Cumulative Life Course Adversity and Cognition: Investigation of this Association and its Underlying Mechanisms

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Abstract

The association between adversity and cognition varies according to the specific adversity, when the adversity was experienced, and the cognitive domains investigated. Disentangling the effect of one type of adversity and the underlying mechanistic pathway is therefore difficult.

The association between one type of adversity accumulated over the life course (i.e., maltreatment) and executive function (i.e., cognitive flexibility), as well as two mechanisms that may underlie this association were investigated.

A path analysis was performed on the baseline population of the UK Biobank study ($N = 73,489$, $Mdn_{age} = 56$, $SD_{age} = 7.63$, 55.74% of women).

Higher cumulative adverse experiences were associated with lower performance in cognitive flexibility and this effect was partly mediated by the level of depression.

The association between cumulative life course adversity, depression, and performance in cognitive flexibility has been highlighted as well as the specificity of these findings to the cumulative effect of life course adversity.

Keywords: adversity, maltreatment, life course, cognitive functioning, flexibility, intra-individual variability in reaction time, depression

Introduction

Existing literature on the associations between adversity and cognition later in life have reported both a negative (Aartsen et al., 2019; Künzi et al., 2021; Richards & Wadsworth, 2004; Shonkoff et al., 2012) and a positive relationship (Feeney et al., 2013; Künzi et al., 2022; Rosnick et al., 2007). Given the diversity of adverse experiences ranging from everyday life conditions to traumas (Nelson et al., 2020; Stern & Thayer, 2019; YoungMinds, 2018), these findings highlight that further factors should be considered when exploring the relationship between adversity and cognition. Indeed, existing results investigating the association between adversity and brain and/or cognition vary according to the specificity (severity), number, duration as well as the chronicity of adversity, the life course period at which the adversity was experienced, and the cognitive domains under investigation (Bick & Nelson, 2016; Künzi et al., 2022; Nelson et al., 2020). However, it is difficult to disentangle the effect of one specific type of adversity since different adversities (types) frequently occur simultaneously (Green et al., 2010), adversities experienced at one stage of life are often associated with adversities experienced in the subsequent stage (Künzi et al., 2021), early life events influence brain response to adulthood stressors (McEwen, 2007), and accumulated adversity may foster resilience (Seery et al., 2010).

Therefore, it is important to investigate the effect of adversity accumulated over the life course (i.e., cumulative adversity), and precisely to avoid mixing types of adversity and finding contradictory results; it would be advantageous to avoid confounding the possibly contrary effects of different adversity types by investigating only one specific type of adversity accumulated over time. Moreover, to better understand the association between one specific adversity cumulated over the life course and cognition, it is also important to define the mechanisms underlying this relationship.

Cumulative adversity

Within the context of adversity, it is important to consider stress theory and how individual experiences in early and adult life shape the response to stress (McEwen, 2007). Stressful experiences may lead to structural and functional changes in the brain and under certain conditions may impair mental and physical health (McEwen & Gianaros, 2011). Too much stress (allostatic load) that may be caused by repeated hits from multiple stressors or by a chronic stressor, results in wear and tear on the body and brain (McEwen, 2007; McEwen & Gianaros, 2011). More specifically, repeated stress has been shown to be associated with functional and structural changes (e.g., dendritic remodeling, shortening and growth) in different brain regions (hippocampus, cortex prefrontal, and amygdala; McEwen, 2006, 2007). Indeed, a study has found an association between the accumulation of adverse experiences with lower gray matter volume in key regions of the brain involved in emotion regulation, contextual processing, and self-control (Ansell et al., 2012). Furthermore, this smaller gray matter volume in specific brain regions (medial prefrontal cortex) in individuals with a history of more cumulative adverse life events has been hypothesized as potentially partially playing a role in the increased risk for depression, addiction, and other stress-related psychopathology (Ansell et al., 2012). Interestingly, an association between the accumulation of adverse experiences and the increase risk of depressive disorders as well as lower cognitive performance, has also been reported (Chapman et al., 2004; Letkiewicz et al., 2021). However, this view has been challenged by the findings of a study suggesting that rather than the ‘accumulation of adversities’, it is the ‘dosing’ of adversity experienced that plays a key role in the relationship between adversity and mental health, as well as well-being outcomes. Indeed, this former research suggests that a moderate level of adversity experienced may be important to foster resilience and lead to better mental health and well-being outcomes compared to individuals with no experience of adverse experience and too many adverse experiences (Seery et al.,

2010). This result is consistent with the biological sensitivity to context (BSC) theory, which posits that a moderately stressful environment leads to lower reactivity to stress (thus protecting individuals from chronic stressors), whereas a highly stressful environment or highly supportive/safe environment leads to higher reactivity to stress (Ellis & Boyce, 2008). A further study suggests that the severity of each adverse experience should also be considered in the study of cumulative adversity. Indeed, an association between young adults who have experienced higher cumulative adverse events and poor emotional and behavioral functioning has been found, but interestingly the study highlighted that this association seems to be due to both the number and the severity of the adverse events experienced (Schilling et al., 2008).

In the present study, to avoid mixing (types of) adversities and differential impacts on investigated outcomes (e.g., low-impact adversities with high-impact adversities) and therefore underestimating the effect of high-impact adversities, it has been decided to investigate the association between severe adversities belonging to the same category (i.e., maltreatment) accumulated over the life course. Importantly, maltreatment definition includes physical, sexual, emotional, and financial abuse and neglect (YoungMinds, 2018).

Mechanisms

The mechanistic pathways underlying the links between adversity and cognition are yet to be understood, however, one of the most commonly cited adversity- or stress-induced effects are thought to be structural brain changes (e.g., Lupien et al., 2009). Stress or adversity experienced in a sensitive period of life (childhood and/or late-life) has been shown to lead to long-lasting effects on brain structures, impacting cognition (Lupien et al., 2009; Shonkoff et al., 2012). Specifically, adversity or stress experienced in childhood and adolescence may affect the developmental brain process. The prefrontal cortex (PFC), due to its late maturation, has been highlighted as being a brain region particularly vulnerable to the effects of stress and

particularly severe stressors such as maltreatment (Hart & Rubia, 2012; Lupien et al., 2009). Importantly this brain region is important for specific cognitive functions, such as executive functions (De Bellis, 2005; Siddiqui et al., 2008). The experience of adversity (specifically the experience of childhood maltreatment) has also been associated with white matter integrity (Bick & Nelson, 2016; De Bellis, 2005; Hanson et al., 2013; Nelson et al., 2020). White matter integrity in turn is linked to processing speed and cognitive performance such as executive functioning (Madden et al., 2009). Of importance is that, since alterations in white matter integrity affect processing speed, intra-individual variability in reaction time (RT) is also thus a sensitive indicator of white matter integrity (Nilsson et al., 2014), and further, it is also associated with impairment and decline in cognitive performance (Haynes et al., 2017; Lövdén et al., 2007). These works suggest a tentative mechanistic relationship between the experience of adversity, the development of the PFC, the disruption of white matter integrity, an increase in intra-individual variability in RT, and lower performance in cognitive tasks, especially, tasks assessing executive functioning.

But the mechanistic pathways underlying the links between specific types of adversity and cognition remain largely unknown. Interestingly, maltreatment (i.e., childhood maltreatment) has been reported to affect memory, working memory, attention, and motor inhibition (Hart & Rubia, 2012). In line with these cognitive results, the brain regions shown to be consistently impacted by childhood maltreatment are the PFC, and the anterior cingulate cortex (ACC). Furthermore, prefrontal white matter microstructure has been found to be affected in children that experienced early neglect, which may be linked to the deficit in cognition associated with early neglect (Hanson et al., 2013). It has also been found that children who suffered from early neglect had lower total white matter volume compared to children who did not (Hanson et al., 2013). In terms of cognitive performances, cumulative childhood maltreatment has been shown to be related to lower executive functioning in

adulthood (Letkiewicz et al., 2021). These studies show how vulnerable the PFC and the white matter microstructure are to the experience of early maltreatment. Hence, maltreatment may be associated with lower performance in executive functions due to the disruption of the development of the PFC, especially white matter integrity which may subsequently be reflected in intra-individual variability in RT performance values.

A second mechanism that seems to play a key role in explaining the relationship between adversity and cognition is depression. Depression is adversely affected by adversity and stress, and adversely affects cognitive performance. A strongly graded relationship between the total number of cumulative adverse childhood experiences and recent, as well as lifetime history of depression, has been found (Chapman et al., 2004; Poole et al., 2017). This finding suggests that childhood adversity has mental health consequences extending far into adulthood. Interestingly, emotional abuse, a form of maltreatment, has been found to have a stronger relationship with depression compared to other childhood adverse experiences (Chapman et al., 2004; Poole et al., 2017). In line with this finding, a stronger positive association between emotional abuse and neglect (further specific experiences of maltreatment) with depression has been reported (Humphreys et al., 2020). Although it is important to note that a positive association between each type of childhood maltreatment and depression has also been found (i.e., physical abuse, sexual abuse, and physical neglect; Humphreys et al., 2020). Moreover, it has been suggested that several neuroendocrine findings found in patients with major depression may be a consequence of early-life stress and represent a risk of developing depression in response to stress (Heim et al., 2008). In this regard, the authors argue that the higher prevalence of depression in women compared to men might be explained by the higher rates of early adversity experienced by girls relative to boys. One proposed pathway of explanation is that a trauma experienced in childhood is associated with sensitization to stress and alteration of the hypothalamic-pituitary-adrenocortical (HPA) axis, which in turn is

associated with symptoms of depression (Heim et al., 2008). Consistent with this alteration of the HPA axis, a further model proposes that early adversity affects the development of brain structures in specific regions (hippocampus, amygdala, and PFC), and de facto the cognitive functions associated with these regions. These specific brain regions, necessary for the regulation of the HPA axis, then, in turn, affect the regulation of the stress system leading to increased vulnerability to psychopathologies in adulthood (Raymond et al., 2018).

To determine whether depression may be a potential explanatory pathway by which adversity and specifically early maltreatment influences cognition (i.e., executive functions), a link between depression and cognition needs to be explored. An association between patients currently depressed or in remitted states and cognitive impairment (i.e., executive function and attention) is well established (e.g., Rock et al., 2014), with an increase in depression severity associated with cognitive impairment in executive function, episodic memory, and processing speed (McDermott & Ebmeier, 2009). One suggestion is that depression-related cognitive impairment may be due to hyperactivity of the HPA axis leading to the elevated production of cortisol which in turn leads to the cognitive impairments (Belanoff et al., 2001; Holsboer, 2001). Precisely, corticosteroid receptor function, key in the regulation of the HPA axis, is altered which leads to the elevated secretion of corticotropin-releasing hormone (CRH) and corticotropin (ACTH; Holsboer, 2001).

Hence, these various studies suggest an important relationship between adversity, depression, and cognition, particularly executive functioning, through the HPA axis. Thus, it may be plausible that adversity, specifically maltreatment, might lead to depression, which in turn could affect cognition (i.e., executive functioning) and that depression may explain the relationship between adversity and cognition.

The aim of the present study is to investigate the association between one type of adversity (i.e., maltreatment) accumulated over the life course and cognitive performance. In

light of the relationships highlighted in the literature between adversity, intra-individual variability in RT, depression, and executive functioning, this study aims to investigate whether intra-individual variability in RT and depression are the mediators of the association between cumulative experiences of maltreatment over the life course and performance in cognitive flexibility (executive function). We predicted that 1) cumulative experiences of maltreatment over the life course predict lower performance in cognitive flexibility, 2) cumulative experiences of maltreatment over the life course predict both higher intra-individual variability in RT and depressive symptoms, 3) both higher intra-individual variability in RT and depressive symptoms predict lower performance in cognitive flexibility and 4) both intra-individual variability in RT and depressive symptoms mediate the relationship between cumulative experiences of maltreatment over the life course and performance in cognitive flexibility.

Methods

Participants

The study included the baseline population of the UK Biobank study which collected comprehensive mental health, cognitive and biomedical data on 502,665 participants aged 37 to 73 years at baseline (Bauermeister & Gallacher, 2019; Sudlow et al., 2015). Only participants without missing values in the variables and items used to create the variables included in the model (i.e., cumulative life course adversity, depression, Trail Making Test ratio, age, gender, and education) except intra-individual variability in RT (for which multiple rounds were available) were used in the analysis ($N = 73,489$, $Mdn_{age} = 56$, $SD_{age} = 7.63$, 55.74% of the participants were women).

Materials

Adversity

Items representing adversity were selected based on the existing definitions of adversity (Gheorghe et al., 2020; YoungMinds, 2018), whilst also focusing on the specific concept of maltreatment experienced in childhood as well as in adulthood. The items assessing childhood adversity (i.e., I felt that someone in my family hated me, I felt loved a child, people in my family hit me so hard that it left me with bruises or marks, and there was someone to take me to the doctor if I needed it) were based on the Childhood Trauma Questionnaire (CTS-5; Glaesmer et al., 2013), and those assessing adulthood adversity (i.e., a partner or ex-partner repeatedly belittled me to the extent that I felt worthless, and a partner or ex-partner deliberately hit me or used violence in any other way) were adapted from the British Crime Survey (Khalifeh et al., 2015). The items were dichotomized and recoded as 0 = never having experienced the adverse event, and 1 = having experienced the adverse event, following the same procedure as Gheorghe et al. (2020). In addition to the dichotomizing and recoding of the items, a cumulative score of adversity was computed by summing up the four childhood adversity items and the two adulthood adversity items. This cumulative life course adversity score ranges from 0 = no adversity experienced up to 6 = all adversities experienced (see Table 1).

Table 1*Frequency table of the cumulative adversity over the life course*

Cumulative adversity over the life course	Frequency	Percent	Cumulative percent
0	41,112	55.94	55.94
1	17,626	23.98	79.93
2	9,569	13.02	92.95
3	3,595	4.89	97.84
4	1,390	1.89	99.73
5	183	0.25	99.98
6	14	0.02	100
Total	73,489	100	

Intra-individual variability in reaction time

To measure intra-individual variability in reaction time, the item “*Duration to first press of snap-button in each round*” was used for each of the rounds (0 to 11). This item is a measure of the time interval (ms) between the display of the two cards and the button press made by the participant to indicate a match between the two symbols of the two displayed cards. Note that this item does not differentiate between proven matches and mistakes. Following the procedure of Haynes et al. (2017), a coefficient of variation (CV) was calculated by dividing the intra-individual standard deviation in reaction time (RT) by the intra-individual mean RT. This CV has the advantage to control for the individual mean RT producing a metric which reflects variability rather than processing speed (Bunce & Bauermeister, 2019). Training rounds (rounds 0-4), as well as reaction times under 50ms (anticipation) and over 2000ms (timing at which the cards had disappeared), were excluded (for the same procedure, see Piumatti et al., 2018). The CV was only calculated for participants having at least four rounds without missing data. Note that none of the participants had a reaction time greater than 3 standard deviations that required to be excluded.

Depression

Following the procedure of Bauermeister and Gallacher (2019), an Item Response Theory (IRT) graded response model for Likert-type items was fitted to the 9 items of the Patient Health Questionnaire-9 questions (PHQ-9; coded from 0 not at all to 3 nearly every day to the question: “how often have you been bothered by any of the following problems”). The aim of performing an IRT analysis on the items assessing depression is to obtain a prediction of the individual θ scores on the fitted IRT model that will be used as a latent construct in the Structural Equation Models (SEM), an alternative to the summed scores allowing to avoid some limitations (e.g., equality of differences in the Likert scale; Acock, 2018).

This IRT analysis suggested that the 9 items of the Patient Health Questionnaire-9 questions (PHQ-9) measure only the absence or presence of depression (high levels of depression) and do not differentiate people with absent or low (-4, -3, -2, and -1) levels of depression. The questions are mostly differentiating individuals with high levels of depression (1, 2, and 3). Although less information is reliable for individuals with average (0) and extreme (4) levels of depression, this is still acceptable (Table 2; Bauermeister & Gallacher, 2019).

Table 2

Reliability for values of Θ from a graded response model fit for the Patient Health Questionnaire-9 questions (PHQ-9)

Θ	TIF	TIF SE	Reliability
-4	1.01	1.00	0.01
-3	1.03	0.99	0.03
-2	1.16	0.93	0.14
-1	1.89	0.73	0.47
0	4.87	0.45	0.79
1	15.84	0.25	0.94
2	20.42	0.22	0.95
3	10.96	0.30	0.91
4	3.43	0.54	0.71

A second IRT model was fitted by removing the item ("Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual") with a discriminant value lower than 1.27. Since no discriminant value was lower than 1.7, no more items were removed from the scale, and a prediction of the individual θ scores on the fitted IRT model was computed only for the participant without missing values.

Cognition

The Trail Making Test (TMT) A and B were used as a measure of executive functioning (Reitan, 1958). Part A (TMTA) is the time in seconds to correctly connect the numbers 1 to 25 in ascending order. Part B (TMTB) is the time in seconds to correctly connect the numbers 1 to 13 and the letters A to L in ascending and alphabetic order alternating between number and letter (1-A, 2-B, 3-C,...,12-L-13). To keep only the flexibility component (executive function) a ratio score was calculated by dividing the TMTB by the TMTA (Arbuthnott & Frank, 2000).

Control variables

Age, gender (coded 0 for women and 1 for men), and education, item named qualifications in the UK Biobank (coded from 1 to 6 with higher values meaning lower educational level) were used as control variables.

Statistical Analyses

The analyses were performed with STATA V.16.1 (StataCorp, College Station, TX, USA). First, Spearman correlations with a Bonferroni correction were computed, then a path analysis including all covariate variables was performed. To avoid the problem of the non-normality of the data, the asymptotic distribution-free (ADF) estimation method was used. The links in the path analysis model were defined such as the TMT ratio was predicted by cumulative life course adversity, CV, and depression. Depression and CV were predicted by

cumulative life course adversity. Given the lack of consensus in the literature regarding the direction of the relationship between CV (used as an indicator of the white matter integrity in the study) and depression (Bauermeister & Bunce, 2015; Bunce et al., 2008; Firbank et al., 2012; Godin et al., 2008), it was decided to correlate the errors of CV and depression. Regarding the covariate variables, gender and age predicted depression and TMT ratio, and age also predicted CV, finally, education only predicted TMT ratio (see Figure 1 for a simplified illustration of the model tested). The model's goodness of fit was assessed using the comparative Fit Index (CFI), considered as good when it is equal to or higher than 0.95, the Root Mean Squared Error of Approximation (RMSEA), considered as good when lower than 0.06, and the Standardized root-mean-square residual (SRMR), considered as good when equal to or lower than .08 (Hu & Bentler, 1999; Kline, 2015).

Results

Table 3 shows the Spearman correlations with a Bonferroni correction between all the variables entered in the model including covariate variables. Higher cumulative life course adversity was significantly correlated with a higher level of depression, being younger and female. Higher intra-individual variability was significantly correlated with lower performance in cognitive flexibility, being older and female, and having lower education level. A higher level of depression was significantly correlated with being younger age, female, and having lower education level. Lower performance in cognitive flexibility was correlated with older age, being male, and lower education level. Finally, age and gender, as well as age and education significantly and positively correlated, and gender and education were significantly negatively correlated.

Table 3*Descriptive statistics and Spearman correlations with a Bonferroni correction for all the variables of the model*

Variable	<i>M</i>	<i>Mdn</i>	<i>SD</i>	Minimum	Maximum	1	2	3	4	5	6	7
1. Cumulative Life course adversity	.736	0	1.015	0	6	1.000						
2. CV	.134	.119	.078	0	.945	-.003	1.000					
3. Depression	-.024	-.104	.821	-.799	3.49	.235*	-.007	1.000				
4. TMT ratio	1.745	1.67	.501	.248	16.218	.005	.032*	.011	1.000			
5. Age	55.531	56	7.628	38	72	-.119*	.074*	-.146*	.087*	1.000		
6. Gender						-.111*	-.023*	-.077*	.035*	.100*	1.000	
7. Education	2.103	1	1.445	1	6	.011	.031*	.024*	.083*	.076*	-.019*	1.000

* $p < .001$

For the path analysis, the fit of the model was very good, CFI = 0.98, RMSEA = 0.03 and SRMR = 0.01. Figure 1 shows the relationships between the variables entered in the model. Note that for clarity, the covariate variables were not drawn. There was no multicollinearity between the exogenous variables of the model (i.e., cumulative life course adversity, age, gender, and education) as indicated by the variance inflation factor (VIF) values equal or lower than 1.03. Higher cumulative life course adversity significantly predicted a higher level of depression and lower performance in cognitive flexibility but did not predict intra-individual variability. Higher intra-individual variability and a higher level of depression significantly predicted lower performance in cognitive flexibility (see Table 4). No correlation between the errors of intraindividual variability and depression was found ($r = .003, p = .44, 95\% \text{ CI } [-0.004, 0.01]$).

The indirect effect of cumulative life course adversity on TMT ratio mediated via depression was significant, i.e., higher cumulative life course adversity was associated with lower performance in cognitive flexibility, and this effect was partly mediated by higher level of depression (see Table 5). Precisely, 50% of the total effect of cumulative life course adversity on the TMT ratio was mediated by depression. The indirect effect of cumulative life course adversity on TMT ratio via CV was not significant.

For the covariates, older individuals showed higher intraindividual variability, a lower level of depression, and lower performance in cognitive flexibility. Being male was associated with a lower level of depression and lower performance in cognitive flexibility, and having a higher education level was associated with better performance in cognitive flexibility (see Table 4).

Figure 1

Standardized coefficient estimates for the path analysis and explained variance for each endogenous variable of the model

* $p < .001$

Note. For clarity, pathways with the covariate variables are not reported.

Table 4

Standardized estimates for regression weights of the model, with z test, p-value, and associated 95% confidence interval

Dependent variables	Predictors	Standardized	z test	p-value	95% confidence interval	
		coefficients estimates			Lower limit	Upper limit
TMT ratio	Cumulative life	.015	3.95	< .001	.008	.023
	course adversity					
	CV	.025	6.65	< .001	.018	.033
	Depression	.023	5.88	< .001	.015	.030
	Age	.082	21.83	< .001	.074	.089
	Gender	.020	5.29	< .001	.012	.027
CV	Education	.081	21.07	< .001	.073	.088
	Cumulative life	.009	2.43	.015	.002	.016
	course adversity					
	Age	.075	20.70	< .001	.068	.082

Depression					
Cumulative life	.236	61.81	< .001	.229	.244
course adversity					
Age	-.126	-35.24	< .001	-.133	-.119
Gender	-.035	-9.73	< .001	-.042	-.028

Table 5

Standardized estimates for regression weights of the indirect effect of cumulative life course adversity on TMT ratio via CV and depression

Mediator	Standardized	z test	p-value	95% confidence interval	
	coefficients estimates			Lower limit	Upper limit
CV	.0002	2.27	.023	.00003	.0004
Depression	.005	5.85	< .001	.004	.007

Discussion

The present study investigates the association between cumulative adversity (i.e., maltreatment) over the life course and performance in cognitive flexibility, and two potential mechanisms (i.e., intra-individual variability in RT and depression) that underlie the understanding of this association. The results show that higher cumulative life course adversity (i.e., maltreatment) is associated with lower performance in cognitive flexibility and this effect is partly mediated by the level of depression. This finding is in line with the literature showing a negative association between the experience of (cumulative) adversity and cognitive performance (Aartsen et al., 2019; Hanson et al., 2013; Hart & Rubia, 2012; Künzi et al., 2021; Letkiewicz et al., 2021; Richards & Wadsworth, 2004; Shonkoff et al., 2012). Although cumulative life course adversity (i.e., maltreatment) has a direct effect on the performance in cognitive flexibility, this result is partly mediated by the level of depression. The results found are in accordance with the literature showing an association between (cumulative) adversity and depression (Chapman et al., 2004; Heim et al., 2008; Humphreys et al., 2020; Poole et al., 2017; Stern & Thayer, 2019) as well as the association between depression and lower cognitive performance mainly in executive functioning (McDermott & Ebmeier, 2009; Rock et al., 2014). Hence our results support the hypothesis of a direct association between cumulative experiences of maltreatment over the life course and performance in cognitive flexibility, but also suggest that depressive symptoms partially mediate this association.

However, although our results exploring the association between higher intra-individual variability in RT and lower cognitive performance replicated those found in the literature (Haynes et al., 2017; Lövdén et al., 2007), the association between cumulative life course adversity (i.e., maltreatment) and performance in cognitive flexibility is not explained by the intra-individual variability in RT, an indicator of white matter integrity. Contrary to the association between adversity (specifically the experience of childhood maltreatment) and

white matter integrity shown in the literature (Bick & Nelson, 2016; De Bellis, 2005; Hanson et al., 2013; Nelson et al., 2020), cumulative life course adversity (i.e., maltreatment) was not associated with intra-individual variability in RT in the present analysis. As existing research suggests stress or adversity affects the brain and hence cognition mostly during childhood or late-life (Lupien et al., 2009; Shonkoff et al., 2012) it might be possible that in this study, the effect of adversity experienced in childhood is masked by the adversity experienced in adulthood, as the adversities are cumulated over the life course and not separated according to the life course stages. To test this hypothesis, we used the same model but replaced cumulative adversity over the life course with cumulative adversity experienced in childhood (model 1) and cumulative adversity experienced in adulthood (model 2) and added both cumulative adversity experienced in childhood and adulthood in the same model (model 3; the results are available in the supplements; see Tables A to F). Our results did not support this hypothesis and suggested that only cumulative adversity experienced in adulthood was associated with intra-individual variability in RT and by implication, white matter integrity. Importantly to note, this association disappeared when cumulative childhood adversity was included in the model. An explanation of this unexpected result may be that intra-individual variability in RT is not an optimal indicator of white matter integrity in this sample. Interestingly, the results of this third model show that neither cumulative childhood adversity nor cumulative adulthood adversity individually significantly predicted performance in cognitive flexibility and no mediating effect via depression was significant. This result suggests a specific effect of cumulative adverse experiences over the life course on performance in cognitive flexibility as well as a specific mediating effect of depression in this association.

Strengths and limitations

The present study investigated the associations between cumulative experiences of maltreatment over the life course, intra-individual variability in RT, depression, and a component of executive functioning (i.e., flexibility) using a large sample size. This study has the advantage to focus on one type of severe adversity (i.e., maltreatment) accumulated over the life course, therefore, avoiding mixing types of adversity of different impacts which would underestimate the effect of high impact adversities (Schilling et al., 2008).

In terms of limitations, this study assessed adversity retrospectively which may lead to recall biases (which could explain the higher cumulative life course adversity reported in younger adults), although good test-retest of the adverse childhood experiences have been previously demonstrated (Dube et al., 2004). Moreover, the onset of depressive symptoms may be prior to the adverse experiences, and the influence of participants' level of depression on the reporting of adverse experiences cannot be excluded. Moreover, intra-individual variability in RT may be a better indicator of white matter integrity whether mismatches are accounted for, which was not possible with this data. Finally, it cannot be excluded that individuals participating in this study are in better cognitive and mental health. Possibly, individuals reporting adverse experiences in this sample may be particularly resilient, while individuals that are not resilient did not participate to the study or did not answer questions related to adversities. Importantly, however, this potential selection bias, would lead to an underestimation of the results found.

Outlook

To determine if the results found are cohort-specific and to better understand the results found, future research should replicate the findings of this study to other cohorts. Moreover, to have direct access to the brain, diffusion tensor imaging (DTI) based measures of white matter integrity in addition to intra-individual variability in RT should be included.

Our results and those of Ansell et al. (2012) shed light on a potential new interesting association that future studies should investigate: the association between cumulative adversity, gray matter volumes, depression, and cognition. Furthermore, as the experience of maltreatment in childhood has been related to functional brain differences (Hart & Rubia, 2012), it would be interesting to examine the associations between childhood maltreatment experiences with structural brain changes and functional brain differences in relation to cognitive performance. Finally, our approach should be adapted and extended to other adverse experiences categories and cognitive outcomes to determine what are the mechanisms in play. For example, it would also be interesting to examine the relationship between trauma (i.e., maltreatment), depression, and memory, given the important role of the HPA axis and cortisol in this relationship (Belanoff et al., 2001; Chamberlain & Sahakian, 2006; Heim et al., 2008; Holsboer, 2001).

Conclusion

In conclusion, the results found have great relevance for understanding the association between cumulative experiences of maltreatment and cognitive flexibility as well as the mechanisms in play in this association in order to promote resilience. The findings suggest that one way to reduce the negative association between cumulative experiences of maltreatment over the life course and cognitive flexibility later in life could be the use of interventions targeting and working on diminishing the level of depression. Furthermore, our results appear to be specific to cumulative experiences of maltreatment over the life course, suggesting that different mechanisms are in play for accumulated experiences of maltreatment in childhood and adulthood when both (cumulative experiences of maltreatment in childhood and adulthood) are included in the model without being summed. Moreover, to promote resilience after accumulated maltreatment experiences, future research should also determine whether white matter integrity, using DTI, plays a role in the association between cumulative experiences of

maltreatment over the life course and performance in cognitive flexibility and determine whether other factors underlie this association.

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