Positive memory specificity reduces adolescent vulnerability to depression

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Depression is the leading cause of ill health and disability worldwide[1]. A known risk factor of depression is exposure to early life stress[2]. Such early stress exposure has been proposed to sensitise the maturing psychophysiological stress system to later life stress[3,4]. Activating positive memories dampens acute stress responses with resultant lower cortisol response and improved mood in humans[5] and reduced depression-like behaviour in mice[6]. It is unknown whether recalling positive memories similarly reduces adolescent vulnerability to depression through lower cortisol and less negative self-cognitions during low mood. Here we used path modelling to examine the effects of positive memory specificity on later morning cortisol and negative self-cognitions during low mood in adolescents at risk for depression due to early life stress (n = 479, age: 14 years)[7]. We found that experimentally assessed positive memory specificity was associated with lower morning cortisol and less negative self-cognitions during low mood one year later. Moderated mediation analyses demonstrated that positive memory specificity reduced later depressive symptoms through lowering negative self-cognitions in response to negative life events. Positive memory specificity actively dampened the negative effect of stressors over time, thereby operating as a resilience factor reducing the risk of subsequent psychopathology[8]. These findings may have important clinical implications for at-risk populations. Our findings suggest that developing methods to improve positive memory specificity in at-risk adolescents may counteract vulnerability to depression.

"The Patronus is a kind of positive force, a projection of the very things that the Dementor feeds upon – hope, happiness, the desire to survive (...). It will work only if you are concentrating, with all your might, on a single, very happy memory."

- Professor Lupin, Harry Potter and the Prisoner of Azkaban by J. K. Rowling

Remembering specific positive life experiences may be an important protective process when stress occurs[5]. Being unable to do so, or having low autobiographical memory specificity, is an important characteristic of depression[9]. Depressed individuals are more likely to give categorical descriptions when asked to remember a specific episode from their lives (e.g. 'I was always bullied at school'). Such low memory specificity is a trait-like characteristic of individuals at-risk for depression[10,11], and currently depressed individuals[12,13], also after remission[13]. Crucially, low memory specificity predicts the onset and course of depression[14], especially in response to stress[15]. Thus, low memory specificity may comprise a cognitive mechanism through which stress increases the risk of developing depression[16]. As depression is a highly recurrent disorder[17] that often has its first onset in adolescence[7], it is crucial to examine factors that may reduce adolescent vulnerability to depression. Here we examined whether positive memory specificity is related to lower current and later vulnerability to depression in adolescents at risk due to high emotionality and/or exposure to early life stress.

We examined the effect on positive memory specificity on two types of vulnerability for depression: negative self-cognitions during low mood and high morning cortisol. Negative self-cognitions refer to the tendency to blame and be derogatory about oneself ("I am useless"). Negative self-cognitions constitute a cognitive vulnerability factor for depression[18–20], particularly when variations in dysphoric mood are taken into account[21]. Morning cortisol is a trait marker of vulnerability to depression; high morning cortisol is associated with familial risk for[22], onset[7,11], presence[23] and history of[24] major depression. These two factors respectively represent a cognitive and physiological pathway to vulnerability for depression[25].

All participants (n = 479, 223 girls, age 14; see descriptive statistics in Supplementary Table 1) completed the experimental cued recall Autobiographical Memory Test at baseline[26]. We used the ratio of total specific divided by total categorical responses to positive cues as our predictor variable (from here: '*positive memory specificity*'). At baseline and 1-year follow-up, all participants reported the frequency of moderate to severe negative life events during the last 12 months in a semi-structured interview. At both times, all participants reported depressive symptoms during the last two weeks (Mood and Feelings Questionnaire[27]), and negative self-cognitions and dysphoric mood experiences during episodes of low mood in the past month[21]. In accordance with Teasdale's Differential Activation hypothesis[21], we used the ratio of negative self-cognitions divided by dysphoric mood as our measure of cognitive vulnerability to depression. To acquire a stable trait-like measure of morning cortisol, a latent factor was extracted from morning cortisol across four sampling days at both baseline and follow-up (see Supplementary Results and Supplementary Figure 1). The morning cortisol factor showed strong measurement invariance over time, therefore, changes in cortisol can be meaningfully interpreted (see Supplementary Table 2).

We used path modelling in R (*lavaan*[28]) with a robust estimator to examine whether positive memory specificity was related to less negative self-cognitions during low mood and lower morning cortisol currently and/or one year later. IQ and gender were specified as covariates since they have been associated with cognitive and physiological vulnerability for depression[11,29]. We also included negative life events as a covariate in the model because we were interested in depressive vulnerability relative to the extent of exposure to recent life stress[30]. We found that positive memory specificity at baseline was related to less negative self-cognitions during low mood at follow-up (Pearson's r effect size = -.15, P = .001), but

not at baseline (r = -.07, P = .158). Positive memory specificity was also related to lower morning cortisol (r = -.12 at follow-up, P = .009; and r = -.10 at baseline, P = .038; see Figure 1 and Table 1). The main findings were not influenced by outliers (except the relationship with baseline morning cortisol which was not significant; see Supplementary Table 3), selective attrition (see Supplementary Table 4), and were not found for negative memory specificity (see Supplementary Results). The absence of robust cross-sectional relations was not explained by the inclusion of follow-up assessments in the model, as post-hoc analyses showed no significant raw correlations between positive memory specificity and baseline cortisol (r = -.08, P = .067) or negative self-cognitions during low mood (r = -.07, P = .116).

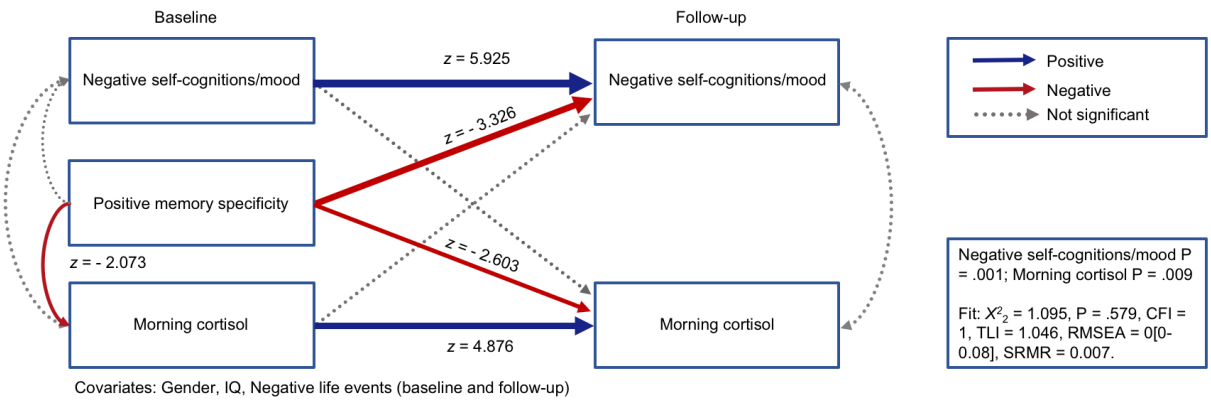

Figure 1. Positive memory specificity predicts lower cognitive and physiological vulnerability at follow-up. Path model showing that positive memory specificity is related to both lower negative self-cognitions during low mood and morning cortisol at follow-up, and only morning cortisol at baseline. Broader arrows indicate stronger relationships. *z*-value = standardised path coefficient.

Table 1.

Outcome	Predictor	Estimate	S.E.	*z*-value	P(>|z|)
Morning cortisol (b)	Positive memory specificity (b)	-0.320	0.154	-2.073	**.038**
	Negative life events (b)	0.012	0.057	0.212	.832
	Gender (b)	0.659	0.107	6.134	**.001**
	IQ (b)	-0.002	0.003	-0.599	.549
Morning cortisol (f)	Morning cortisol (b)	0.367	0.075	4.876	**.001**
	Positive memory specificity (b)	-0.319	0.122	-2.603	**.009**
	Negative self-cognitions/mood (b)	0.124	0.130	0.950	.342
	Negative life events (b)	0.027	0.052	0.529	.597
	Negative life events (f)	0.081	0.046	1.766	.077
	Gender (b)	0.257	0.096	2.669	**.008**
	IQ (b)	0.010	0.003	3.936	**.001**
Negative self-cognitions/mood (b)	Positive memory specificity (b)	-0.061	0.043	-1.412	.158
	Negative life events (b)	0.023	0.015	1.558	.119
	Gender (b)	0.027	0.030	0.908	.364
	IQ (b)	-0.001	0.001	-0.828	.408
Negative self-cognitions/mood (f)	Negative self-cognitions/mood (b)	0.381	0.064	5.925	**.001**
	Positive memory specificity (b)	-0.126	0.038	-3.326	**.001**
	Morning cortisol (b)	-0.017	0.011	-1.534	.125
	Negative life events (b)	0.020	0.012	1.734	.083
	Negative life events (f)	0.016	0.013	1.287	.198
	Gender (b)	0.034	0.029	1.186	.236
	IQ (b)	0.000	0.001	0.366	.714
Morning cortisol (b) ~~	Negative self-cognitions/mood (b)	0.023	0.017	1.324	.185
Morning cortisol (f) ~~	Negative self-cognitions/mood (f)	-0.004	0.012	-0.349	.727

Positive memory specificity predicts lower negative self-cognitions during low mood and morning cortisol. n = 479. (b) = baseline, (f) = follow-up. Boys are coded as 1, girls as 2. Significant paths are bolded. Robust model fit indices: X^2_2 = 1.095, P = .579, CFI = 1, TLI = 1.046, RMSEA = 0[0.000-0.078], SRMR = 0.007. Estimate = unstandardised path coefficient, S.E. = robust standard error, *z*-value = standardised path coefficient.

Accessing specific positive memories in the face of stress may activate a cognitive mechanism that 'disconfirms' negative self-cognitions, leading indirectly to mood improvement over time. To test this mechanistic hypothesis, we first ran a moderation analysis with prospective negative life events as a moderator of the relationship between positive memory specificity at baseline and negative self-cognitions at follow-up. We conducted a bias-corrected moderation analysis with 5.000 bootstrapped samples using the PROCESS macro in SPSS[31]. This analysis supported our hypothesis (see Table 2 and Supplementary Figure 2), showing a significant overall moderation ($F_{1,471}$ = 7.276, P < .01),

controlling for negative self-cognitions at baseline. Positive memory specificity predicted lower negative self-cognitions only in those who experienced at least one negative life event (Pearson's r effect size = -.20). In contrast, post hoc analyses showed that negative life events did not moderate the relationship between positive memory specificity and dysphoric mood ($F_{1,471} = 1.764$, $P > .05$) or depressive symptoms ($F_{1,471} = 1.030$, $P > .05$) at follow-up, controlling for baseline values. Next, we explored whether negative self-cognitions mediated an indirect relationship between positive memory specificity and later depressive symptoms depending on exposure to negative life events (i.e. a moderated mediation; Figure 2). In line with the path model in Figure 1, we controlled for baseline depressive symptoms and negative self-cognitions in the moderated mediation analysis to focus on differences over time. This analysis (see Table 2 and Figure 2) showed a significant indirect effect of positive memory specificity through lower negative self-cognitions on depressive symptoms, depending on exposure to negative life events (Index = -2.782, S.E. = 1.26, CI = [-5.326; -0.409]).

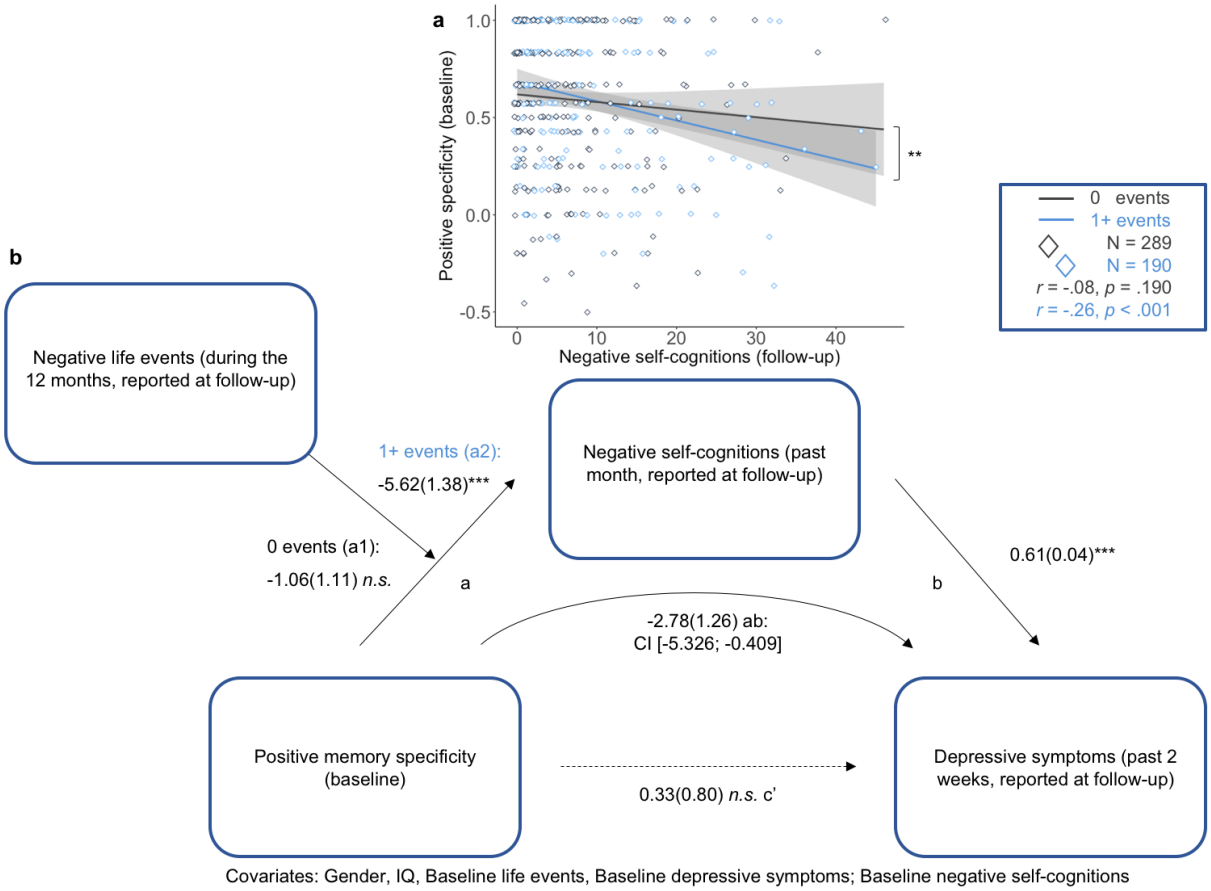

Figure 2. Positive memory specificity lowers depressive symptoms after recent negative life events. n = 479. Plot **a** is showing a significant interaction where the effect of positive memory specificity on negative self-cognitions depends on exposure to recent negative life events. Specifically, positive memory specificity is moderately related to lower negative self-cognitions in those exposed to one or more recent negative life events (during the 12 months of the study; blue line). The relationship is small and not significant in those not exposed to recent negative life events (black line). Lines show raw correlations, and grey bands show confidence intervals. Figure **b** shows a moderated mediation model where positive memory specificity at baseline decreases depressive symptoms indirectly over time. Its effect is mediated by less negative self-cognitions, depending upon exposure to negative life events. *Path a:* Effect of positive memory specificity on negative self-cognitions, depending on exposure to recent negative life events; *path b:* relationship between negative self-cognitions and depressive symptoms; *path c':* Effect of positive memory specificity at baseline on depressive symptoms at follow-up, controlling for the indirect effect; *path ab:* the index of the conditional indirect effect of positive memory specificity on depressive symptoms. The 95 % confidence interval (CI) for this indirect path does not include 0, suggesting that the moderated mediation is significantly different from 0 (at P < .05). Path values represent unstandardised coefficients and bootstrapped standard errors; *P < .05; **P < .01; ***P < .005; *n.s.* not significant.

The moderation and moderated mediation models showed the same results without any covariates and with outliers excluded (see Supplementary Table 5). Importantly, the moderated mediation model was specified on data from two and not three waves (see correlations between the cross-sectional measures in the model in Supplementary Results). However, a moderated mediation model with the mediator and outcome interchanged showed

that depressive symptoms did not mediate the effect of positive memory specificity on negative self-cognitions (see Table 2). Finally, negative life events did not moderate the influence of positive memory specificity on morning cortisol ($F_{1,471} = 0.791$, $P > .05$).

Table 2.

Path	Predictor	Moderator	Mediator	Outcome	Effect	S.E.	df	t	95% CI	P(>|z)
c1	Pos memory	0 events		Neg cognitions	-1.354	1.14	470	-1.187	[-3.595; 0.887]	.236
c2	Pos memory	1+ events		Neg cognitions	-6.190	1.42	470	-4.338	**[-8.994; -3.386]**	**.001**
a1	Pos memory	0 events	Neg cognitions		-1.063	1.11	470	-0.963	[-3.234; 1.107]	.336
a2	Pos memory	1+ events	Neg cognitions		-5.619	1.38	470	-4.059	**[-8.339; -2.899]**	**.001**
b			Neg cognitions	Dep sympt	0.611	0.04	471	14.815	**[0.530; 0.692]**	**.001**
ab	Pos memory	Neg events	Neg cognitions	Dep sympt	-2.782	1.26	471		**[-5.326; -0.409]**	
c'	Pos memory	Neg events	Neg cognitions	Dep sympt	0.334	0.80	471	0.416	[-1.242; 1.909]	.677
a1	Pos memory	0 events	Dep sympt		-0.671	1.20	470	-0.559	[-3.031; 1.689]	.577
a2	Pos memory	1+ events	Dep sympt		-2.567	1.51	470	-1.706	[-5.524; 0.390]	.089
b			Dep sympt	Neg cognitions	0.521	0.04	471	14.815	**[0.452; 0.590]**	**.001**
ab	Pos memory	Neg events	Dep sympt	Neg cognitions	-0.987	1.12	471		[-3.307; 1.135]	
c'	Pos memory	Neg events	Dep sympt	Neg cognitions	-2.086	0.73	471	-2.841	**[-3.528; -0.643]**	**.005**

Results of moderation and moderated mediation models. The index of the moderated mediation (ab) is significant for confidence intervals that do not include 0. All significant values are bolded. Predictor: baseline, moderator: between baseline and follow-up, mediator and outcome: follow-up. Pos memory = positive memory specificity, Neg events = Negative life events, Neg cognitions = Negative self-cognitions, Dep sympt = Depressive symptoms. Levels of the moderator are 0 (no events) and 1+ (one or more events). Path a1/a2 = conditional effect of predictor on mediator, b = relationship between mediator and outcome, ab = indirect effect of predictor on outcome, through mediator, c' = direct effect of predictor on outcome controlling for the indirect effect, c1/c2 = conditional direct effect of predictor on outcome. Effect = standardised coefficient, S.E. = bootstrapped standard error, df = degrees of freedom, 95 % CI = 95 % bootstrapped confidence interval of the estimate.

In this study, we show a novel dual processing effect of positive memory specificity on both cognitive and physiological vulnerability for depression in at-risk adolescents. We further reveal a potential cognitive mechanism whereby specific positive memories are associated with lower negative self-cognitions in response to stress. Specific positive memories may help form boundaries to the scope of negative self-cognitions, thereby preventing the emergence of depressogenic symptoms[32]. We recently showed that positive experiences in adolescence (i.e. family support and friendships[30,33]) facilitate resilience in adolescents at risk of depression due to early life stress. We also showed that emphasising the value of positive social experiences as part of a brief psychological treatment programme can lead to depressive

symptom reduction on par with existing treatments in depressed adolescents[34]. Our findings suggest a potential cognitive mechanism for these effects, whereby encoding of current positive social experiences may increase the probability of specific positive memories being retrieved later in life, disconfirming negative self-cognitions arising from low mood.

We propose that positive memory specificity is an adaptive mnemonic mechanism that may be especially relevant in adolescents at risk for depression. Early adverse experiences confer risk in part because being recurrently told 'you are worthless' and/or ignored are associated with the emergence of negative self-cognitions[35]. These comprise a cognitive vulnerability to depression which is 'activated' in the face of stress[19], leading to subsequent low mood. Early adversities have also been found to alter activation of brain areas involved in the specification of positive memories (i.e. reduced hippocampal activation), suggesting a neural substrate of lower positive memory specificity after early life stress[36]. Here, we find that positive memory specificity may act as a naturalistic defense against the negative cognitive consequences emerging from new incoming stress in at-risk adolescents.

Our findings conceptually replicate and extend findings that positive memory recall lowers acute cortisol and mood responses to stress induction in the laboratory, where mood improvements were particularly seen in resilient individuals[5]. This conceptual replication is important given calls to triangulate research findings with multiple methods and lines of evidence[37]. Our effect of positive memory specificity on depressive symptoms was dependent on exposure to stressful events as they occurred naturally over time. This conditional effect is in line with findings in a recent longitudinal community study, which did not find an association between low memory specificity and subsequent depression; however, the study did not take the potential interaction with recent life events into account[38]. Importantly, robust

effects of positive memory specificity on negative self-cognitions during low mood and morning cortisol were only present over time. This is in line with research finding a delayed symptomatic and morning cortisol reduction after positive attentional bias modification training[39]. The effect of a positive memory and/or attentional bias may unfold over time, through interactions with the social environment. Positive memory specificity may similarly dampen cortisol responses to everyday hassles over time. Compared to such everyday stressors, the negative life events measured here may have been too infrequent to affect the relationship between positive memory specificity and morning cortisol[40].

Positive memory specificity may be a resilience factor that facilitates adaptive responses to stress. An international consortium recently proposed a resilience framework where resilience is defined as *'The maintenance or quick recovery of mental health following an adverse life event or a period of adversity'*[8]. In this framework, stable pre-existing factors (resilience factors) facilitate resilient responses to future stress. These are distinguished from resilience mechanisms, which reflect adaptive responses to stress. Our findings suggest that positive memory specificity comprises a pre-existing resilience factor[10,11] that confers adaptive responses to stress (lower negative self-cognitions after negative life events; the resilience mechanism). This process may in turn lead to the maintenance or quick recovery of mental health (i.e. lower depressive symptoms) after stressful life events.

Our findings have important clinical implications, as memory specificity is malleable and suitable for secondary prevention in at-risk populations. That is, training in recall of specific positive memories may lower risk of developing depression. Such training has already shown promise[41]. For example, real-time amygdala neurofeedback during positive memory recall improved positive memory specificity and in turn lowered depressive symptoms after

training[42]. Training may address the disturbed specificity and vividness of positive memory recall observed in depressed and recovered individuals (hampering the experience of "reliving" positive memories and thereby its mood-repairing effects)[43]. A recent study of positive memory enhancement training which emphasised specific positive memory recall provided preliminary support for this hypothesis. This study found higher memory specificity and higher perceived ability to "relive" positive memories after training, improving mood in depressed individuals[44]. The mechanistic role of negative self-cognitions in our study indicates that in particular, training in accessing specific self-affirming positive memories[45] may prevent the development of depressive symptoms. Thus, our findings may be translated into early-phase trials seeking prevention of depression onset and relapse in at-risk populations.

The current findings should, however, be interpreted with the caveat that we did not have strict experimental control over the studied variables, thereby limiting the causal inferences that can be drawn. However, the use of longitudinal path modelling allows probabilistic conclusions about causality. That is because temporal precedence (the most important criterion for causality in the absence of experimental manipulation[46]) can be established. All our analyses took baseline measures into account, together with important confounds, which strengthens the inferences that can be made. Furthermore, we conceptually replicate findings from an experimental study[5], which provides a foundation for our inferences about causal direction. Changes in morning cortisol attributable to positive memory specificity may be interpreted as potentially causal, because we established strong longitudinal measurement invariance of the cortisol assessments. An alternative explanation is that cortisol moderated positive memory specificity[47]. While this competing hypothesis cannot be fully discounted, it was partially controlled for by including baseline morning cortisol in the path model. It

should further be noted that as only current and not previous psychopathology was among the exclusion criteria, it is possible that 'scarring' effects from previous episodes of psychopathology affected the results. However, this issue is limited by that participants were recruited in early adolescence, before the age of onset of many depressive disorders[48].

A further caveat is that in the exploratory moderated mediation models, the mediator and outcome variables were assessed at the same time. However, if shared measurement variance fully explained the mediating role of negative self-cognitions on depressive symptoms, one would assume to find a significant mediation when the variables were interchanged. Yet, depressive symptoms did not mediate the effect of positive memory on negative self-cognitions at follow-up. Similarly, participants reported both negative life events in the last 12 months and depressive symptoms in the last two weeks at the same time point at follow-up, possibly inflating their (small to moderate) interrelation. This may have been affected in part by recall bias, where participants with high depressive symptoms may have overestimated the occurrence of recent negative life events. However, negative life events were ascertained in a validated semi-structured interview with particular emphasis on reducing recall bias, showing high parent-child and panel agreement in previous reports[49]. Also, any time-invariant recall bias was taken into account by controlling for baseline reporting of negative life events. In addition, negative life events showed a similar correlation with morning cortisol at follow-up, which was less likely to be affected by self-report and recall biases. Finally, the moderated mediation analyses were exploratory, and need to be replicated in independent samples. With the above caveats in mind, we tentatively suggest that lower negative self-cognitions may comprise a cognitive mechanism through which positive memory specificity decreases vulnerability to depression in response to negative life experiences.

In sum, we show that positive memory specificity is associated with lower morning cortisol and negative self-cognitions during low mood over time in at-risk adolescents. We propose that positive memory specificity comprises a resilience factor in at-risk adolescents, by moderating cognitive and physiological pathways to depressive vulnerability after life stress. Our findings replicate and extend previous experimental work[5], showing the potential role of positive memory specificity in regulating responses to stressors as they occur naturally over time. These findings have important clinical implications, highlighting the profound importance of remembering specific positive life experiences in adolescent mental health resilience.

Methods

The analyses were carried out on data from the Cambridge Hormones and Mood Project[7]. We used a subsample of participants with data available for all measures (n = 479), and these did not significantly differ from the full sample (n = 643; see Supplementary Table 1). The exclusion criteria were: current mental illness, current medical illness, pervasive developmental disorders, history of epilepsy or central neurological disease or non-English speaking. Data was collected at secondary schools in the county of Cambridgeshire in the middle 1990s (see Supplementary Methods for information about recruitment). Interviews were conducted in the school setting, which increases generalisability to a context relevant for early interventions. Parents and youths gave written informed consent to join the study. The study was approved by the Cambridge Local ethics committee and was conducted in accordance with the Helsinki guidelines.

Adolescents at risk of developing depression due to high emotional temperament or exposure to early adversity were selected and followed up over 12 months. Emotional temperament was

assessed with the EAS scales (Emotionality, Activity, Sociability and Shyness)[50] completed by parents. Emotionality is associated with development of clinical depression[51]. At-risk status was defined as a combination of two risk factors, which could be: scoring high (>80 percentile) on the emotionality scale; current marital disharmony or past breakdown; loss of/ permanent separation from a close relative or friend; history of parental psychiatric disorder; moderately to severely undesirable events in the past twelve months. Detailed information on the selection of this targeted at-risk population has been provided elsewhere[7]. Moderate to severe negative life events in the past 12 months were assessed by semi-structured interview at baseline and follow-up[49]. A clear benefit over self-report were objective panel ratings of severity, taking factors such as social context and personal behaviour into account (see Supplementary Methods for an overview of the types of events).

The Autobiographical Memory Test (AMT)[26] was developed to assess the content of memories evoked by an experimental cued recall procedure. The AMT is well validated and shows good psychometric properties in young adolescents[52]. Participants were presented with one of six positive and six negative cues at a time (e.g. 'happy') and instructed to recall a specific episode in relation to that cue. 60 seconds were allowed to produce a response. Specific memories were defined as an episode with a specific time and place lasting no longer than a day. Responses were coded as categorical if they referred to repeated events. We used the ratio of specific to categorical responses in our analyses.

The Depressed States Checklist[21] is a measure of negative self-cognitions and dysphoric experience during episodes of low mood. Participants were asked to report how they felt when their mood went down at an occasion in the last month and rate their experience on 28 adjectives (i.e. not at all; slightly; moderately; very; or extremely) of which 14 were dysphoric

mood descriptors (e.g. “sad”) and 14 assessed negative self-cognitions (implying a globally negative view of the self, e.g. “useless”). The distinct and interactive nature of these two components of dysphoric experience has been supported[21].

The Moods and Feelings Questionnaire (MFQ) is a 33-item measure of self-reported depressive symptoms for use in children and adolescents[27]. Participants rated their symptoms over the last two weeks on a three-point Likert scale (*0 = not true*, *1 = sometimes*, *2 = true*). The scale has good psychometric properties ($\alpha = 0.91$, test-retest: $r = 0.84$)[53].

Morning cortisol was measured at 08.00 AM at four occasions within a week after the baseline measurements (see Supplementary Methods for information about assay technique). The same procedure was followed 12 months later. Participants took samples on four consecutive schooldays and recorded their time of waking. The mean time from waking to sampling was 50 minutes. Morning cortisol is relatively stable over time in this cohort (estimated to 48-60% using latent state-trait modeling[11]), and our analyses focused on the proportion that changed over time.

Adolescents’ current mental state was ascertained with the Kiddie Schedule for Affective Disorders and Schizophrenia patient version[54] and history of psychiatric illness was assessed by semi-structured interview with both adolescents and parents. General cognitive ability (IQ) was estimated from a short version of the Wechsler Intelligence Scale for Children–II[55] including the block design and vocabulary subtests.

Path modelling and confirmatory factor analyses (CFA) were carried out in R version 3.4.1 (Single Candle), using the packages *psych*[56], *ggplot2*[57] and *lavaan*[28]. CFA is a confirmatory

latent variable technique where a theorised latent construct ('morning cortisol') load on separate indicators (cortisol assessments across several mornings), which also have a unique variance not accounted for by the latent factor (i.e. 'measurement error'; see Supplementary Figure 1). Path modelling is a more flexible and powerful extension to the regression model where directional hypotheses about linear relationships between exogenous variables ('independent'; positive memory specificity) and endogenous variables can be tested ('dependent'; morning cortisol and negative self-cognitions/mood). In the path and CFA models, we used a robust maximum likelihood estimator ('MLR'). This allowed computing reliable statistics despite deviations from normality[28]. Results were validated in a structural equation model (SEM; which combines CFA and path modeling in the same model) using the Full Information Maximum Likelihood method, estimating missing values by assuming that they follow patterns in the observed data. This estimation method offers conservative path estimates which are penalised for the total number of estimated parameters, effectively adjusting the model estimates for multiple testing. The path model described in the main analyses had 32 free parameters, which is above the common guideline of minimum $n > 10$ per parameter ($n = 479$)[58]. The secondary, supplementary SEM model had 52 free parameters, which is below this minimum guideline (see Supplementary Table 4).

The moderation and moderated mediation analyses were conducted in PROCESS 3.0 (model 1 and 7 respectively; processmacro.org) using IBM SPSS Statistics Version 25.0. We followed the recommendations of Hayes[31] for these analyses, given its superior power and conceptual advantages over the traditional causal steps approach[59]. PROCESS offers computation of a single index testing the significance of the moderated mediation model, removing the need for separate significance tests of each path. Removing 40 outliers with *z*-scores ± 3 did not change any of the main findings reported (see Supplementary Tables 3 and

5 for results with outliers removed). All hypothesis tests conducted were two-sided. Effect sizes reported here (Pearson's r) represent conservative estimates, as they were calculated based on *z* and *t* scores from the baseline-adjusted longitudinal models.

We report chi-square (X^2) fit statistics, the root mean squared error of approximation (RMSEA) with its 90 % confidence interval, and standardized root mean square residual (SRMR). RMSEA of less than 0.05 and an SRMR below 0.1 implies a good fit[60]. We also report the comparative fit index (CFI) and the Tucker-Lewis index (TLI), where values of CFI and TLI over .95 represent good fit[60].

Code availability statement

The code used during the current study is available at the University of Cambridge research repository [https://doi.org/10.17863/CAM.23436] and the first author's website (www.adriandahlaskelund.com).

Data availability statement

The data supporting the analyses presented in this paper is available at the University of Cambridge research repository [https://doi.org/10.17863/CAM.23436] and the first author's website (www.adriandahlaskelund.com).

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Contributions

A.D.A., I.M.G and A.L.v.H conceptualised the study. All authors contributed to the study design. A.D.A. did the data analysis and drafted the paper under the supervision of A.L.v.H. S.S. and I.M.G. provided critical revisions to the manuscript. All authors contributed to and approved the final manuscript.

Competing interests

The authors declare no competing interests.

References

1. Barber, R. M. *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* **386,** 743–800 (2015).
2. Green, J. G. *et al.* Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: Associations with first onset of DSM-IV disorders. *Arch. Gen. Psychiatry* **67,** 113–123 (2010).
3. McLaughlin, K. A., Conron, K. J., Koenen, K. C. & Gilman, S. E. Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: A test of the stress sensitization hypothesis in a population-based sample of adults. *Psychol. Med.* **40,** 1647–1658 (2010).
4. Wilkinson, P. O. & Goodyer, I. M. Childhood adversity and allostatic overload of the hypothalamic - Pituitary - Adrenal axis: A vulnerability model for depressive disorders. *Development and Psychopathology* **23,** 1017–1037 (2011).
5. Speer, M. E. & Mauricio, R. Reminiscing about positive memories buffers acute stress responses. *Nat. Hum. Behav.* **1,** 93 (2017).
6. Ramirez, S. *et al.* Activating positive memory engrams suppresses depression-like behaviour. *Nature* **522,** 335–339 (2015).
7. Goodyer, I. M., Herbert, J., Tamplin, A. & Altham, P. M. E. First-episode major depression in adolescents. *Br. J. Psychiatry* **176,** 142–149 (2000).
8. Kalisch, R. *et al.* The resilience framework as a strategy to combat stress-related disorders. *Nature Human Behaviour* **1,** 784–790 (2017).
9. Williams, J. M. G. *et al.* Autobiographical memory specificity and emotional disorder. *Psychol. Bull.* **133,** 122–148 (2007).

10. Young, K. D., Bellgowan, P. S. F., Bodurka, J. & Drevets, W. C. Behavioral and Neurophysiological Correlates of Autobiographical Memory Deficits in Patients With Depression and Individuals at High Risk for Depression. *JAMA Psychiatry* **70,** 698 (2013).

11. Owens, M. *et al.* Elevated morning cortisol is a stratified population-level biomarker for major depression in boys only with high depressive symptoms. *Proc. Natl. Acad. Sci.* **111,** 3638–3643 (2014).

12. Brittlebank, A. D., Scott, J., Williams, J. M. G. & Ferrier, I. N. Autobiographical memory in depression: State or trait marker? *Br. J. Psychiatry* **162,** 118–121 (1993).

13. Park, R. J., Goodyer, I. M. & Teasdale, J. D. Categoric overgeneral autobiographical memory in adolescents with major depressive disorder. *Psychol. Med.* **32,** 267–276 (2002).

14. Sumner, J. A., Griffith, J. W. & Mineka, S. Overgeneral autobiographical memory as a predictor of the course of depression: A meta-analysis. *Behav. Res. Ther.* **48,** 614–625 (2010).

15. Sumner, J. A. *et al.* Overgeneral autobiographical memory and chronic interpersonal stress as predictors of the course of depression in adolescents. *Cogn. Emot.* **25,** 183–192 (2011).

16. Barry, T. J., Lenaert, B., Hermans, D., Raes, F. & Griffith, J. W. Meta-Analysis of the Association Between Autobiographical Memory Specificity and Exposure to Trauma. *J. Trauma. Stress* **31,** 35–46 (2018).

17. Boland, R. J. & Keller, M. B. Course and outcome of depression. in *Handbook of Depression* 23–43 (2009).

18. Teasdale, J. D. Cognitive Vulnerability to Persistent Depression. *Cogn. Emot.* **2,** 247–274 (1988).

19. Alloy, L. B., Abramson, L., Stange, J. & Rachel, S. Cognitive Vulnerability and Unipolar Depression. in *The Oxford Handbook of Mood Disorders* (eds. DeRubeis, R. J. & Strunk, D. R.) (Oxford University Press, 2017).

20. Glashouwer, K. A. & De Jong, P. J. Disorder-specific automatic self-associations in depression and anxiety: Results of the Netherlands study of depression and anxiety. *Psychol. Med.* **40,** 1101–1111 (2010).

21. Teasdale, J. D. & Cox, S. G. Dysphoria: self-devaluative and affective components in recovered depressed patients and never depressed controls. *Psychol. Med.* **31,** 1311–1316 (2001).

22. Zola N. Mannie, M. S., Catherine J. Harmer, P. D. & Philip J. Cowen, F. R. C. P. Increased Waking Salivary Cortisol Levels in Young People at Familial Risk of Depression. *Am. J. Psychiatry* **164,** 617–621 (2007).

23. Vreeburg, S. A. *et al.* Major Depressive Disorder and Hypothalamic-Pituitary-Adrenal Axis Activity. *Arch. Gen. Psychiatry* **66,** 617 (2009).

24. Bhagwagar, Z., Hafizi, S. & Cowen, P. J. Increase in concentration of waking salivary cortisol in recovered patients with depression. *Am. J. Psychiatry* **160,** 1890–1891 (2003).

25. Beck, A. T. The evolution of the cognitive model of depression and its neurobiological correlates. *American Journal of Psychiatry* **165,** 969–977 (2008).

26. Williams, J. M. G. & Broadbent, K. Autobiographical Memory in Suicide Attempters. *J. Abnorm. Psychol.* **95,** 144–149 (1986).

27. Costello, E. J. & Angold, A. Scales to Assess Child and Adolescent Depression: Checklists, Screens, and Nets. *J. Am. Acad. Child Adolesc. Psychiatry* **27,** 726–737 (1988).

28. Rosseel, Y. lavaan : An R Package for Structural Equation Modeling. *J. Stat. Softw.* **48,**

1–36 (2012).

29. Koenen, K. C. *et al.* Childhood IQ and adult mental disorders: A test of the cognitive reserve hypothesis. *Am. J. Psychiatry* **166,** 50–57 (2009).

30. Van Harmelen, A. L. *et al.* Adolescent friendships predict later resilient functioning across psychosocial domains in a healthy community cohort. *Psychol. Med.* **47,** 2312–2322 (2017).

31. Hayes, A. *Introduction to mediation, moderation, and conditional process analysis*. (Guilford Press, 2013).

32. Hitchcock, C., Rees, C. & Dalgleish, T. The devil's in the detail: Accessibility of specific personal memories supports rose-tinted self-generalizations in mental health and toxic self-generalizations in clinical depression. *J. Exp. Psychol. Gen.* **146,** 1286–1295 (2017).

33. van Harmelen, A. L. *et al.* Friendships and Family Support Reduce Subsequent Depressive Symptoms in At-Risk Adolescents. *PLoS One* **11,** e0153715 (2016).

34. Goodyer, I. M. *et al.* Cognitive behavioural therapy and short-term psychoanalytical psychotherapy versus a brief psychosocial intervention in adolescents with unipolar major depressive disorder (IMPACT): a multicentre, pragmatic, observer-blind, randomised controlled superiori. *The Lancet Psychiatry* **4,** 109–119 (2017).

35. van Harmelen, A.-L. *et al.* Child abuse and negative explicit and automatic self-associations: the cognitive scars of emotional maltreatment. *Behav. Res. Ther.* **48,** 486–94 (2010).

36. McCrory, E. J. *et al.* Autobiographical memory: a candidate latent vulnerability mechanism for psychiatric disorder following childhood maltreatment. *Br. J. Psychiatry* **211,** 216–222 (2017).

37. Munafò, M. R. & Davey Smith, G. Repeating experiments is not enough. *Nature* **553,**

399–401 (2018).

38. Gutenbrunner, C., Salmon, K. & Jose, P. E. Do Overgeneral Autobiographical Memories Predict Increased Psychopathological Symptoms in Community Youth? A 3-Year Longitudinal Investigation. *J. Abnorm. Child Psychol.* **46,** 197–208 (2018).

39. Browning, M., Holmes, E. A., Charles, M., Cowen, P. J. & Harmer, C. J. Using attentional bias modification as a cognitive vaccine against depression. *Biol. Psychiatry* **72,** 572–579 (2012).

40. Hallford, D. J., Austin, D. W., Raes, F. & Takano, K. A test of the functional avoidance hypothesis in the development of overgeneral autobiographical memory. *Mem. Cognit.* 1–14 (2018).

41. Hitchcock, C., Werner-Seidler, A., Blackwell, S. E. & Dalgleish, T. Autobiographical episodic memory-based training for the treatment of mood, anxiety and stress-related disorders: A systematic review and meta-analysis. *Clinical Psychology Review* **52,** 92–107 (2017).

42. Young, K. D. *et al.* Randomized clinical trial of real-time fMRI amygdala neurofeedbackfor major depressive disorder: Effectson symptoms and autobiographical memory recall. in *American Journal of Psychiatry* **174,** 748–755 (2017).

43. Joormann, J., Siemer, M. & Gotlib, I. H. Mood regulation in depression: Differential effects of distraction and recall of happy memories on sad mood. *J. Abnorm. Psychol.* **116,** 484–490 (2007).

44. Arditte Hall, K. A., De Raedt, R., Timpano, K. R. & Joormann, J. Positive memory enhancement training for individuals with major depressive disorder. *Cogn. Behav. Ther.* **47,** 155–168 (2018).

45. Werner-Seidler, A. & Dalgleish, T. The Method of Loci Improves Longer-Term Retention of Self-Affirming Memories and Facilitates Access to Mood-Repairing

Memories in Recurrent Depression. *Clin. Psychol. Sci.* **4,** 1065–1072 (2016).

46. Biddle, B. J. & Marlin, M. M. Causality, Confirmation, Credulity, and Structural Equation Modeling. *Child Dev.* **58,** 4–17 (1987).

47. Abercrombie, H. C. *et al.* Neural Signaling of Cortisol, Childhood Emotional Abuse, and Depression-Related Memory Bias. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* **3,** 274–284 (2018).

48. Kessler, R. C. *et al.* Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry* **62,** 593–602 (2005).

49. Goodyer, I. M., Herbert, J., Secher, S. M. & Pearson, J. Short-Term Outcome of Major Depression: I. Comorbidity and Severity at Presentation as Predictors of Persistent Disorder. *J. Am. Acad. Child Adolesc. Psychiatry* **36,** 179–187 (1997).

50. Buss, A. H. & Plomin, R. Theory and measurement of EAS. *Temperament Early Dev. Personal. Trait.* (1984).

51. Goodyer, I. M., Ashby, L., Altham, P. M., Vize, C. & Cooper, P. J. Temperament and major depression in 11 to 16 year olds. *J. Child Psychol. Psychiatry.* **34,** 1409–23 (1993).

52. Heron, J. *et al.* 40,000 memories in young teenagers: Psychometric properties of the Autobiographical Memory Test in a UK cohort study. *Memory* **20,** 300–320 (2012).

53. Sund, A. M., Larsson, B. & Wichstrøm, L. Depressive symptoms among young Norwegian adolescents as measured by the Mood and Feelings Questionnaire (MFQ). *Eur. Child Adolesc. Psychiatry* **10,** 222–229 (2001).

54. Chambers, W. J. *et al.* The Assessment of Affective Disorders in Children and Adolescents by Semistructured Interview: Test-Retest Reliability of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present Episode

Version. *Arch. Gen. Psychiatry* **42,** 696–702 (1985).

55. Wechsler, D. Manual for the Wechsler intelligence scale for children, revised. (1974).

56. Revelle, W. An overview of the psych package. *R Packag. version* 99 (2013).

57. Wickham, H. *Ggplot2: Elegant Graphics for Data Analysis*. (Springer New York, 2009).

58. Nunnally, J. C. *Psychometric theory*. (McGraw-Hill Book company, 1967).

59. Baron, R. & Kenny, D. The Moderator-Mediator Variable Distinction in Social The Moderator-Mediator Variable Distinction in Social Psychological Research: Conceptual, Strategic, and Statistical Considerations. *J. Pers. Soc. Psychol.* **51,** 1173–1182 (1986).

60. Kline, R. B. *Principles and Practice of Structural Equation Modeling*. (Guilford Press, 2011).