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Components of schizophrenia liability affect the growth of psychological stress sensitivity following major life events

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ABSTRACT

Background: Some argue that physiological and psychological stress sensitivities contribute causally to schizophrenia. Indeed, evidence shows that those with or at risk for schizophrenia have highly sensitive stress responses. However, it is unclear how psychological stress sensitivity develops. Our aim was to test whether psychological stress sensitization develops longitudinally in association with major life events and components of schizophrenia liability. We expected schizophrenia liability to predict higher psychological stress sensitivity; life events to predict subsequent increases in psychological stress sensitivity; and schizophrenia liability to moderate this relationship.
Methods: In a prospective study, undergraduates ($n = 184$) completed a measure of schizophrenia liability at baseline. Then at 2-month intervals over 6 months, they reported on the occurrence of major life events and completed measures of psychological stress sensitivity.
Results: Latent variable growth modelling showed that stress sensitivity increased following incident life events when controlling for baseline life events. Higher cognitive-perceptual and interpersonal scores predicted higher baseline sensitivity. Higher cognitive-perceptual features predicted larger increases in psychological stress sensitivity following life events whereas greater disorganization reduced growth.
Conclusions: This evidence is consistent with the idea that psychological sensitization is involved in the development of schizophrenia and suggests an important link between positive features of schizophrenia liability and the magnification of psychological stress sensitivity.

1. Introduction

Stress sensitivity is thought to be a key factor in the development of schizophrenia. Those with or at risk for schizophrenia report higher levels of psychological stress reactivity and have blunted physiological stress responses (Brenner et al., 2009; Lataster et al., 2009; Myin-Germeys et al., 2001; Tso et al., 2012). However, it is unclear whether this heightened stress sensitivity is present from birth or whether it develops in response to the environment. Understanding the development of stress sensitivity in the context of schizophrenia liability could extend current early intervention efforts and inform new approaches to treatment.

In the diathesis-stress model (Walker and Diforio, 1997), the behavioral expressions of genetic and biological factors linked to schizophrenia interact with environmental stressors to increase liability for developing the disorder. Change in the hypothalamic-pituitary-adrenal (HPA) axis drives the increased liability through its influence on the regulation of dopamine, a key factor in positive schizophrenia symptoms. It is thought that repeated stressors induce sensitization of the HPA axis. This process is also highlighted in sensitization theory. According to sensitization theory, when an individual at risk for schizophrenia is exposed to repeated environmental stressors, they develop greater stress responses over time (Collip et al., 2008). These changes in stress responses may involve sensitization of the HPA axis, psychological stress responding, or both.

Research evidence offers some support for sensitization theories of schizophrenia. Episodes of schizophrenia and psychosis are associated with major life events, suggesting major stressors can trigger onset (Ventura et al., 1989). Environmental risk factors are linked with schizophrenia liability, suggesting stressors may affect risk (Glaser et al., 2006; Lederbogen et al., 2011). Moreover, in help-seeking populations, experience sampling work shows that stress sensitivity rises immediately following major life events (Rauschenberg et al., 2017). However, other theoretical assumptions remain untested. For example, it is unclear whether stress sensitivity remains elevated following repeated stressors—a key component of the sensitization and diathesis-stress models.

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Biological sensitization differs from psychological sensitization. Whereas groups with high psychological sensitivity often present with blunted cortisol reactivity, the two phenomena are not consistently related (Faresjö et al., 2013; van Eck et al., 1996). Although biological stress sensitization in schizophrenia has received thorough review (e.g., Bradley and Dinan, 2010), psychological sensitization is less understood. High psychological stress sensitivity is consistently associated with schizophrenia symptoms (Norman and Malla, 1994) and schizophrenia liability (Grattan et al., 2015). In cross-sectional studies, psychological stress sensitivity mediates the relationships of life events and some environmental risk exposures with schizophrenia symptoms in help-seeking and non-help-seeking populations (Gibson et al., 2014; Grattan et al., 2015; Laloyaux et al., 2016). Over time, liability for schizophrenia increases with psychological stress sensitivity (Lincoln et al., 2015) and in at-risk help-seekers, stress sensitivity appears to decrease over time (DeVylder et al., 2012). This longitudinal decrease in sensitivity may reflect on-going treatment effects or symptom remission.

If sensitization is a central process in the development of schizophrenia, increasing psychological sensitization or reactivity will occur prior to disorder onset (van der Steen et al., 2017). This should be particularly evident among non-help-seekers reporting subclinical expressions of schizophrenia. Therefore, our aims were to examine changes in psychological stress sensitivity following major life stressors and whether those reporting liability for schizophrenia experience greater changes in sensitivity. We measured major life events and psychological stress sensitivity prospectively, at four time points each separated by 2 months. We hypothesized that high psychological sensitivity to stress would be associated with schizophrenia liability, that negative life events would predict increases in psychological sensitivity to stress, and that higher schizophrenia liability scores will predict larger increases in psychological sensitivity to stress following life events.

2. Method

2.1. Participants

Undergraduate students enrolled in introductory psychology courses ($n = 210$, $M = 20.7$ years, $SD = 4.1$, 76.2% female) were recruited to participate in the study. Participants primarily identified as NZ European (66.7%), other European (8.1%), Māori (4.8%), or Indian (4.8%). There were no other inclusion or exclusion criteria.

At the end of the study, participants could learn additional information about the purpose, design, and methods of the study, and then earn extra credit based on assessment of this learning. The University of Otago Human Ethics Committee (Health) reviewed and approved the study. After receiving full information about the study, participants provided written informed consent.

2.2. Measures

Two interviews were used to assess exposure to major life events: a 10-item baseline life events interview (LEI) and a 27-item follow-up (interval) LEI. Both are semi-structured interviews developed from the Life Events List (Cohen et al., 1991), which was modified to include items appropriate to an undergraduate population in New Zealand. The baseline LEI includes items addressing lifetime exposure to relocation, severe financial hardship, unwanted sexual experience, physical mistreatment, pregnancy (including termination and miscarriage), loss of a home, parental divorce or separation, bereavement, arrest, and hospitalization for serious health problems. The interval LEI includes these items as well as items addressing changes and infidelity in intimate relationships, being victim of assault or mugging or property offending, loss of employment, significant educational setbacks, and other major stressors. After identifying an event, respondents rate the pleasantness of each event (5 = *pleasant*, 0 = *neutrali* and −5 = *unpleasant*). The key dependent measures were the numbers of unpleasant events (pleasantness <0) that respondents identified in their lifetime (at baseline) and in the interval since the previous assessment (follow-up). Sensitivity analyses were undertaken using four cuts from pleasantness <−1 to <−4.

The Acute Hassles Scale (AHS) was used to measure psychological stress sensitivity. The AHS contains 19 items that describe non-chronic, non-illness-related daily hassles (e.g., planning or preparing meals, transportation problems, need for new clothes, having to wait or wasting time, inconsiderate people, the weather, misplacing or losing things). Respondents rate how much they have been affected by each hassle in the past 2 weeks (0 = *not at all*, 1 = *somewhat severely*, 2 = *moderately severely*, and 3 = *extremely severely*). The AHS was developed by Grattan et al. (2015) using items from the Kanner Hassles Scale (Kanner et al., 1981) and the Undergraduate Stress Questionnaire (Crandall et al., 1992) that describe non-chronic and non-illness-related minor hassles. An independent sample of undergraduates ($n = 88$; 84% female; age $M = 21.1$ years, $SD = 3.0$) rated stressors described in an initial pool of 62 such items as *acute* or *chronic* in nature, terms that were not further defined (Grattan, 2016). Items were retained for the AHS if they were rated as *acute* by ≥65% of those undergraduates. AHS ratings from a second independent undergraduate sample ($n = 216$; 75% female; age $M = 20.0$ years, $SD = 2.1$) showed that the AHS has high internal consistency ($\alpha = 0.85$), suggesting the items tap an internally consistent response style and not the objective experience of unrelated daily hassles (Ruzibiza et al., 2018). The key dependent measure from the AHS was the sum of ratings.

Schizophrenia liability was assessed with the Likert version of the Schizotypal Personality Questionnaire (SPQ; Raine, 1991; Wuthrich and Bates, 2005). The SPQ contains 74 items that respondents rate on a 5-point agreement scale (0 = *strongly disagree* to 4 = *strongly agree*). The SPQ comprises nine subscales, reflecting the nine features of *DSM-III-R* schizotypal personality disorder. Subscale scores are summed to yield cognitive-perceptual (positive features), interpersonal (negative features), and disorganization factor scores (Raine et al., 1994). The SPQ is widely used as a measure of schizotypy and schizophrenia liability (Fonseca-Pedrero et al., 2018). Compared to the dichotomous response format of the original SPQ, the Likert response format better reflects the quantitative variation in the expression the phenotype (Strauss, 1969). The Likert version subscales are internally consistent ($\alpha = 0.77$ to 0.90), correlate with interviewer ratings, and are stable over time (Wuthrich and Bates, 2005).

Inattentive responding was assessed using three infrequency items dispersed in the AHS. These items referred to stress due to being unable to keep a birdbath full, cleaning ceilings, and poor canned vegetable selection in the supermarket.

2.3. Procedure

Participants completed 4 assessments spaced approximately 2 months apart. The baseline assessment (Time 0, T0) took place at the start of the academic year with follow-up assessments at the end of the first semester (T1; $M = 53.8$ days after T0, $SD = 6.0$), the start of the second semester (T2; $M = 71.0$ days after T1, $SD = 5.0$), and the end of the second semester (T3; $M = 63.0$ days after T2, $SD = 6.1$). The mean total follow-up period from T0 to T3 was 187.5 days ($SD = 8.9$). At T0 participants provided demographic data and completed the SPQ, AHS, and the baseline (lifetime) LEI. At T1, T2, and T3 participants completed the AHS and the interval LEI (i.e., for events since the previous assessment).

2.4. Data analyses

Data were excluded from participants with missing ratings (>3 ratings on the SPQ or AHS) or with total inattention scores (across T0 to T3) over 2. Bivariate correlations were examined using bootstrapped confidence intervals (1000 replications) with Pearson's correlation coefficient. Hypotheses were tested using latent variable growth modelling in Mplus 8 (Muthén and Muthén, 2017), as follows: In Step 1, we tested whether negative life events predicted increased stress sensitivity by modelling fixed growth factors (intercepts and slopes) for stress sensitivity in the context of time-varying (incident) and time-invariant (baseline lifetime) negative life events (Fig. S1). Sex and age were entered as time-invariant effects. In Step 2, we tested the association of schizophrenia liability with stress sensitivity by regressing fixed growth factors onto SPQ factor scales. That is, in Steps 1 and 2, growth parameters for stress sensitivity are fixed and individual differences in growth are influenced by incident negative life events as well as time-invariant characteristics such as age and SPQ scores. In Step 3, we tested whether schizophrenia liability moderated the effect of life events on stress sensitivity by adding random slopes for SPQ factor scores (Fig. S1). In contrast to Steps 1 and 2, here the relationship of AHS ratings with life events is freed to vary as a function of time-invariant characteristics of people. Subsequent steps addressed whether AHS residuals were correlated (Step 4) and whether findings were specific to schizophrenia liability by adding DASS Anxiety as a covariate (Step 5).

Analyses were conducted using maximum likelihood estimation with and without integration and with bias-corrected bootstrapped confidence intervals (2000 replications). Model fit was assessed using the Akaike, Bayesian, and sample-size adjusted Bayesian information criteria (AIC, BIC, ssBIC, respectively). The root mean square error of approximation (RMSEA), comparative fit index (CFI), Tucker-Lewis index (TLI), and standardized root mean square residual (SRMR) were obtained for Steps 1 and 2 but were not available for models with random effects. Good model fit is suggested when RMSEA $\leq$0.06, CFI $\geq$ 0.95, TLI $\geq$ 0.95, and SRMR $\leq$0.08 (Hu and Bentler, 1999). The significance of differences in BIC coefficients was tested using posterior odds and estimated t, as described by Raftery (1995).

3. Results

Data from 8 participants were excluded: 7 due to inattentive responding and 1 due to missing SPQ item ratings. Nineteen participants did not complete assessments at all time points, leaving an analysis sample of $n = 184$. The 19 non-completers did not differ from completers in respect of sex but were more likely to be New Zealand European and were marginally younger than non-completers (Table 1). Compared to completers, non-completers had higher SPQ Cognitive-perceptual and AHS scores at baseline but did not differ on SPQ Interpersonal and Disorganization scores or on DASS Anxiety.

Positive skew affected AHS scores (skewness = 0.53 to 1.06, all $p < .001$), negative life events (skewness = 0.97 to 1.38, all $p < .001$), and DASS Anxiety scores (skewness = 1.33, $p < .001$). Therefore, bias-corrected bootstrapped confidence intervals were used to evaluate significance.

3.1. Linear growth of stress sensitivity

Bivariate correlation coefficients are shown in Table S1. In the first step of growth modelling, AHS scores at T1 to T3 were regressed on incident negative life events (i.e., reported at T1 to T3), with baseline life events entered as a predictor of intercept and slope growth factors. Table 2 shows model fit statistics and Table 3 the shift in AHS scores, in *SD* units, for each additional life event. Stress sensitivity increased with a greater number of negative life events. Life events at baseline predicted a higher starting point for AHS growth but did not affect the slope of the growth. Incident life events also predicted higher AHS scores for the corresponding time point. Age was associated with lower stress sensitivity ($\beta = -0.07$, $p < .01$) and females reported higher stress sensitivity at baseline ($\beta = 0.57$, $p < .01$) but a steeper decline in stress sensitivity across time ($\beta = -0.73$, $p < .05$). As would be expected with an incompletely specified model (Muthén, 2004), some model fit indices fell short of good-fit thresholds (Table 2).

Model fit improved (and surpassed good-fit thresholds) when SPQ factor scores were added as time-invariant predictors at Step 2 (Table 2). At Step 2, the effect of baseline life events on the intercept growth factor was diminished ($0.05 < p < .10$; Table 3) but strong evidence remained that incident life events predicted higher AHS scores across follow-up (Table 3). Schizophrenia liability predicted stress sensitivity. Cognitive-perceptual and interpersonal components of schizophrenia liability were associated with higher baseline stress sensitivity but not growth slopes (Table 4). The fixed effects of the SPQ Disorganization score were not significant.

At Step 3, AIC and ssaBIC improved when random slopes were included in the model, although the BIC deteriorated somewhat

Table 1
Characteristics of completers ($n = 184$) and non-completers ($n = 19$).

Variable	Completers		Non-completers			χ^2/t
	M (*n*)	*SD* (%)	*M* (*n*)	*SD* (%)	*n*	
Females	(42)	(22.3)	(7)	(36.8)	19	1.84
NZ European	(130)	(71.0)	(8)	(42.1)	19	6.66**
Age (years)	20.51	3.90	22.42	6.10	19	1.92†
DASS Anxiety (T0)	8.99	8.25	11.58	10.40	19	1.27
SPQ-CP (T0)	38.40	19.62	49.67	21.56	18	2.31*
SPQ-I (T0)	45.02	21.61	52.22	22.19	18	1.35
SPQ-D (T0)	23.80	12.64	27.61	9.83	18	1.24
NLE						
T0	2.91	2.13	2.95	1.84	19	0.08
T1	1.76	1.68	2.50	2.68	16	1.59
T2	1.41	1.50	2.00	0.00	3	–
T3	1.26	1.41	1.00	–	1	–
AHS						
T0	13.45	6.85	17.39	7.83	18	2.30*
T1	12.97	7.43	15.81	5.81	16	1.49
T2	11.83	7.15	5.33	1.53	3	–
T3	11.21	7.42	8.00	–	1	–

Note. DASS = Depression, Anxiety, Stress Scales; SPQ = Schizotypal Personality Questionnaire; SPQ-CP = Cognitive-perceptual factor score; SPQ-I = Interpersonal factor score; SPQ-D = Disorganization factor score; NLE = Negative Life Events; AHS = Acute Hassles Scale; T0 to T3 = Time 0 (baseline) to Time 3, respectively.
† $p < .10$.
* $p < .05$.
** $p < .01$.

Table 2
Model fit statistics.

Fit statistic	Step 1	Step 2	Step 3	Step 4	Step 5
AIC	4522.509	4490.896	4485.782	4482.706	**4481.850**
BIC	4580.378	4568.054	4569.370	**4559.865**	4565.438
Posterior odds *t*	–	4.19***	2.56*	3.84***	3.29**
ssaBIC	4523.368	4492.040	4487.022	**4483.851**	4483.090
RMSEA	0.077	0.038	–	–	–
CFI	0.956	0.987	–	–	–
TLI	0.935	0.978	–	–	–
SRMR	0.128	0.076	–	–	–

Note. AIC = Akaike information criterion; BIC = Bayesian information criterion; ssaBIC = sample-size adjusted BIC; RMSEA = root mean square error of approximation; CFI = comparative fit index; TLI = Tucker-Lewis index; SRMR = standardized root mean square residual. The posterior odds *t*-value is a test of the significance of the difference between BIC values for the indicated step with the previous step.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

Table 3
Standardized beta coefficients for effects of life events on growth in stress sensitivity.

AHS outcome	Negative life events	Step 1 β	Step 2 β
Growth intercept	Time 0	0.12**	0.06†
Growth slope	Time 0	0.04	0.08
Time 1 AHS	Time 1	0.12**	0.12**
Time 2 AHS	Time 2	0.11**	0.11**
Time 3 AHS	Time 3	0.16**	0.16**

Note. AHS = Acute Hassles Scale total score. Coefficients are the shift in the standardized outcome for each additional negative life event. Step 1: AHS total regressed onto number of negative life events. Step 2: SPQ factor scores added as time invariant effects. Sex and age were included as covariates in all analyses. Statistical significance based on bias-corrected bootstrapped 90%, 95%, and 99% confidence intervals.
† $p < .10$.
** $p < .01$.

($p = .011$; Table 2). Nevertheless, schizophrenia liability moderated the influence of life events on stress sensitivity (Table 4): Higher SPQ Cognitive-perceptual factor scores predicted greater influence of negative life events on AHS ratings whereas higher SPQ Disorganization factor scores predicted a lesser influence of negative life events on AHS ratings. The relationships of SPQ factor scores with fixed growth factors were unchanged from Step 2 (Table 4).

At Step 4, although there was no evidence of autocorrelation across residuals ($r = -0.02$, $p = .87$), modelling autocorrelation led to improved model fit relative to Step 3 (Table 2) and Step 2 (estimated $t = 3.66$, $p < .001$). The fixed and random effects of SPQ factor scores (Table 4) remained the same as at Step 3 except for a small reduction in the effect of cognitive-perceptual features on the random slope (here, the 95% bootstrapped confidence interval for the unstandardized beta coefficient was −0.001 to 0.042, compared to 0.000 to 0.042 at Step 3). Model fit deteriorated significantly with the addition of DASS Anxiety as a fixed effect at Step 5 (Table 2). DASS Anxiety did not predict baseline or growth in stress sensitivity but its inclusion in the model reduced evidence of an influence of interpersonal features on baseline stress sensitivity (Table 4).

3.2. Sensitivity analyses

The robustness of findings was tested by examining the effects of using the four available, more stringent cuts for classifying life events as negative (i.e., from <−1 to <−4). These analyses were undertaken using the Step 4 model, which was the best-obtained model. The effects of schizophrenia liability components on fixed growth factors were unchanged regardless of the cut (Table S2). In contrast, cuts <−2 and ≤−3 yielded stronger evidence that schizophrenia liability components moderated the effects of negative life events on stress sensitivity. Although the magnitude of the unstandardized coefficients for cognitive-perceptual features did not diminish at the most extreme cut (<−4), error variance increased, reducing the significance of the effect (Fig. 1).

Table 4
Standardized beta coefficients for effects of SPQ components on linear growth in stress sensitivity.

SPQ factor score	Step 2 β	Step 3 β	Step 4 β	Step 5 β
Fixed intercepts				
Cognitive-perceptual	0.32**	0.30*	0.30**	0.28**
Interpersonal	0.18*	0.18*	0.18*	0.14
Disorganized	0.09	0.10	0.10	0.10
Fixed slopes				
Cognitive-perceptual	−0.16	−0.09	−0.09	−0.12
Interpersonal	−0.01	−0.05	−0.05	−0.15
Disorganized	−0.18	−0.21	−0.20	−0.19
Random slopes				
Cognitive-perceptual		0.57*	0.54†	0.53†
Interpersonal		−0.23	−0.22	−0.22
Disorganized		−0.56*	−0.52*	−0.51*

Note. SPQ = Schizotypal Personality Questionnaire. Step 2: AHS total regressed onto number of negative life events with SPQ factor scores as time invariant effects. Step 3: As with Step 2 with the addition of random slopes for SPQ factor scores. Step 4: Step 3 with autocorrelation among residuals. Step 5: Anxiety added to Step 4 as a fixed effect. Sex and age were included as covariates in all analyses. Statistical significance based on bias-corrected bootstrapped 90%, 95%, and 99% confidence intervals.
† $p < .10$.
* $p < .05$.
** $p < .01$.

4. Discussion

Psychological stress sensitivity was significantly impacted by the experience of negative life events. Lifetime history of negative life events predicted higher stress sensitivity at baseline and at the three time-points across an academic year. The experience of incident negative life events during the follow-up periods predicted higher ratings of stress sensitivity above and beyond of the influence of lifetime negative life events reported at baseline.

Components of schizophrenia liability affected the impact of negative life events on growth in psychological stress sensitivity. Cognitive-perceptual features predicted a greater influence of negative life events on stress sensitivity, particularly with more negative life events. Disorganized features appeared to have the opposite effect, mitigating the negative impact of events on stress sensitivity. These random effects occurred in the context of two fixed effects of schizophrenia liability components: Cognitive-perceptual and interpersonal features of schizophrenia liability were associated with higher stress sensitivity at baseline. In contrast, disorganized features did not predict stress sensitivity. There were no fixed effects of schizophrenia liability on change in stress sensitivity across time. That is, the influence of schizophrenia liability components on growth in stress sensitivity only occurred via the influence of negative life events on stress sensitivity. The contributions of interpersonal features of schizophrenia liability diminished when anxiety was included as a fixed effect, albeit yielding a model that did not fit the data as well as one without anxiety.

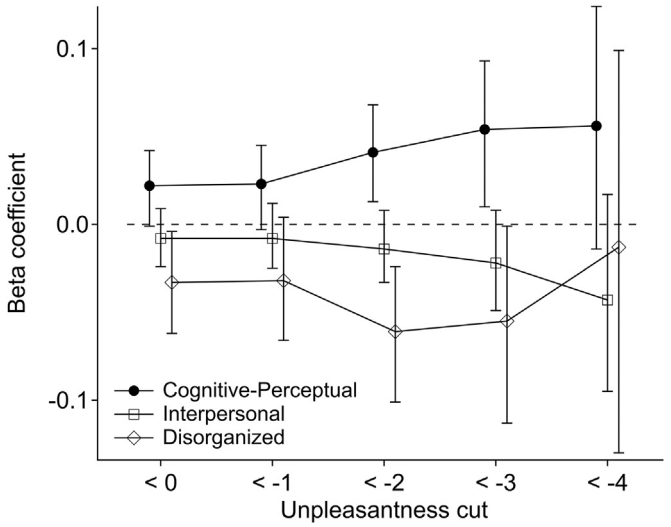

Fig. 1. Unstandardized beta coefficients for the effects of Schizotypal Personality Questionnaire factor scores on the relationship between negative life events and stress sensitivity, for increasingly restrictive unpleasantness cuts, which were used to classify life-events as negative. Event pleasantness was rated on the scale, −5 = *unpleasant*, 0 = *neutral*, and 5 = *pleasant*. Error bars represent 95% bias-corrected bootstrapped confidence intervals, with zero (no effect) as the dashed horizontal line.

These findings extend the characterization of schizophrenia-related stress sensitivity. Previous literature has indicated that minor stressors occurring throughout the day can increase emotional reactivity (Myin-Germeys et al., 2003), liability for schizophrenia is greater where psychological stress sensitivity is higher (Lincoln et al., 2015), and psychological stress sensitivity mediates the relationships of life events and environmental risk exposures with subclinical expressions of schizophrenia (Gibson et al., 2014; Grattan et al., 2015). Whereas it is well established that stressors can impact on-going biological sensitivity to stress (Miller et al., 2007; Walker and Diforio, 1997), a corresponding effect in psychological stress sensitivity has not previously been studied prospectively.

Our findings are consistent with the stress-sensitization (Collip et al., 2008) and diathesis-stress models of schizophrenia (Walker and Diforio, 1997). In respect of stress sensitization, baseline and incident life events predicted greater stress sensitivity over time. The influence of baseline events diminished when the background influence of schizophrenia liability was incorporated into fixed effect models of sensitivity, suggesting some of the influence of baseline life events on stress sensitivity are moderated by schizophrenia liability. Incident life events increased sensitivity beyond the influence of baseline life events, suggesting stressors change future responsiveness to stressors (Collip et al., 2008). However, in combination with subclinical positive features of schizophrenia, this effect is increased in a manner consistent with sensitization (Walker and Diforio, 1997).

Unexpectedly, disorganized features of schizophrenia liability appeared to have a protective function that contrasted with the effect of positive features. Although this protective effect was not robust, if real, a protective effect of disorganization may reflect a general limitation in the self-report measurement of disorganized behavior and speech. For example, an easy-going disposition may contribute to variance in SPQ disorganization scores if the associated behavior is construed as odd. Along similar lines, high levels of goal-focus, routine-dependence, and problem orientation are often interpreted as signs of resilience but when combined with stress sensitivity, these predict increased expression of positive features of schizophrenia liability (Ruzibiza et al., 2018). Notably, compared to positive features of schizophrenia liability, disorganization is a poorer predictor of schizophrenia. For example, past studies have found that cognitive-perceptual scores predict biological vulnerability for schizophrenia (higher scores for siblings and children of those with schizophrenia compared to parents of those with schizophrenia) whereas disorganization scores do not (Vollema et al., 2002). Similarly, cognitive-perceptual scores predict a family history of schizophrenia whereas disorganization scores do not (Yaralian et al., 2000).

Several aspects of our study may affect interpretation of the findings. First, the findings may reflect qualities of the sampling population. Compared to the general population, undergraduates are relatively high functioning and may be better equipped to cope with stressors (Parker et al., 2004), express less extreme schizotypal traits or other psychopathology (Meehl, 1964; Newman et al., 1998), or both. The sampling population included a high proportion of females, in contrast to the population affected by schizophrenia. A more representative sample may have changed the results. However, sex was included in analyses as a fixed effect to mitigate this. In addition, we would anticipate these factors to have diminished observed effects; that given females and undergraduates are less at risk for early development of psychosis, in a sample that is more representative of the general population, stronger effects would occur.

Second, non-completion was associated with ethnic minority status, high cognitive-perceptual SPQ scores, and higher stress sensitivity. Given this, if non-completers were to have completed participation, the observed effects would be unlikely to have diminished. Third, the temporal resolution of the study was limited. Significant fluctuations in stress sensitivity could have occurred in the 2-month intervals between assessments. Additionally, we did not consider the temporal proximity of life-events to the assessment interval for stress sensitivity nor distinguish the occurrence vs. non-occurrence of daily hassles. For the latter, we assumed participants would differentiate hassles with no effects from those with effects. Finally, the level of evidence obtained for some effects—particularly the effect of cognitive-perceptual component on the relationship between negative life events and stress sensitivity—was modest. A larger sample and restricting focus to those more significant life events may have provided a more robust test of these effects.

With these factors in mind, the results indicate that major life stressors can result in increases in psychological stress sensitivity across a period of 6 months, and more so for those expressing cognitive-perceptual features of schizophrenia liability. Critically, this is among the first longitudinal support for the sensitization hypothesis (Collip et al., 2008; Tessner et al., 2011). The longitudinal nature of the study adds strength to previous cross-sectional findings in support of the sensitization hypothesis (Gibson et al., 2014), and experience-sampling findings that stressors result in immediate increases in sensitivity (Rauschenberg et al., 2017).

Future research should replicate and address the generalizability of these findings. Key questions concern the linkage between changes in biological and psychological sensitivities, and the relationship of growth in sensitivity with morbidity outcomes. For example, the measurement of growth in sensitivity over adolescence and early adulthood would inform understanding of whether growth distinguishes those who go on to develop schizophrenia from those who do not develop clinically significant symptoms. This generalizability is important given psychological sensitization may also have implications for a neurobiological perspective of schizophrenia. If those at risk become psychologically more sensitive, as the findings indicate, we speculate this may raise the risk for the negative impacts of chronic stressors, including aspects of dopaminergic dysfunction, hippocampal atrophy, and epigenetic changes linked to schizophrenia symptomatology (Gill and Grace, 2013; Sabbagh et al., 2014).

Contributors

REG conceived the study, designed the study protocols, and assessed participants. RJL provided consultation on the study conception, design, and execution. REG and RJL completed the analyses and wrote the manuscript. Both authors contributed to and have approved the final manuscript.

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Declaration of competing interest

All authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.07.056.

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