females, the uneven gender distribution in our sample (29% male, 71% female, a distribution that was similar among the high and low risk groups) potentially limits our ability to interpret the absence of the mediation relation for males. While the number of males was lower than females, there were 192 males in our sample; therefore, it is unlikely that unequal gender distributions completely accounted for our findings, especially since gender differences were consistent when we had the most power to detect findings (i.e., stress sensitivity did not mediate the Any TLE–APPS relationship for males, in which 192 male participants were included). Nevertheless, the unequal gender distribution was a study limitation that should be remedied by future studies of a similar design.

Additional limitations include the retrospective nature of the TLE data and the fact that the study was cross-sectional, the latter of which limits causal inferences and complicates conclusions about the directionality of results. For instance, stress sensitivity may impact the degree to which prior trauma is reported. However, research indicates that trauma reports are not significantly influenced by mood state or general psychopathology in various psychiatric samples (Brewin et al., 1993; Fisher et al., 2011). It is also possible that endorsement of APPS as distressing may be conflated with perceived stress. This possibility is mitigated by our findings that perceived stress mediated the link between TLEs and APPS when the distressing component was absent. Several findings have also discounted the idea that retrospective trauma recall inflates trauma reporting in studies with psychotic samples, instead finding TLE rates among psychotic individuals to be underrepresented, stable over time, and in accordance with corroborating reports of abuse (Cutajar et al., 2010; Fisher et al., 2011). Lastly, we did not control for co-occurring symptomatology, which may have influenced the findings. However, studies have found the TLE–APPS and stress sensitivity–APPS associations to persist despite comorbid psychopathology (Lataster et al., 2010; Collip et al., 2011; Varese et al., 2012). Nevertheless, future studies would benefit from controlling for concurrent symptoms that are linked to psychotic disorders.

Elucidating the potential mechanisms that explain the association between TLEs and psychosis outcomes such as APPS is critical for informing treatment and early intervention strategies. TLEs have also been shown to affect the trajectory of psychosis, indicating a more persistent and increasingly severe clinical course, thus underscoring the importance of understanding the contributors to this relationship (Heins et al., 2011; Wigman et al., 2011). Adapting current treatments to reduce stress sensitivity or emotional dysregulation may prove useful in the treatment of those at risk for psychosis or those experiencing APPS (Pilling et al., 2002; Birchwood and Trower, 2006). Although therapeutic efforts cannot completely control the number of stressors a person experiences, improvement of coping skills and social supports, as well as incorporating techniques used for the treatment of PTSD (e.g., cognitive behavioral therapy) may offer promising treatment avenues. Overall, our results highlight the importance of considering TLEs and stress sensitivity in the assessment of psychosis, especially among females. Our findings also lend further support for the existence of an explanatory mechanism (i.e. individual variations in perceived stress sensitivity) for subclinical psychosis, which has been found to be linked to environmental and genetic risk factors associated with psychosis, and could be a potential target for early intervention and prevention efforts.

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Contributors

Author L. Gibson contributed to the concept of the paper, wrote the first draft of the manuscript and performed the statistical

analyses. Author L. Ellman contributed to all aspects of the study, including designing and writing the study protocol, contributing to the concept of the paper, consulting on statistical analyses and contributing to manuscript writing. Author J. Klugman assisted in statistical analyses and manuscript revisions. Author D. Anglin contributed to the design of the study protocol and manuscript revisions. Authors L. Reeves, A. Fineberg, S. Maxwell and C. Kerns helped with manuscript revisions, data collection, and modifications of study protocol as needed. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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