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CHILD DEVELOPMENT

EMPIRICAL ARTICLE

Family-based care buffers the stress sensitizing effect of early deprivation on executive functioning difficulties in adolescence

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Abstract

We examined whether family care following early-life deprivation buffered the association between stressful life events (SLEs) and executive functioning (EF) in adolescence. In early childhood, 136 institutionally reared children were randomly assigned to foster care or care-as-usual; 72 never-institutionalized children served as a comparison group. At age 16 years, adolescents (n = 143; 54% female; 67.1% Romanian) self-reported recent SLEs, completed a battery of memory and EF tasks, and completed a go/nogo task in which mediofrontal theta power (MFTP) was measured using electroencephalogram. More independent SLEs predicted lower EF and more dependent SLEs predicted lower MFTP, but only among adolescents with prolonged early deprivation. Findings provide preliminary evidence that family care following early deprivation may facilitate resilience against stress during adolescence on EF.

Early life adversity (ELA) is one of the strongest predictors of psychopathology, accounting for approximately 30% of psychiatric disorders by adulthood (Kessler et al., 2010). The mechanisms by which ELA increases the risk of mental health problems are complex and include neurobiological, cognitive, and emotional pathways (McLaughlin, 2016). One hypothesis posits that ELA increases sensitivity to the effects of later stressful life events (SLEs) that trigger or exacerbate psychopathology. This "stress sensitization" effect has been reported for depression, anxiety, aggression, and substance abuse (Bandoli et al., 2017; Espejo et al., 2007; McLaughlin et al., 2010; Myers et al., 2014; Roberts et al., 2011). The non-specific nature of this association

Abbreviations: ACC, anterior cingulate cortex; CANTAB, Cambridge Neuropsychological Test Automated Battery; CI, credibility interval; EF, executive functioning; ELA, early life adversity; FDR, false discovery rate; MFTP, mediofrontal theta power; PFC, prefrontal cortex; RCT, randomized controlled trial; SLE, stressful life event.

suggests that transdiagnostic processes may explain this heightened vulnerability to stress. However, limited research has explored the transdiagnostic neurocognitive mechanisms of stress sensitization (Stroud, 2020). In the current study, we examined whether a similar pattern of stress sensitization is observed for behavioral and neural indices of executive functioning (EF). Using data from a longitudinal randomized controlled trial (RCT) of family-based foster care for youth with a history of institutionalization, we also tested whether social enrichment following childhood adversity buffers this stress sensitization effect, which may ultimately protect against stress-related psychopathology.

Executive functioning is a broad term that describes multiple cognitive processes that enable individuals to plan, monitor, and adjust behavior in response to changing goals or task demands, and includes processes such as cognitive flexibility, inhibitory control, and working memory (Miyake & Friedman, 2012). Among the environmental factors most strongly linked to EF is psychosocial deprivation, a form of ELA characterized by the absence of expected social and cognitive stimulation. Exposure to deprivation is consistently linked to reduced EF in childhood and adolescence (Bick et al., 2018; Hostinar et al., 2012; Merz et al., 2013; Wade, Fox, et al., 2019), as well as alterations in brain function and structure in the frontoparietal network that subserves EF (Berens et al., 2017; McLaughlin et al., 2019).

Reduced EF is associated with susceptibility to numerous mental health problems and is therefore thought to be a transdiagnostic risk for psychopathology (Snyder et al., 2015). Consistent with this proposal, altered structure and function of the frontoparietal network—encompassing the medial and dorsolateral prefrontal cortex (PFC), superior parietal, and insular cortices—has been observed across many psychiatric disorders (McTeague et al., 2016). In the current study, we assessed EF using two separate measures: the first is a validated behavioral measure of EF that captures multiple attention and memory-related functions that are likely mediated by dorsolateral PFC activity (Luciana, 2003). The second, mediofrontal theta power (MFTP), is a neural correlate of EF that indexes conflict and performance monitoring. MFTP has been shown in both human and animal models to reflect a readout of neural oscillations arising, at least in part, from the dorsomedial PFC (Cavanagh & Frank, 2014; Narayanan et al., 2013). In humans, both of these measures have been associated with early psychosocial deprivation and predict vulnerability to psychopathology (Buzzell et al., 2020; Wade, Zeanah, et al., 2020). Despite the fact that EF and MFTP are both associated with early deprivation and mediate later psychopathology risk, no study has examined whether early deprivation sensitizes individuals to the negative effects of recent stress on behavioral and neural measures of EF.

Another critical unexplored question is whether there are environmental factors that safeguard against the stress-sensitizing effect of early adversity. Caregiving is a potent regulator of the stress response (Gunnar, 2017), yet the regulatory effects of caregiving may depend on exposure to early adversity. For instance, post-institutionalized children appear to be less responsive to the social-buffering effects of caregivers than non-institutionalized children (Fries et al., 2005; Hostinar et al., 2015). Examining whether family-based care causally buffers the stress-sensitizing effects of early adversity requires experimental designs that are exceedingly rare in humans. In a prior experimental study involving the same sample as the current study, it was shown that children removed from institutional care early in development and placed into enriched family care were protected from the negative effect of SLEs on externalizing psychopathology during adolescence (Wade, Zeanah, et al., 2019). However, it is unclear whether this buffering effect is also observed for neurocognitive correlates of psychopathology.

When examining the relation between SLEs and psychopathology or its neurocognitive correlates, one factor that needs to be considered is the controllability of the SLEs. In the stress sensitization literature, researchers typically make a distinction between independent and dependent SLEs—independent SLEs are defined as events over which an individual has very little or no control (e.g., a loved one dying), and dependent SLEs are defined as events over which the individual has at least partial control (e.g., termination of a romantic relationship). Prior work suggests that stress sensitization may be stronger for independent compared with dependent SLEs in relation to psychopathology (Harkness et al., 2006; La Rocque et al., 2014; Wade, Zeanah, et al., 2019; Young-Wolff et al., 2012). However, recent studies have provided mixed evidence with respect to whether there are stronger direct associations between independent versus dependent SLEs and mental health outcomes during adolescence (Moya-Higueras et al., 2020; Schneider et al., 2021). It has been shown that dependent SLEs have larger heritabilities than independent SLEs (Bemmels et al., 2008; Boardman et al., 2011; Johnson et al., 2013) and that there is a modest genetic correlation between dependent, but not independent, SLEs and EF (Morrison et al., 2021). This is consistent with the notion of "stress generation" in which certain characteristics or predispositions of individuals may evoke stressful experiences that, in turn, increase the risk of psychopathology. In support of this idea, it has been shown that poor EF is associated with higher general psychopathology among youth through exposure to more dependent stress (Snyder et al., 2019). When the direction of association is considered, early EF is longitudinally associated with later dependent SLEs, while both dependent and independent SLEs are longitudinally associated with later EF (Morrison et al., 2021). This is consistent with the idea that stress generation effects may be stronger for dependent SLEs (which follow from earlier EF) than independent SLEs. However, it is

unclear from these findings whether independent versus dependent SLEs would show stronger stress sensitization effects in relation to EF.

Current study

In the current study, we used data from a longitudinal RCT of foster care for children reared in psychosocially deprived Romanian institutions to examine whether the pattern of stress sensitization frequently observed for psychopathology could be detected for behavioral and neural measures of EF in adolescence. We also examined whether family-based care protected against this stress-sensitizing effect in an experimental design. Given the more reliable evidence for stress sensitization involving independent SLEs than dependent SLEs in relation to psychopathology, and given that EF is considered a transdiagnostic mechanism of psychopathology, we hypothesized that more independent SLEs would be associated with lower EF among those with a history of prolonged deprivation compared with those removed from deprived environments and placed into family-based care early in life. However, given a lack of prior evidence, we did not hypothesize differences in the category of SLEs (independent vs. dependent) in relation to behavioral versus neural markers of EF. Finally, as the methods and hypotheses were not preregistered, and because the sample is relatively small, we consider this to be an exploratory study.

METHOD

Study design and participants

The Bucharest Early Intervention Project is an RCT of foster care for children reared in deprived institutions in Bucharest, Romania (http://clinicaltrials.gov; NCT00747396). As described previously, the original study was approved by the institutional review boards of the three principal investigators (C.A.N., N.A.F., and C.H.Z.) and by the local Commissions on Child Protection in Bucharest (Humphreys et al., 2017). The study began in April 2001, and the most recent (age 16) follow-up was completed in October 2018. Full sample details and ethical considerations can be found elsewhere (Millum & Emanuel, 2007; Zeanah et al., 2012). Briefly, children were enrolled in the study between 6 and 31 months and, after completing baseline assessments, 136 institutionally reared children were randomly assigned to either high-quality foster care or care-as-usual at an average age of 22 months by drawing names from a hat. Table S1 shows baseline characteristics and differences between the care-as-usual and foster care groups. Moreover, an age- and sex-matched sample of 72 children who had never experienced institutionalization and who were reared in their biological families were recruited as a comparison group. The CONSORT flow diagram in Figure 1 shows changes in sample composition over time. Signed informed consent was obtained from legal guardians and written or verbal assent was obtained from all children. The 16-year follow-up assessment was completed in 2018, which the current study is based on. Table 1 presents statistics on background characteristics for the three study groups.

Measures

Stressful life events

At age 16 years, 144 youth reported on their experience of 30 major and minor life events (absent = 0; present = 1) that occurred over the past 12 months. The measure is a modified version of Coddington's Child Life Events Scale (Coddington, 1972). Items were then categorized as *independent* life events, reflecting those that the adolescent had minimal or no control over (e.g., "a family member was attacked or robbed") or *dependent* life events, reflecting those that the adolescent had some degree of control over (e.g., "you got in trouble with the police"). The specific items and their categorization can be found in two prior studies from our group (Wade, Sheridan, et al., 2020; Wade, Zeanah, et al., 2019), and in Supporting Information. This categorization of independent versus dependent SLEs is common in the stress sensitization literature (Stroud, 2020). The distribution of the life events variables were as follows: *total* SLEs (0 events = 3.5%; 1 event = 10.5%; 2 events = 14.7%; 3 events = 17.5%; 4 events = 19.6; 5 events = 14.0%; 6 events = 5.6%; 7+ events = 14.7%); *independent* SLEs (0 events = 12.6%; 1 event = 25.2%; 2 events = 25.9%; 3 events = 17.5%; 4 events = 9.8; 5+ events = 9.1%); and *dependent* SLEs (0 events = 18.2%; 1 event = 32.9%; 2 events = 24.5%; 3 events = 15.4%; 4+ events = 9.1%).

Executive functioning

Executive functioning was assessed using a well-validated behavioral measure, the Cambridge Neuropsychological Test Automated Battery (CANTAB; http://www.cantab.com). The CANTAB is a set of computerized tasks assessing memory and EF in a number of different domains. Following prior work from our group (Wade, Zeanah, et al., 2020), four subtests were administered at the 16-year follow-up: (1) *Delayed Match to Sample*, which assesses attention and short-term visual memory, (2) *Stockings of Cambridge*, which tests spatial planning and problem-solving, (3) *Spatial Working Memory*, which assesses the ability to update spatial information in memory; and (4) *Paired Associates Learning*, which

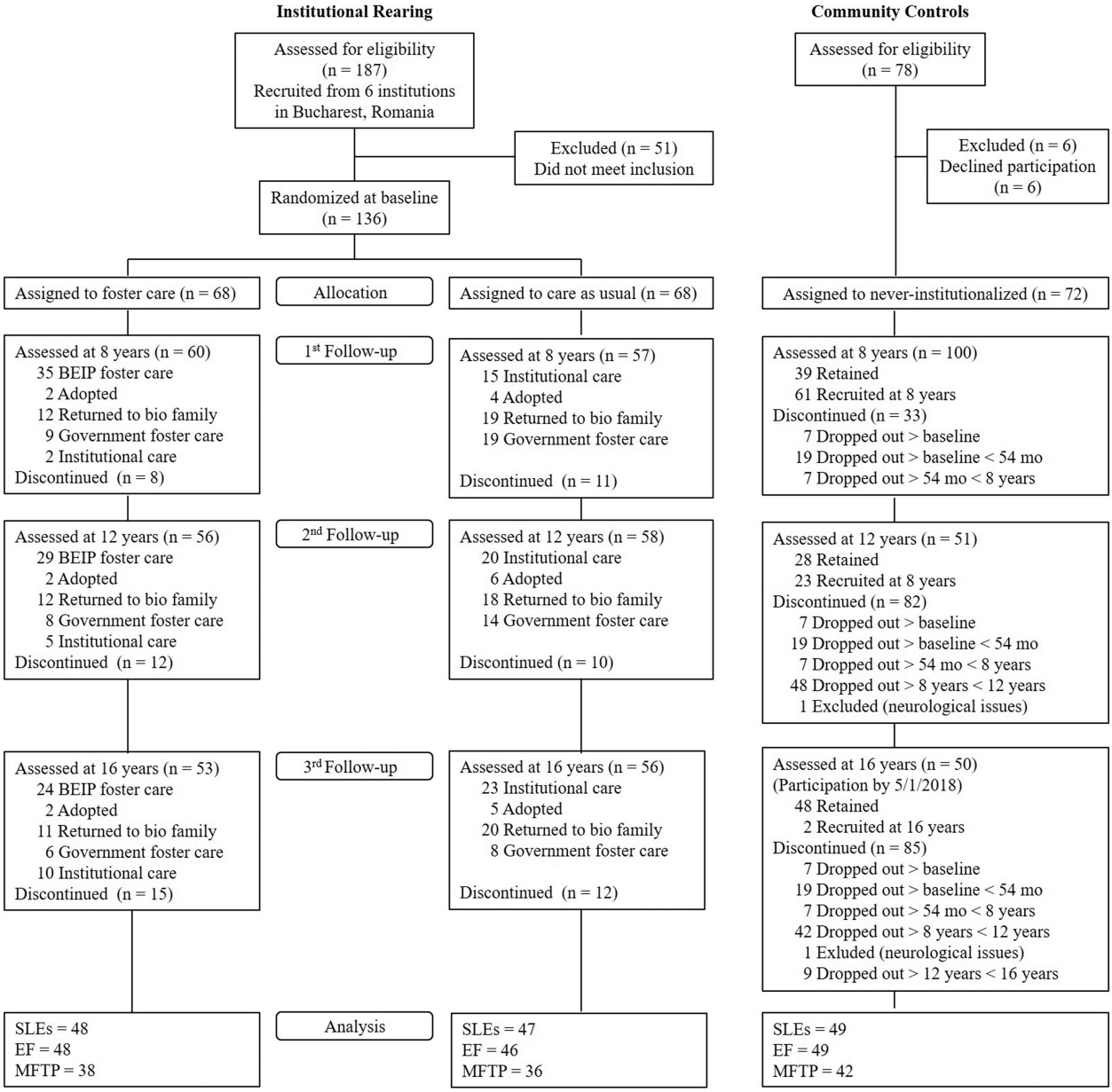

FIGURE 1 CONSORT flow diagram showing group placements over time. BEIP, Bucharest Early Intervention Project; EF, executive functioning; MFTP, mediofrontal theta power; SLE, stressful life events

assess visual–spatial memory and new learning. Tasks are described in detail on the CANTAB website. As described in Wade, Zeanah, et al. (2020), single outcomes from each task were selected and used to estimate a global memory and EF construct using latent variable modeling. In this model, each of the four CANTAB outcomes served as an indicator of the latent factor, estimated at age 8, 12, and 16 years simultaneously. For this study, we extracted and saved the CANTAB factor scores at 16 years (see Wade, Zeanah, et al., 2020 for details). This latent factor comprises memory-, attention-, and EF-related abilities, though we refer to this behavioral measure simply as "EF" throughout the paper for simplicity.

Mediofrontal theta power

Mediofrontal theta power was assessed by having participants complete a modified go/nogo task (Lamm et al., 2018) while electroencephalogram (EEG) was recorded via a 64-channel HydroCel Geodesic Sensor Net and EGI software (Electrical Geodesic, Inc.). Complete details of the go/nogo task and EEG acquisition procedures appear in a prior study (Buzzell et al., 2020). Briefly, the go/nogo task required making responses to frequently presented go letter stimuli and withholding responses to infrequently presented nogo letter stimuli (240 experimental trials; 70/30 go/nogo ratio). Trials were initiated by presentation of a white fixation point

TABLE 1 Descriptive statistics and sample demographics for study groups at age 16

	Care-as-usual (n = 46)	Foster care (n = 48)	Never-institutionalized (n = 49)
Sex			
Male	52.2% 24/46	47.9% 23/48	38.8% 19/49
Female	47.8% 22/46	52.1% 25/48	61.2% 30/49
Ethnicity			
Romanian	47.8% 22/46	56.3% 27/48	95.9% 47/49
Roma	39.1% 18/46	31.3% 15/48	4.1% 2/49
Unknown	10.9% 5/46	12.5% 6/48	0% 0/49
Other	2.2% 1/46	0% 0/48	0% 0/49
Age at placement into institution (months)	2.67[a]	3.07[a]	—

[a]There was no significant difference in age of placement into the institutions for the two groups of institutionally reared children.

(100 ms) followed by presentation of the letter stimulus (500 ms) and then a blank screen interval (500 ms) with a 1000 ms response deadline. Participants often commit errors of commission on this task (incorrectly responding to nogo stimuli), which leads to increased MFTP (Buzzell et al., 2020) associated with cognitive control (Buzzell et al., 2019; Cavanagh et al., 2009). As described previously (Buzzell et al., 2020), a time-frequency principal components analysis approach (TF-PCA) was employed to extract MFTP from a cluster of mediofrontal electrodes (Electrode E4/FCz and the two nearest electrodes). The analysis focused on response-locked theta (to error vs. correct trials) and hence only nogo-error trials and correct-go trials were used (since these were the only trials that had a response). Complete details of the analysis parameters associated with MFTP extraction can be found in a prior report (Buzzell et al., 2020).

Covariates

We controlled for adolescents' sex and the age (measured in months) at which SLEs were assessed.

Analytic plan

The analyses were conducted in two steps. In Step 1, we used Poisson regression to examine whether there were differences between groups (i.e., foster care, care-as-usual, or never-institutionalized group) in the level of SLEs (total, independent, and dependent) reported. No differences in the number of SLEs across groups suggests that any observed differences in EF or MFTP as a function of increasing SLEs cannot simply be attributed to one group experiencing more SLEs than another, and rather that the groups may respond differently to the same number of SLEs based on their history of adversity.

In Step 2, we used linear regression to examine main and interactive effects between total, independent, and dependent SLEs and intervention group (care-as-usual = 0; foster care = 1) in predicting EF and MFTP in separate analyses, controlling for age and sex. For this step, Bayesian estimation was used in Mplus version 8.0. We report unstandardized B coefficients with 95% credibility intervals (CIs) and β coefficients as a measure of effect size. We hypothesized a specific direction of effect, namely that as SLEs increased, EF and MFTP would decrease (not increase) for those with a history of prolonged deprivation. This directional hypothesis is reflected in the one-tailed p-value that is produced from a Bayesian model (Keysers et al., 2020). This is different from a traditional approach in which a two-tailed test is often used to determine the existence of an effect (positive or negative) against a null hypothesis of no effect. A Bayes p-value of .05 means that 5% of the posterior distribution (plausible range of values) falls on the other side of zero from the directional point estimate. Practically, this means that there is about a one-in-twenty chance that the effect is oppositely signed to one's directional hypothesis, given the data. Thus, the Bayes one-tailed p-value is more diagnostic than a test for existence (Marsman & Wagenmakers, 2017). In the current study, we judged effects to be significant if the 95% CI did not include zero. Given that multiple models were tested, we performed a false discovery rate (FDR; Benjamini–Hochberg) adjustment to correct for the number of interactions tested (i.e., six total: two outcomes [EF and MFTP] by three categories of SLEs [total, independent, and dependent]). The FDR correction was applied to the two-tailed p-value, which was derived by doubling the one-tailed Bayes p-value. Within each model, we then probed significant

interactions by testing simple slopes to further clarify the nature of these interactions.

For all analyses, only participants with complete data on the predictors/covariates were included. There was no additional missing data on the outcomes (EF and MFTP) once missing on the predictors/covariates was accounted for. As missing data theory does not apply to predictors/covariates, this means that participants with missing predictor/covariate data were listwise deleted, and the remaining participants had complete data. For CANTAB, there were 143 total participants included in the analyses: foster care = 48; care-as-usual = 46; never-institutionalized = 49. For MFTP, there were 116 total participants included in the analyses: foster care = 38; care-as-usual = 36; never-institutionalized = 42. As noted above, all analyses controlled for participant sex and age at which SLEs were measured.

RESULTS

Descriptive analysis

Descriptive statistics and bivariate correlations between study variables are presented in Table 2. As expected, both dependent and independent SLEs were significantly correlated with total SLEs but were only modestly correlated with one another, across the whole sample. Total SLEs were negatively correlated with EF (assessed by the CANTAB), but not MFTP. Dependent SLEs were not associated with either EF or MFTP, whereas more independent SLEs were related to lower EF, but not MFTP. EF and MFTP were marginally correlated ($r = .17$, $p = .06$).

Step 1: Differences in SLEs across groups

Poisson regression revealed no association between institutional rearing (i.e., never-institutionalized = 0; ever-institutionalized = 1) and the number of total SLEs, *B* (SE) = −.16 (.09), 95% Wald CI [−.34, .03], Wald $\chi^2 = 2.87$, $p = .09$, dependent SLEs, *B* (SE) = −.21 (.14), 95% Wald CI [−.49, .07], Wald $\chi^2 = 2.09$, $p = .15$, or independent SLEs, *B* (SE) = −.15 (.12), 95% Wald CI [−.39, .10], Wald $\chi^2 = 1.41$, $p = .24$. Moreover, there was no association between foster care intervention (i.e., care-as-usual = 0; foster care = 1) and the number of total SLEs, *B* (SE) = −.04 (.10), 95% Wald CI [−.24, .17], Wald $\chi^2 = 0.13$, $p = .72$, dependent SLEs, *B* (SE) = −.19 (.16), 95% Wald CI [−.50, .12], Wald $\chi^2 = 1.45$, $p = .23$, or independent SLEs, *B* (SE) = .01 (.14), 95% Wald CI [−.26, .28], Wald $\chi^2 = 0.01$, $p = .92$. Because there were no significant differences between the groups on the number of SLEs reported, differences in EF and MFTP as a function of increasing SLEs cannot simply be attributable to one group experiencing more SLEs than another, and instead reflect differential responsiveness to SLEs on the basis of their history of deprivation.

Step 2: Interaction between intervention group and SLEs

Next, we examined the main and interactive effects between intervention group (care-as-usual = 0; foster care = 1) and SLEs (total, independent, and dependent) with EF and MFTP in separate models. Results for EF are presented in Table 3. Each model controlled for age and sex. As seen from the 95% CI in Model 1 of Table 3, more total SLEs were negatively associated with EF at age 16 years, while group status was not associated with EF. After controlling for these main effects, there was a significant interaction between group and total SLEs in predicting EF. Simple slope analyses revealed that the association between total SLEs and EF was significant among the care-as-usual youth, *B* [95% CI] = −.21 [−.35, −.09], $p < .001$, but not the foster care youth, *B* [95% CI] = −.04 [−.15, .07], $p = .28$. When FDR correction was applied to the two-tailed test, the interaction effect was no longer significant ($p_{FDR} = .06$).

When broken down into independent and dependent SLEs, this same pattern held for independent SLEs

TABLE 2 Descriptive statistics and bivariate correlations between study variables across entire sample

	1.	2.	3.	4.	5.	*M*	SD	Range
1. Length of institutionalization (months)	—					28.08	26.80	3–100
2. Total life events	−.02	—				3.77		0–7
3. Dependent life events	−.10	.71***	—			1.64	1.21	0–4
4. Independent life events	.03	.83***	.23**	—		2.14	1.46	0–5
5. Executive functioning	−.10	−.26**	−.13	−.24**	—	−0.02	0.88	−2.60 to 2.02
6. Mediofrontal theta power	−.37***	−.04	−.01	−.05	.17†	0.042	0.040	−0.036 to 0.19

Note: Executive functioning was assessed using the Cambridge Neuropsychological Test Automated Battery. Mediofrontal theta power was assessed using EEG during a go/nogo task.

†$p < .10$

**$p < .01$; ***$p < .001$.

TABLE 3 Main and interactive effects between intervention group and SLEs with executive function at age 16 years

	Model 1: total SLEs			Model 2: independent SLEs			Model 3: dependent SLEs		
	B **[95% CI]**	***p*-value**	***β***	***B*** **[95% CI]**	***p*-value**	***β***	***B*** **[95% CI]**	***p*-value**	***β***
Covariates									
Sex	−.05 [−.53, .32]	.40	−.06	−.05 [−.53, .32]	.40	−.06	−.03 [−.53, .36]	.45	−.04
Age	−.01 [−.04, .02]	.20	−.09	−.01 [−.04, .02]	.21	−.10	−.01 [−.03, .03]	.40	−.04
Main effects									
Group (FCG vs. CAUG)	.12 [−.22, .48]	.24	.07	.10 [−.24, .47]	.27	.06	.16 [−.20, .53]	.18	.09
SLEs	**−.20 [−.36, −.09]**	<.001	−.50	**−.25 [−.44, −.11]**	<.001	−.46	−.06 [−.29, .14]	.28	−.09
Interaction									
Group × SLEs	**.15 [.03, .34]**	.01	.30	**.23 [.05, .45]**	.01	.30	.01 [−.19, .31]	.48	.01

Note: The *p*-value is the Bayes one-tailed *p*-value reflecting the direction of the hypothesized effect. The two-tailed *p*-value can be derived by doubling the one-tailed *p*-value. Bolded coefficients are significant at $p < .05$ (two-tailed). No effects survived false discovery rate (FDR) correction.

Abbreviations: 95% CI, 95% credibility interval from Bayesian regression analysis; CAUG, care-as-usual group; FCG, foster care group; SLEs, stressful life events.

(Table 3, Model 2), but not dependent SLEs (Table 3, Model 3). Similar to the analysis involving total SLEs, simple slope analyses revealed that the association between independent SLEs and EF was significant among the care-as-usual youth, *B* [95% CI] = −.26 [−.43, −.11], $p < .001$, but not the foster care youth, *B* [95% CI] = −.02 [−.18, .15], $p = .43$. The pattern of this interaction is presented in Figure 2a, and is consistent with a buffering effect of foster care on the association between independent SLEs and EF at age 16 years. Again, when FDR correction was applied to the two-tailed test, the interaction effect was no longer significant ($p_{FDR} = .06$).

Results for MFTP are presented in Table 4. Each model controlled for age and sex. As seen from the 95% CI in Model 1 of Table 4, neither group nor total SLEs were significantly associated with MFTP at age 16 years, and there was no significant interaction between group and total SLEs. However, when broken down into independent and dependent SLEs, a significant main effect of SLEs and a significant interaction between SLEs and group in predicting MFTP were observed for dependent (Table 4, Model 3) but not independent (Table 4, Model 2) SLEs. Simple slope analyses revealed that the association between dependent SLEs and MFTP was significant among the care-as-usual youth, *B* [95% CI] = −.01 [−.02, −.001], $p = .02$, but not the foster care youth, *B* [95% CI] = .003 [−.007, .01], $p = .29$. The pattern of this interaction is presented in Figure 2b. Specifically, it is seen that MFTP is high among the foster care youth regardless of the level of SLEs, whereas MFTP declines as a function of increasing SLEs for those in the care-as-usual group. This is consistent with a buffering effect of foster care on the association between dependent SLEs and MFTP at age 16 years. When FDR correction was applied to the two-tailed test, the interaction effect was no longer significant ($p_{FDR} = .08$).

Sensitivity analysis including the never-institutionalized group

Our primary analyses focused on the interaction between intervention group (care-as-usual vs. foster care) and SLEs in predicting EF and MFTP in adolescence. To confirm that the negative association between SLEs and EF and MFTP reported above was specific to the care-as-usual group, we examined within-group associations between independent and dependent SLEs with EF and MFTP for each of the care-as-usual, foster care, and never-institutionalized adolescents. Inclusion of the never-institutionalized comparison group in this analysis permits an examination of the expected pattern of association when deprivation is not experienced early in development. These results are presented in Supporting Information (Table S2). Controlling for age and sex, the same directional pattern reported above was observed, with independent

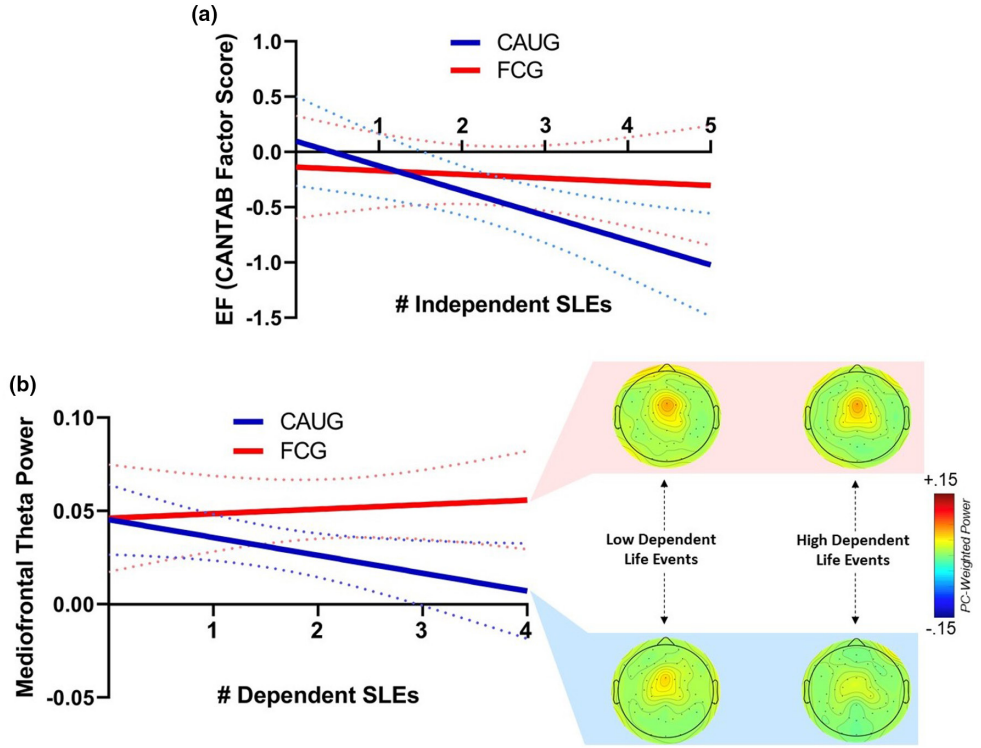

FIGURE 2 Association between (a) independent stressful life events (SLEs) and executive functioning (EF; assessed using the Cambridge Neuropsychological Test Automated Battery) and (b) dependent SLEs and mediofrontal theta power (MFTP; assessed using EEG during a go/nogo task) for the foster care group (FCG) and care-as-usual group (CAUG). Dotted lines are 95% confidence bands. The topoplots in (b) show the distribution of MFTP at high versus low levels of SLEs, based on a median split. The main and interactive effects are presented in the main text, and demonstrate significantly lower EF and MFTP as the number of SLEs increase for the CAUG, but not the FCG.

SLEs predicting EF, and dependent SLEs predicting MFTP, but only among the care-as-usual youth, not the foster care or the never-institutionalized group (note that these effects did not survive FDR correction for nine total tests). These results suggest that prolonged early deprivation sensitizes individuals to later SLEs with respect to EF and MFTP, whereas SLEs are not associated with EF or MFTP among those without a history of deprivation or those removed from deprived environments and placed into family care early in development.

DISCUSSION

In the current study, we examined whether a pattern of stress sensitization could be detected for behavioral and neural measures of EF during adolescence. We focused on EF given that it appears sensitive to the effects of early-life deprivation (Johnson et al., 2021) and has been shown to mediate the association between early deprivation and transdiagnostic psychopathology in adolescence (Buzzell et al., 2020; Wade, Zeanah, et al., 2019). Moreover, the frontoparietal network that subserves EF exhibits altered function in many psychiatric disorders (McTeague et al., 2017; Menon, 2011; Sha et al., 2019), and children who have experienced early deprivation show altered function and structure within frontoparietal regions (McLaughlin et al., 2019). This is the first study to test whether the association between SLEs and multiple indices of EF varies as a function of exposure to early deprivation. We show that greater exposure to SLEs at 16 years is associated with reduced EF and MFTP among youth who experienced prolonged institutional care, but not those who were randomly assigned to foster care intervention early in childhood or never-institutionalized youth. As outlined below, the type of SLEs was also relevant, with independent (uncontrollable) SLEs predicting EF performance, and dependent (controllable) SLEs predicting MFTP. This study provides preliminary evidence for the stress-sensitizing effect of prolonged early-life deprivation on EF difficulties in adolescence and, perhaps most compellingly, the capacity of family-based care to buffer this association. However, results were generally not robust to correction for multiple tests, and thus need to be interpreted cautiously and replicated in larger samples.

To date, studies of stress sensitization have focused primarily on psychopathology as an outcome, with robust evidence that childhood adversity sensitizes individuals to later SLEs proximal to psychopathology (see Stroud, 2020 for a review). The current study extends

TABLE 4 Main and interactive effects between intervention group and SLEs with mediofrontal theta power at age 16 years

	Model 1: total SLEs			Model 2: independent SLEs			Model 3: dependent SLEs		
	B **[95% CI]**	***p*-value**	***β***	***B*** **[95% CI]**	***p*-value**	***β***	***B*** **[95% CI]**	***p*-value**	***β***
Covariates									
Sex	−.02 [−.04, .004]	.06	−.40	−.02 [−.04, .01]	.07	−.38	−.02 [−.04, .003]	.06	−.41
Age	<.001 [−.002, .002]	.44	−.01	<.001 [−.002, .002]	.45	.02	<.001 [−.002, .002]	.46	−.02
Main effects									
Group (FCG vs. CAUG)	.02 [−.003, .04]	.06	.20	.02 [<.001, .04]	.03	.23	.02 [−.002, .04]	.03	.21
SLEs	−.003 [−.01, .004]	.21	−.12	.002 [−.01, .01]	.38	.07	**−.01 [−.02, −.001]**	.02	−.36
Interaction									
Group × SLEs	.004 [−.004, .01]	.24	.15	−.001 [−.01, .01]	.38	−.04	**.01 [.002, .03]**	.02	.31

Note: The *p*-value is the Bayes one-tailed *p*-value reflecting the direction of the hypothesized effect. The two-tailed *p*-value can be derived by doubling the one-tailed *p*-value. Bolded coefficients are significant at $p < .05$ (two-tailed). No effects survived false discovery rate (FDR) correction.

Abbreviations: CAUG, care-as-usual group; FCG, foster care group; SLEs, stressful life events.

these findings by showing that behavioral and neural markers of EF may be susceptible to recent stress in the context of prolonged early adversity. Given the stress-sensitizing effects of psychosocial deprivation on psychopathology shown previously (Wade, Zeanah, et al., 2019), and the role of EF in transdiagnostic psychopathology (Buzzell et al., 2020; Wade, Zeanah, et al., 2020), these results raise the possibility that reduced EF may be one neurocognitive mechanism accounting for the stress-sensitizing effects of early deprivation.

In addition to the stress-sensitizing effects of early-life deprivation on EF, the current study provides novel evidence for the capacity of family-based care to buffer against this effect. Specifically, the relation between SLEs and behavioral and neural measures of EF at age 16 was only observed for adolescents with prolonged deprivation, but not those randomly assigned to foster care intervention in early childhood. This is particularly notable given the early-emerging and persistent difficulties with EF that have been reported among institutionally reared children, and for which intervention effects have generally been equivocal (Lamm et al., 2018; Wade, Fox, et al., 2019). Thus, rather than directly promoting EF development, foster care may instead protect against the deleterious effect of SLEs during adolescence on EF difficulties. In this regard, foster care may have a protective-stabilizing effect on EF during adolescence (Luthar et al., 2000), with positive downstream consequences for psychopathology. Further supporting this idea, it has been shown that foster care is related to less of a decline in MFTP from age 12 to 16 years compared with prolonged deprivation, which is in turn associated with a greater reduction in general psychopathology over this same period (Buzzell et al., 2020). These results suggest that family-based care following early deprivation may buffer against declines in EF that underpin psychopathology risk in adolescence. In addition to these neurocognitive mechanisms, there may also be involvement of physiological stress responsiveness systems. For example, foster care has previously been shown to facilitate recovery of hypothalamic–pituitary–adrenal axis and autonomic nervous system functioning in the aftermath of deprivation, especially when placement occurs early in development (McLaughlin et al., 2015). Thus, family-based care following early deprivation may enable individuals to mount an adaptive physiological response to stressful events, and this may support effective engagement of EF systems that help one to cope with stress, ultimately mitigating risk of psychopathology.

It is unclear why the type of SLEs related to EF performance and MFTP differed, with independent SLEs associated with the former and dependent SLEs associated with the latter. It could be that our two measures of EF are capturing discrete domains of EF that are differentially related to independent versus dependent stress. MFTP is, by its nature, indexing cortical activity in dorsomedial PFC regions, including the anterior

cingulate cortex (ACC), which is related to functions such as conflict and performance monitoring (Cavanagh & Frank, 2014; Fiske & Holmboe, 2019). Our behavioral measure of EF entailed multiple attention and memory-related functions which may be more strongly related to a broader network centered on the dorsolateral PFC (Petersen & Posner, 2012). Although both medial and lateral PFC are widely regarded as being central to a broad EF network, increasing evidence suggests these structures are associated with distinct subdomains of EF—medial frontal areas are more closely associated with internalized forms of control, whereas lateral structures are more closely linked to external, rule-based control (Crone & Steinbeis, 2017). EF and MFTP were only modestly correlated in the current study, suggesting that they are indeed indexing different aspects of EF, which is also consistent with extensive work demonstrating that medial and lateral frontal cortex exhibit distinct developmental time courses (Bethlehem et al., 2022). In early studies on the unity and diversity of EFs, correlations between different abilities were generally small (Miyake et al., 2000), many falling in same range as that shown between EF and MFTP in the current study (r = .17). Moreover, not only were EF (CANTAB) and MFTP (Go/Nogo) measured using different tasks in the current study, the latter constituted a neural correlate of EF while the former was a performance-based behavioral measure. Even when behavior and neural function are captured on the same task, correlations between these are often weak or non-significant (Buzzell et al., 2020; Lamm et al., 2006). Thus, it may not be surprising that these measures were weakly associated in the current study.

The differential pattern of association between different types of SLEs with these two measures raises the possibility that independent and dependent stress may have distinct effects on specific aspects of EF. However, there is limited prior evidence for such a distinction. One recent study examining the structural brain correlates of independent and dependent SLEs in a sample of adolescents and young adults found that perceived lack of control over dependent stressors, but not independent stressors, was associated with cortical thickness in a cluster of regions typically involved in cognitive control, including the dlPFC, superior frontal gyrus, inferior parietal lobule, and rostral ACC (Fassett-Carman et al., 2022). The latter region has been implicated in performance monitoring (Di Pellegrino et al., 2007) and the regulation of emotional conflict (Etkin et al., 2015). While an association between dependent stress and cortical thickness in these regions is consistent with the association between dependent SLEs and MFTP observed in the present study, a strict mapping of cortical thickness to neural activity cannot be assumed. Moreover, the study by Fassett-Carman et al. (2022) revealed only a single association between *independent* SLEs and cortical thickness that survived correction, which was a cluster in lateral orbitofrontal cortex (though this was also detected for dependent SLEs). This region is involved in executing cognitive control within the context of emotion (Kuusinen et al., 2018; Rubien-Thomas et al., 2021). We have argued that our behavioral measure (CANTAB) may be indexing dorsolateral aspects of EF, while our neural measure (MFTP) may be indexing dorsomedial functions. Compared with independent stress, dependent stress may have more social and interpersonal content during adolescence (Fassett-Carman et al., 2022). Moreover, in addition to performance monitoring, dorsomedial PFC is involved in social cognition, mental state inference, and social judgments (Eickhoff et al., 2016). Thus, during adolescence, it may be that dorsomedial regions of the brain are particularly sensitive to social and interpersonal stress, which characterize most dependent stressors, perhaps especially when there is a history of early adversity. In other words, a history of adversity may increase one's sensitivity to social and interpersonal stress during adolescence, which is related to altered function in brain regions that mediate social cognition and performance monitoring. In contrast, a lack of objective control over external events (i.e., independent stress) may be more strongly related to the non-social cognitive abilities that facilitate one's sense of being able to solve problems and coordinate behavior towards desired goals. In effect, a lack of objective control over stress during adolescence may impinge on the cognitive processes needed to execute control over one's behavior. At present, these ideas are purely speculative, and future research is clearly needed to determine whether particular measures of EF are sensitive to the type, timing, or controllability of specific stressors, or whether a common mechanism underlies both effects.

There may be a number of other cognitive, socioemotional, and neurobiological mechanisms involved in stress sensitization and heightened risk of psychopathology. For instance, it has been shown that child maltreatment and trauma are associated with altered reactivity, awareness, and regulation of emotion which increase the risk of psychopathology (Heleniak et al., 2016; Weissman, Nook, et al., 2020; Weissman et al., 2019). Reduced recruitment of prefrontal regions involved in cognitive control during threat processing, such as the dorsal ACC, may also confer increased risk of transdiagnostic psychopathology (Weissman, Jenness, et al., 2020). Reduced recruitment of the dorsal ACC and modulation of amygdala reactivity during cognitive reappraisal is also linked with higher depression risk among maltreated youth (Rodman et al., 2019). Moreover, it has recently been demonstrated that reductions in amygdala and hippocampal volume may underlie stress sensitization to depression in adolescence following early exposure to violence (Weissman, Lambert, et al., 2020). Finally, in addition to these neurobiological pathways, it has been shown that polygenic risk related to serotonergic and hypothalamic–pituitary–adrenal axis functioning interacts with both childhood adversity and recent life stress

in predicting depression risk among adolescents (Starr et al., 2020). Dysregulation of diurnal cortisol patterns has been proposed as one psychobiological mechanism underlying stress sensitization (Young et al., 2019). Thus, the mechanisms of stress sensitization are likely complex and may include neurobiological structure and function, physiological stress system responsiveness, and genetic-neurotransmitter signaling. The current results add EF to the growing list of cognitive and biological processes that may be vulnerable to the stress-sensitizing effects of early adversity.

There are several limitations of this study. First, the current approach should be considered exploratory rather than confirmatory given the relatively small sample, lack of preregistration, and general novelty of the findings (especially the unexpected difference between independent and dependent SLEs). The primary interaction effects also did not survive correction for multiple tests and thus require replication. Second, our measure of SLEs was based on self-reports, which could be susceptible to reporting biases. However, our measure of ELA (i.e. deprivation) was objectively assessed, thereby reducing risk of shared-method bias. Third, we only surveyed two domains of EF that have been shown in our sample to be reliably different between deprived and non-deprived youth. Determining whether the stress-sensitizing and stress-buffering associations reported here apply to other domains of EF and cognition more broadly is important to uncover other domains of functioning that may be involved in stress sensitization. In general, a more expansive search for intermediate phenotypes connecting stress sensitization to psychopathology is required, with candidates including reward responsiveness, fear learning, social cognition, and linguistic competence. Finally, this study consisted of a unique sample of institutionally reared children who experienced profound early neglect and deprivation, and it is unclear whether less severe levels of neglect or different types of adversity would yield comparable results.

CONCLUSION

Exposure to early-life deprivation increases risk of psychopathology, perhaps by sensitizing individuals to the effects of recent stress. Here, we argue that one mechanism underlying this stress sensitization effect is EF. We demonstrate that recent SLEs are associated with lower EF and reduced MFTP—an established neural correlate of cognitive control—but that this effect is only observed for adolescents who experienced prolonged early deprivation. In contrast, among non-deprived adolescents and those assigned to early foster care intervention, SLEs were not associated with reduced EF or MFTP. Given the RCT design of this study, we provide strong, albeit preliminary, evidence for the stress-sensitizing effects of prolonged early adversity on measures of EF, and the stress-buffering effects of social enrichment following early adversity.

AUTHOR CONTRIBUTIONS

Conceptualization: Mark Wade, Charles A. Nelson, Charles H. Zeanah, Nathan A. Fox; Methodology: Mark Wade, Charles A. Nelson, Charles H. Zeanah, Nathan A. Fox; Visualization: Mark Wade, George A. Buzzell; Funding acquisition: Charles A. Nelson, Nathan A. Fox, Charles H. Zeanah; Project administration: Charles A. Nelson, Charles H. Zeanah, Nathan A. Fox; Writing—original draft: Mark Wade; Writing—review and editing: Katie A. McLaughlin, George A. Buzzell, Charles A. Nelson, Charles H. Zeanah, Nathan A. Fox.

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CONFLICT OF INTEREST

NAF has received grant support from the National Institute of Mental Health (NIMH), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Science Foundation (NSF), the National Institutes of Health Environmental influences on Child Health Outcomes (NIH ECHO) consortium, the Russell Sage Foundation, and the Lumos Foundation. He has received royalties from Guilford Press and Harvard University Press. He has received honoraria for lectures to professional audiences. CHZ has received grant support from the NIMH, the Palix Foundation, the Irving Harris Foundation, the Substance Abuse and Mental Health Services Administration (SAMHSA), the Lumos Foundation, and the Inter-American Development Bank. He has received royalties from Guilford Press and Harvard University Press. He has received consulting fees from the National Society for the Prevention of Cruelty to Children. He has received honoraria for lectures to professional audiences.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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