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Impact of lifetime stressor exposure on neuroenergetics in schizophrenia spectrum disorders

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ABSTRACT

N-acetylasparate and lactate are two prominent brain metabolites closely related to mitochondrial functioning. Prior research revealing lower levels of NAA and higher levels of lactate in the cerebral cortex of patients with schizophrenia suggest possible abnormalities in the energy supply pathway necessary for brain function. Given that stress and adversity are a strong risk factor for a variety of mental health problems, including psychotic disorders, we investigated the hypothesis that stress contributes to abnormal neuroenergetics in patients with schizophrenia. To test this hypothesis, we used the Stress and Adversity Inventory (STRAIN) to comprehensively assess the lifetime stressor exposure profiles of 35 patients with schizophrenia spectrum disorders and 33 healthy controls who were also assessed with proton magnetic resonance spectroscopy at the anterior cingulate cortex using 3 Tesla scanner. Consistent with the hypothesis, greater lifetime stressor exposure was significantly associated with lower levels of *N*-acetylasparate ($\beta = -0.36$, $p = .005$) and higher levels of lactate ($\beta = 0.43$, $p = .001$). Moreover, these results were driven by patients, as these associations were significant for the patient but not control group. Though preliminary, these findings suggest a possible role for stress processes in the pathophysiology of abnormal neuroenergetics in schizophrenia.

1. Introduction

Life stressors, such as interpersonal difficulties and childhood trauma, are a significant risk factor for a wide variety of psychopathologies, including psychosis (Monroe and Slavich, 2016; Slavich, 2016; van Nierop et al., 2015). Stressor exposure at nearly any point in development can increase the risk for schizophrenia. Indeed, maternal exposure to stressful life events in pregnancy (van Os and Selten, 1998; Khashan et al., 2008) and adversity in early childhood (Varese et al., 2012) increase the risk of developing schizophrenia. Likewise, stressors in adolescence and adulthood can precipitate the onset or relapse of psychosis (Beards et al., 2013; Docherty et al., 2009).

The mechanisms by which life stressors contribute to neurobiological changes in psychotic disorders remain to be fully elucidated. One potential pathway involves the effects of stress on neuroenergetics. A critical response to stress-induced glucocorticoids and catecholamines is energy mobilization, accomplished through increased mitochondrial activity. However, prolonged exposure to these stress-induced mediators may impair the efficacy of mitochondrial enzymes as well as increase oxidative stress that could cause longer-term damage (Manoli et al., 2007; Mitsui et al., 2002). Evidence from animal models suggests that stressor exposure during early development can impact mitochondrial enzyme functioning even in adulthood (Krolow et al., 2012; Ridout et al., 2020; Ruigrok et al., 2021). Although the role of stress in schizophrenia is well-recognized and several recent reviews have focused on mitochondrial dysfunction in schizophrenia (Whitehurst and Howes, 2022; Roberts, 2021), we are not aware of direct clinical evidence linking stressor exposure to bioenergetic dysfunction in the brain in schizophrenia. Based on the research described above, however, we hypothesize that greater lifetime stressor exposure is associated with markers of abnormal cerebral bioenergetics in patients with schizophrenia.

The brain is an intense consumer of glucose due in considerable part to the cost of maintaining ion gradients for excitatory neurotransmission (Rothman et al., 2003). However, the brain contains only a limited glycogen reserve. Glucose imported from the blood and oxidized

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through the tricarboxylic acid cycle provides most of the energy necessary for brain activity under normal conditions; in conditions in which glucose supply may be limited, though, other metabolites such as lactate can be used (Pellerin et al., 1998). As the brain does not import cholesterol from the periphery, de novo synthesis of cholesterol for myelin sheath represents another major energetic demand in brain tissue (Dietschy, 2009); as a possible means of sparing glucose, acetyl groups from ketone bodies can be incorporated into *N*-acetylaspartate (NAA) and stored as a reserve for production of myelin lipids (Lopes-Cardozo et al., 1984; Chakraborty et al., 2001). Both the tricarboxylic acid cycle and NAA synthetic pathway are dependent on mitochondrial functioning. Not all the key substrates in these energy pathways can be noninvasively measured in patients, but metabolites including NAA and lactate can be readily assessed using proton magnetic resonance spectroscopy (MRS).

Prior studies using MRS have demonstrated lower cortical levels of NAA and higher levels of lactate in schizophrenia, including in the anterior cingulate cortex (Bertolino et al., 1998; Reid et al., 2019; Wang et al., 2019; Rowland et al., 2016a; Rowland et al., 2016b). As NAA is synthesized through a mitochondrial-dependent pathway, and lactate is used by the brain as a source of energy in conditions of insufficient oxidative glycolysis, these findings indicate abnormalities in neuroenergetics in schizophrenia. Further evidence of neuroenergetic abnormality comes from findings of decreased creatine kinase activity in the brain of patients with first episode psychosis; creatine kinase is coupled with mitochondrial oxidative phosphorylation to produce ATP, and reduced activity further suggests an impairment of mitochondrial activity that forces a greater reliance on glycolysis (Yuksel et al., 2021). Consistent with the role of NAA as a reservoir of acetate for myelin lipid synthesis, levels of NAA are strongly correlated with tract-averaged fractional anisotropy (FA) as measured with diffusion tensor imaging (Chiappelli et al., 2015; Wijtenburg et al., 2013; Assaf et al., 2005; Tang et al., 2007). Decreased FA in turn is strongly associated with cognitive impairments (Kochunov et al., 2017). Increased lactate levels have been associated with cognitive impairments as well (Rowland et al., 2016b). Identification of the mechanisms leading to these neuroenergetic abnormalities may therefore have implications for treatment of cognitive deficits.

Another challenge in this line of research is determining the optimal instrument for assessing stressor exposure. Many available instruments concentrate on childhood trauma or exposure to recent stressors but few assess them systematically in one platform. To address this measurement issue, we use the Stress and Adversity Inventory for Adults (Adult STRAIN), which was developed as a comprehensive assessment of stressor exposure over the entire life course (Shields et al., 2017). The STRAIN is a system for assessing a wide variety of acute and chronic stressors, as well as their severity, frequency, exposure timing, and duration. The STRAIN has been shown to have excellent validity and predictive value for several stress-related health outcomes (e.g., Goldfarb et al., 2017; Shields et al., 2017; Slavich and Shields, 2018).

In this study, we examine how cumulative life stressors, as measured using the STRAIN, related to neurochemical biomarkers as measured by MRS, in order to test the hypothesis that greater stressor exposure may contribute to decreased NAA and increased lactate in the brain in schizophrenia.

2. Methods

2.1. Participants

People with schizophrenia spectrum disorders (including schizophrenia, schizoaffective disorder, and schizophreniform disorder, $n = 35$) and healthy controls ($n = 33$) participated in the study. Patients were recruited from the outpatient clinics of the Maryland Psychiatric Research Center and several nearby mental health clinics. Healthy control participants were recruited through local media advertisements. Structured Clinical Interview for DSM-5 was used to confirm or exclude psychiatric diagnoses. Exclusion criteria included a history of neurological conditions, head trauma with cognitive sequelae, and active and uncontrolled medical conditions. Participants with substance abuse and dependence other than nicotine or cannabis in the 6 months prior to study were excluded. Chlorpromazine dose equivalent (CPZ) was calculated for each patient's medication regimen at the time of the study (Woods, 2003). Except for 3 medication-free participants, all patients were on antipsychotic medications, including 7 taking typical antipsychotics, 20 taking atypical (including 8 taking clozapine), and 5 taking a combination of typical and atypical antipsychotics. The mean CPZ was 457 mg, with a range of 0–2033 mg daily.

2.2. Clinical measures

Overall psychiatric symptoms and negative symptoms were rated by clinicians trained to ensure high inter-rater reliability, using the Brief Psychiatric Rating Scale (Overall and Gorham, 1962) and Brief Negative Symptom Scale (BNSS - Kirkpatrick et al., 2011), respectively. To assess cognitive functioning, we focused on processing speed as measured with the digit symbol coding task from the Wechsler Adult Intelligence Scale-3 (Wechsler, 1997) and working memory as measured with the Digit Sequencing task (Keefe et al., 2008), as these are two of the cognitive functions most profoundly affected in schizophrenia (Dickinson et al., 2008).

2.3. Stress assessments

The Stress and Adversity Inventory (STRAIN) is an online system that provides a reliable and effective way to assess cumulative stressor exposure over the life course (http://www.uclastresslab.org/STRAIN, http://www.strainsetup.com/). The STRAIN assesses a total of 55 major lifetime stressors, with additional measures of the severity, frequency, exposure timing, and duration of each stressor endorsed. The scoring of the STRAIN includes the total count of all stressors experienced and the severity of those stressors. For this study, the total count of stressors was used as the primary measure, with secondary analyses using the count of stressors in childhood, adulthood, and over the past 6 months (i.e., recent). STRAIN data were unavailable for 5 controls and 7 patients. Secondary analyses also used the Childhood Trauma Questionnaire - Short Form (CTQ) to assess experiences of physical, emotional, and sexual abuse, and neglect during childhood (Bernstein et al., 2003), and the Perceived Stress Scale (PSS) to measure subjective levels of stress over the past month (Cohen et al., 1983), to compare associations of neurochemistry to STRAIN with more commonly used measures of trauma and recent perceived stress.

2.4. Magnetic resonance spectroscopy

Scanning was completed using a 3 T Prisma scanner (Siemens) equipped with 64-channel head coil and high-performance gradient system. Spectra were acquired from a 40 × 30 × 20 mm voxel centered on the anterior cingulate cortex using PRESS (TR/TE = 2000/30-ms), 2500 Hz spectral width, 2048 complex points, 16-step phase cycle, NEX = 128 (see Fig. 1 for voxel placement and representative spectrum). A water suppressed spectra (NEX = 16) was acquired and used for water-scaling, eddy current correction and quantification. LCModel (http://s-provencher.com/lcmodel.shtml) was used for quantification using a simulated basis set of 19 metabolites. Metabolite levels were referenced to water and are reported in institutional units. Spectra with FWHM >0.1 ppm and S/N < 10 reported by LCModel were excluded from analyses. Only metabolites with CRLB %SD <20 % were included in further statistical analyses; as an exception to this we used %SD ≤ 30 % for lactate, as the 20 % threshold may be too conservative for low-concentration metabolites (Kreis, 2016; Soeiro-de-Souza et al., 2016; Rowland et al., 2016a, 2016b). Using this threshold, lactate data from 8

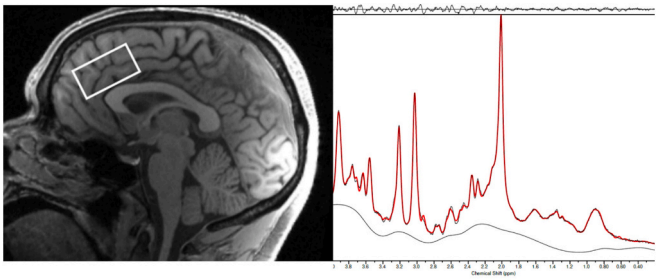

Fig. 1. Voxel placement in the anterior cingulate cortex for MRS (left); representative spectrum and LCModel metabolite fit (red), with residual shown in gray above (right). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

participants (4 patients, 4 controls) were excluded from analyses. Proportion of the cerebrospinal fluid (CSF) within the spectroscopic voxel was calculated based on segmentation of MP-RAGE images. Metabolite values were corrected by dividing raw values by (1-CSF fraction) (Quadrelli et al., 2016).

2.5. Statistics

Group differences on key variables were tested using analysis of covariance (ANCOVA) with age and sex as covariates. Linear regression analyses were used to determine associations between stress measures and neurochemistry, with age and sex as covariates. Benjamini-Hochberg corrections were used to adjust for multiple comparisons within each set of analyses; reported *p*-values are unadjusted. All tests were two-tailed.

3. Results

3.1. Preliminary analyses

Participants in the patient vs. control groups did not differ with respect to age, but women were overrepresented in the control group as compared to the patient group (see Table 1). Those in the patient vs. control group did not differ with respect to the primary metabolites examined (see Table 2). Age was significantly associated with NAA in patients ($r = -0.47$, $p = .005$) but not in controls ($r = -0.26$, $p = .15$).

Table 1
Demographic and clinical characteristics of the sample.

	Schizophrenia spectrum ($n = 35$)	Healthy controls ($n = 33$)	t / $\chi 2$	p
Age (years)	39.6 ± 15.5	44.8 ± 16.8	$t = 1.33$	0.19
Sex (male/female)	25/10	13/20	$\chi^2 = 7.07$	0.014*
Current smoker/ non-smoker	8/27	2/31	$\chi^2 = 3.82$	0.051
STRAIN total stressor count	32.3 ± 18.1	19.9 ± 12.7	$t = 2.97$	0.004*
CTQ total	42.2 ± 13.2	41.5 ± 18.0	$t = 0.17$	0.86
PSS total	13.0 ± 6.3	10.4 ± 7.5	$t = 1.47$	0.15
BPRS total	34.4 ± 8.1	23.1 ± 5.0	$t = 6.19$	<0.001*
BNSS total	26.0 ± 17.5	n/a		
Digit symbol coding task raw score	55.2 ± 17.9	76.1 ± 17.4	$t = 4.53$	<0.001*
Digit sequence task raw score	17.8 ± 4.7	22.6 ± 4.3	$t = 4.09$	<0.001*

± standard deviation * Significant.

Table 2
Group differences in ACC metabolite levels (institutional units) and voxel composition.

	Schizophrenia spectrum	Healthy controls	F (p)
Metabolites			
N-acetylaspartate	8.19 ± 0.76	8.11 ± 0.65	0.04 (0.85)
Glutamate+glutamine	7.70 ± 1.02	7.49 ± 0.81	0.00 (0.96)
Total choline	1.82 ± 0.24	1.77 ± 0.22	1.24 (0.27)
Total creatine	6.27 ± 0.58	6.44 ± 0.51	0.55 (0.46)
Myo-inositol	5.35 ± 0.81	5.62 ± 0.74	0.62 (0.43)
Glutathione	1.49 ± 0.24	1.44 ± 0.19	0.40 (0.53)
Lactate	0.76 ± 0.21	0.73 ± 0.17	0.48 (0.49)
Voxel composition			t (p)
Gray matter (%)	41.1 ± 3.0	42.0 ± 3.3	−1.17 (0.25)
White matter (%)	36.7 ± 4.5	36.2 ± 4.8	0.44 (0.66)
Cerebrospinal fluid (%)	22.2 ± 4.3	21.8 ± 5.1	0.36 (0.72)

± standard deviation; p values are in parentheses.

Age was significantly associated with lactate in patients ($r = 0.63$, $p < .001$) but not in controls ($r = 0.30$, $p = .12$). There were no significant effects of sex on NAA or lactate levels.

3.2. Association between STRAIN and neurochemistry

In the full sample, associations that were significant after correction for 7 comparisons were found between total lifetime stressor exposure and two metabolites (Table 3). Experiencing more stressors over the life course was associated with lower levels of NAA ($\beta = -0.36$, $p = .005$) and higher levels of lactate ($\beta = 0.43$, $p = .001$). Among patients, greater lifetime stressor exposure was related to less NAA ($\beta = -0.49$, $p = .006$) and more lactate ($\beta = 0.44$, $p = .006$). No significant associations were found for the control group (all $ps > 0.09$).

3.3. Follow-up analyses

Given that total lifetime stressor exposure was significantly related to NAA and lactate, we next examined if the timing of stressor exposure (i.e., childhood, adulthood, recent) was related to these outcomes (see Table 4). To do this, we repeated regression analyses predicting NAA and lactate levels from participants' CTQ total scores (childhood trauma), PSS (recent stress), and STRAIN total lifetime stressor exposure broken down by early life, adulthood, and recent (6 months) categories. CTQ scores were not associated with any neurometabolite after correction for multiple comparisons. PSS scores was positively correlated with lactate levels ($\beta = 0.28$, $p = .024$), though this association did not survive correction for multiple comparisons. STRAIN scores for both early life ($\beta = 0.39$, $p = .001$) and adulthood ($\beta = 0.37$, $p = .003$) were significantly associated with participants' lactate levels, and STRAIN recent stressors were nominally significantly associated with lactate levels ($\beta = 0.25$, $p = .050$; see Table 4). In contrast, greater early life

Table 3
Linear regression coefficients examining associations between count of total lifetime stressors as measured by STRAIN and neurochemistry in anterior cingulate cortex, controlling for age and sex.

	Entire sample ($n = 68$)	Schizophrenia spectrum ($n = 35$)	Healthy controls ($n = 33$)
N-acetylaspartate	−0.360[a]	−0.489[a]	−0.093
Glutamate+glutamine	−0.142	−0.159	−0.001
Total choline	−0.132	−0.330	0.056
Total creatine	−0.066	−0.201	0.301
Myo-inositol	−0.147	−0.214	0.164
Glutathione	−0.002	0.044	0.042
Lactate	0.428[a]	0.440[a]	0.251

[a] Significant after multiple comparison corrections.

Table 4
Linear regression coefficients for association of neurometabolites to total scores from childhood trauma questionnaire (CTQ), perceived stress scale, and STRAIN events divided by stage of life, in entire sample. All analyses controlled for age, sex, and diagnosis. Significant *p*-values are in parentheses.

	CTQ	Perceived stress	STRAIN – total early life stressor count	STRAIN – total adulthood stressor count	STRAIN – Total recent (6 months) stressor count
N-acetylaspartate	−0.23	−0.01	−0.38 (0.003)[b]	−0.29 (0.031)[a]	−0.21
Glutamate+glutamine	−0.31 (0.019)[a]	0.17	−0.08	−0.15	0.04
Total choline	−0.20	0.17	−0.17	−0.09	0.00
Total creatine	−0.14	0.34 (0.007)[a]	−0.14	−0.02	0.11
Myo-inositol	−0.17	0.09	−0.17	−0.10	−0.08
Glutathione	−0.27	0.00	0.00	0.01	−0.01
Lactate	0.02	0.28 (0.024)[a]	0.39 (0.001)[b]	0.37 (0.003)[b]	0.25 (0.05)[a]

[a] Nominally significant.
[b] Significant after multiple comparison corrections.

stressor exposure as assessed by the STRAIN was significantly related to lower NAA ($\beta = -0.38$, $p = .003$), whereas the association for adulthood stressor exposure was marginally significant but did not survive correction for multiple comparisons ($\beta = -0.29$, $p = .031$).

3.4. Association of neurochemistry and clinical variables

For patients, there were no significant associations between either NAA or lactate and total symptoms (BPRS), negative symptoms (BNSS), processing speed score or working memory performance (all $ps > 0.16$). Antipsychotic dose, calculated as chlorpromazine equivalents, was not significantly associated with NAA or lactate ($p = .23$ and $p = .55$, respectively). Current smoking status was not associated with lactate ($\beta = -0.06$, $p = .63$) or NAA ($\beta = -0.03$, $p = .81$) in the whole sample, covarying for age, sex and diagnosis. BMI was not associated with lactate ($\beta = 0.07$, $p = .56$) or NAA ($\beta = -0.02$, $p = .85$).

4. Discussion

The present data demonstrate that greater exposure to acute and chronic stressors over the life course is related to higher levels of lactate and lower levels of NAA in the anterior cingulate cortex. These findings were driven by the patients with schizophrenia, as these associations were not significant for healthy individuals. We did not find significant differences in levels of lactate or NAA between patients and controls in this sample, though as decreased NAA and increased lactate levels have been found in multiple prior studies (Regenold et al., 2009; Rowland et al., 2016a; Rowland et al., 2016b; Pruett and Meador-Woodruff, 2020; Whitehurst et al., 2020) the lack of differences in the present study may be due to limited power. Given an effect size of d = 0.36 from a meta-analysis of NAA changes in schizophrenia (Whitehurst et al., 2020) we calculate that our current study only achieved about 31 % power to detect a significant difference in NAA. As such, the results should be considered preliminary. Nonetheless, the results support the hypothesis that stressor exposure contributes to abnormalities in the energy supply pathway for brain function in schizophrenia.

The association between stress and the two neuroenergetic-related molecules is consistent with findings from both preclinical and clinical studies. For example, two rodent studies have found increased lactate in frontal cortex following exposure to stressors (Lim et al., 2017; Sun et al., 2021). Although physical stress and exercise are well-known to rapidly increases plasma lactate levels, plasma levels of lactate also rise acutely in response to psychosocial stressors (Kubera et al., 2012; Hermann et al., 2019). Similarly, reduced NAA levels in prefrontal cortex have been found in adult mice exposed to early life stress (Gapp et al., 2017) and reduced hippocampal NAA levels were found in rats subjected to chronic forced swim stress (Liu et al., 2011), though opposite findings have been found as well (Yoo et al., 2018). In addition, a prior study of children who had experienced trauma found an inverse correlation between anterior cingulate levels of NAA and scores on the Childhood Trauma Questionnaire (Milani et al., 2018). Here, NAA and lactate levels were significantly associated with stressor exposure as measured with the STRAIN for patients with schizophrenia, but were not associated with scores on the CTQ or PSS. Furthermore, the associations with NAA and lactate were found with STRAIN scores both for experiences during childhood and during adulthood. The CTQ focuses specifically on experiences of abuse and neglect, and the PSS focuses on the emotional experience of being overwhelmed by stress. Therefore, the pattern of findings suggests that changes in neurochemistry may be influenced by stressors across the lifespan, though the effect may be greater for stressors occurring in early life. This pattern appears consistent with animal study findings that early life stress is associated with altered function and biogenesis of mitochondria in the brain in adulthood (Krolow et al., 2012; Ridout et al., 2020; Ruigrok et al., 2021). Further research is necessary to determine if decreased cerebral levels of NAA and increased levels of lactate represent markers of the cumulative effects of stress on homeostatic mechanisms of cerebral energy metabolism, or are the consequence of early stressors causing altered sensitivity to subsequent stressors.

Emerging evidence in diabetes research indicates a role of stress in poor glycemic control (Masters Pedersen et al., 2015; Smith et al., 2020). Impaired glycemic control may be an intrinsic part of schizophrenia pathophysiology, as studies of individuals early in the course of illness with little to no exposure to medications have elevated fasting blood glucose, elevated plasma glucose levels following oral glucose administration, elevated fasting levels of insulin, and elevated indices of insulin resistance in comparison to age and sex matched controls (Pillinger et al., 2017). A Danish population-based study found about a 3-fold increased risk for diabetes even in schizophrenia patients not on antipsychotics (Rajkumar et al., 2017). Additionally, childhood trauma has been associated with higher insulin levels in first-episode psychosis (Tosato et al., 2020), and high levels of fasting insulin across childhood has been related to a greater risk for experiencing psychosis or clinical high risk for psychosis (Perry et al., 2021). NAA production is closely coupled with the tricarboxylic acid cycle. Type II diabetes and glycated hemoglobin have been found to be significantly and negatively correlated with NAA levels (Wu et al., 2017; Chiappelli et al., 2019). Collectively, these findings support the hypothesis that systemic abnormalities in glucose metabolism and distribution could be part of the mechanism linking stress and neuro-energetic abnormalities in schizophrenia, and may help to explain why associations between lifetime stressors and NAA/lactate were primarily found in the patient sample. Ideally this hypothesis would be tested in a cohort of clinical high risk and/or first episode patients, in which measures of glycemic control such as the oral glucose tolerance test would be done in conjunction with neuroimaging and stress assessments.

As noted previously, a primary limitation of this study is the modest sample size. The correlations of age with lactate and NAA were in similar directions in patients and controls though somewhat stronger in patients; these correlations were not significantly different, although this may have been due to limited power. Additional limitations include the patient and control samples being mis-matched for sex and the potential

confounding effects of medications, although we have used sex as a covariate. Lactate is readily quantified by MRS using even clinical scanners when lactate levels are high due to stimulation or pathological changes (Prichard et al., 1991; Burtscher and Holtås, 2001), but can be difficult to quantify reliably at low concentration in resting conditions with MRS at 3 T. For these reasons it will be necessary to replicate the current findings in a larger sample, ideally in conjunction with measures of glycemic control. Furthermore, the study is cross-sectional and the stress measures are based on retrospective self-report, precluding a definitive conclusion regarding causal relationship between past stress and current NAA and lactate levels. Finally, we only assessed the anterior cingulate cortex, leaving open the question on the anatomic specificity of the finding.

Notwithstanding these limitations, these data indicate a contribution of lifetime stressor exposure in bioenergetic abnormalities in patients with schizophrenia. If supported by follow-up studies, this research could improve our mechanistic understanding of the role that stress processes play in shaping vulnerability for schizophrenia. This work could also potentially point to novel strategies for intervening to reduce risk for this very serious and burdensome disorder.

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CRediT authorship contribution statement

Joshua Chiappelli: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Anya Savransky:** Data curation, Investigation, Writing – review & editing. **Yizhou Ma:** Formal analysis, Writing – review & editing. **Si Gao:** Methodology, Writing – review & editing, Data curation. **Mark D. Kvarta:** Writing – review & editing. **Peter Kochunov:** Conceptualization, Methodology, Supervision, Writing – review & editing. **George M. Slavich:** Conceptualization, Data curation, Methodology, Writing – review & editing. **L. Elliot Hong:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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