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Reward-Related Attentional Bias at Age 16 Predicts Onset of Depression During 9 Years of Follow-up

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Objective: This study investigated whether low reward responsiveness marks vulnerability for developing depression in a large cohort of never-depressed 16-year-old adolescents who completed a reward task and were subsequently followed for 9 years, during which onset of depression was assessed.

Method: Data were collected as part of the TRacking Adolescents' Individual Lives Survey (TRAILS), an ongoing prospective cohort study. Reward responsiveness was assessed by the spatial orienting task at 16 years and depression was assessed at 19 years by the World Health Organization Composite International Diagnostic Interview and at 25 years by the Lifetime Depression Assessment Self-Report. Participants who completed the reward task at 16 years, had no previous onset of depression, and were assessed on depression onset at 19 and/or 25 years were included in the present study (N = 531; 81 became depressed during follow-up).

Results: Difficulties in shifting attention from expected non-reward to expected reward and from expected punishment to expected non-punishment at 16 years predicted depression during follow-up. This was found only at an automatic level of information processing.

Conclusion: The findings suggest that decreased reward responsiveness at 16 years marks vulnerability for depression. Prevention programs may aim at increasing at-risk adolescents' responsiveness to cues for potential rewards, particularly in situations in which they are focused on negative experiences.

Key words: vulnerability, depression, attentional bias, reward responsiveness

here is compelling evidence that depressed individuals and those with a high familial risk for depression are less responsive to rewards than healthy and low-risk individuals.[1-4] This is reflected in decreased activity in reward-related brain areas,[3,4] decreased hedonic experience of rewards,[5] decreased reward learning,[1] and decreased attention to rewards.[2] There also are first indications that low reward responsiveness predicts an increase in future depressive symptoms[6-10] and first onset of depressive disorder in adolescents.[6,7,10-13] Particularly the prospective association between reward responsiveness and onset of depressive disorder is important to investigate further because of its high clinical relevance and possible implications for prevention. The evidence of such a prospective association is based on only small groups of individuals (ranging from n = 3[6] to n = 44[12]) who were healthy at baseline and depressed at follow-up. The evidence seems largely consistent, with the exception of 2 studies in which opposite effects were reported, that is, increased activity in reward-related brain areas predicted onset of depression.[9,12]

Our main aim was to investigate whether the idea of low reward responsiveness as a vulnerability marker for subsequent depression would hold up in a large sample of never-depressed 16-year-old adolescents who completed a task that assessed reward-related attentional biases and were subsequently followed for 9 years to assess onset of depressive disorder. We focused on reward responsiveness at the level of attentional processes, because these constitute the first filtering of information and likely contribute to the overall negative cognitive processing biases that characterize depression.[14] We investigated how reward expectancies modified attention, and whether low modification of attention by reward expectancies predicted onset of depression. There is evidence that not only reward processing but also punishment processing could be altered in individuals with depression. Depressed individuals have been found to be more sensitive to negative feedback and to show impaired functioning after negative feedback,[15,16] and responses to reward and punishment may also interact.[4] Therefore, our secondary aim was to investigate how punishment expectancies modify attention, and whether a strong

modification of attention by punishment predicts onset of depression. We hypothesized that decreased attentional engagement toward expected reward and non-punishment and increased attentional disengagement from expected reward and non-punishment at 16 years of age would predict onset of depression between 16 and 25 years of age. Automatic and voluntary attentional processes were explored, as was the specificity of findings for depression as opposed to other psychiatric problems (eg, anxiety).

It is particularly relevant to investigate onset of depression in mid- to late adolescence because this developmental period is marked by a strong increase in incidence of depression,[17] and adolescent onset sets the stage for severe and recurrent depression and impaired academic and interpersonal development in adulthood.[18,19] Normal adolescent development is characterized by large changes in the reward system[20] and a peak in reward responsiveness at approximately mid-adolescence.[21] It has been suggested that depression-related differences in reward function might be most pronounced at the time of this peak.[4] Elucidating mid-adolescent reward-related attentional biases that predict depression could inform the design of prevention programs to modify these biases already in adolescence and promote positive psychosocial and academic development of at-risk youth.

METHOD

Sample and Procedure

The data were collected in a subsample of the TRacking Adolescents' Individual Lives Survey (TRAILS), an ongoing prospective cohort study investigating mental health and social development from early adolescence into adulthood. The TRAILS study was approved by the Dutch Central Committee on Research Involving Human Subjects, participants were treated in accordance with the Declaration of Helsinki, and written consent was acquired from all adolescents and their parents.

Starting at approximately 11 years of age, the TRAILS participants have been assessed every 2 to 3 years. They were recruited from primary schools (response rate 90%) in 5 municipalities in the northern region of the Netherlands. Of all eligible children, 2,230 (76%) agreed to participate at T1. Details on the selection procedure and an overview of all measures used have been described elsewhere.[22,23] For the present study, we used data from the third (T3; mean age 16.3 years, SD 0.7), fourth (T4; mean age 19.1 years, SD 0.6), and sixth (T6; mean age 25.7 years, SD 0.6) waves.[23] At T3 (September 2005 to December 2007), 1,816 of the original 2,230 adolescents participated again (retention rate 81%),[23] 744 of whom were invited for a series of laboratory

tasks in addition to the usual assessments, and 715 (96.1%) agreed to participate. Participants with a high-risk profile were oversampled for the laboratory experiments; 66.0% were characterized by a difficult temperament, lifetime parental psychopathology, or living in a single-parent family. The remaining 34.0% were randomly selected from the TRAILS participants without any of the 3 risk factors.

We selected all participants of the T3 laboratory tasks (n = 715) who 1) completed the reward-related attention bias task, that is, the spatial orienting task (SOT), at T3 with less than 25% outliers (excluded n = 2); 2) had undergone the World Health Organization Composite International Diagnostic Interview (CIDI) at T4 or completed the Lifetime Depression Assessment Self-Report (LIDAS) at T6 (excluded n = 64); 3) did not meet the criteria for bipolar disorder or hypomania, because unipolar and bipolar depressive disorders were expected to be associated with different reward biases (excluded n = 27); and 4) had not had a depressive disorder (ie, major depressive disorder or dysthymia) during or before taking the SOT at T3 (excluded n = 91). This yielded a sample of 531 participants (74.3% of total cohort participating in T3 laboratory tasks). Figure S1, available online, presents a flowchart of the sampling procedure. For a more detailed description of the selection for the laboratory tasks, see Supplement 1 and Table S1, available online.

A power analysis for logistic regression[24] with a 1-sided α value set to .05, 531 included participants, a proportion of prospective depressed participants of 0.153, and power set to 0.8 yielded the possibility of finding effects of approximately 35% increased risk of developing depression per SD increase in the predictor variable (Figure S2, available online).

Measures

Spatial Orienting Task. The SOT was programmed to be similar to the SOT developed and described by Derryberry and Reed.[14] The task consisted of 4 positive and 4 negative games. During positive games, fast responses resulted in the gain of points; slow responses did not change the score. During negative games, slow responses resulted in the loss of points; fast responses did not change the score. Fast and slow scores were determined relative to participants' own performance (see Supplement 1, available online). Positive games were used to investigate attentional bias to expected reward, and negative games were used to investigate attentional bias to expected non-punishment.

During each game, 2 vertical black bars which were displayed against a white background marked the location of the cues and targets, and the score was presented in black at the center of the screen. Participants were instructed to

fixate on the score, which was updated after each response, and to avoid moving their eyes. Each trial started with turning off the fixation score for 200 ms and subsequently turning it on again for 250 ms, after which a cue arrow replaced one of the two vertical black bars. The cue arrow served the purpose of orienting participants' attention to one of the two peripheral locations. After a short (250 ms) or long (500 ms) delay, a target, that is, a small vertical gray rectangle, appeared, either centered within the cue arrow (a so-called cued target, see Figure S3a, available online) or centered within the vertical black bar on the other side of the fixation score (an uncued target, see Figure S3b, available online). Participants were informed that a blue-up arrow (easy cue) signaled that a target appearing in that (cued) location would be easy and a target appearing in the uncued location would be hard. A red-down arrow (hard cue) signaled that a target appearing in the cued location would be hard, and a target appearing in the uncued location would be easy. Participants were also informed that two-thirds of the targets would appear in the location of the cue arrow, and that occasionally no target would appear (catch trials). They were instructed to press the 'b' key on the keyboard as soon as they detected the target and were warned that pressing the key before the target appeared or when no target appeared would result in a loss of 10 points. Five-hundred ms after the 'b' was pressed, or for catch trials 1 s after the delay interval, the cue arrow and target were replaced by the two black bars, and a feedback arrow was presented below the centered score. A blue-up arrow indicated a fast response on target trials or a correct nonresponse on catch trials and a red-down arrow indicated a slow response on target trials or an incorrect response on catch trials. To increase the relevance of the scores and boost the participants' motivation, they were informed that a prize (eg, a balloon ride) would be awarded to those with the highest scores on the positive games, and that very low scores on the negative games could result in having to start over again until performance was sufficient. For a more detailed description and schematic overview of the SOT, see Supplement 1, Figure S3, and Tables S2, S3, and S4, available online.

In accord with the work by Van Hemel-Ruiter et al.,[25] attentional bias for reward was operationalized as a relatively faster engagement toward reward and a relatively slower disengagement from reward, that is, 1) faster responses at locations of expected reward than at locations of expected non-reward (faster engagement toward reward) and 2) slower re-shifting of attention from expected reward to expected non-reward locations than from expected non-reward to expected reward locations (slower disengagement from reward). Attentional bias for non-punishment was

operationalized in a similar way, that is, 1) faster responses at locations of expected non-punishment than at locations of expected punishment (faster engagement toward non-punishment) and 2) slower re-shifting of attention from expected non-punishment to expected punishment locations than from expected punishment to expected non-punishment locations (slower disengagement from non-punishment). Separate engagement and disengagement scores were calculated for short (250 ms) and long (500 ms) delays between cues and targets. The short-delay trials tap into relatively automatic and implicit attentional responses and the long-delay trials tap into more voluntary and explicit attentional responses. Table S5, available online, presents an overview of the calculations of all attentional engagement and disengagement scores used in the statistical analyses. We note that it is not possible to distinguish between difficulties with disengaging from reward and difficulties with shifting toward expected non-reward in the disengagement condition; because there is no neutral condition in the SOT, these are 2 sides of the same coin.[14]

Depressive Disorder and Other Psychiatric Diagnoses. The CIDI 3.0,[26] assessed at T4, and the LIDAS,[27] assessed at T6, were used to determine first onset of depression after T3, which was operationalized as a lifetime major depressive disorder or dysthymia with age at onset older than at T3. The CIDI and LIDAS depression diagnoses were determined according to *DSM-IV* criteria. For information about the reliability, validity, and agreement of the CIDI and LIDAS, see Supplement 1, available online. For depression according to both the CIDI and LIDAS, the youngest age at onset was used to exclude participants with an age at first onset younger than or equal to age at T3. Lifetime T4 CIDI diagnoses of bipolar disorder or hypomania and the T6 LIDAS item about ever having been diagnosed with bipolar disorder by a professional were used to exclude participants with lifetime bipolar disorder or hypomania. Other CIDI and LIDAS diagnoses were used for the sensitivity analyses described in the Statistical Analysis section.

Covariates. Family socioeconomic position was computed by taking the average score on standardized family income, educational level of the father and mother, and occupational level of the father and mother, assessed at T1. The affective problems scale (13 items) of the Youth Self-Report[28] (YSR) was used to assess symptoms of depression at T3.

Statistical Analysis

Reaction times were standardized to mean 0 and SD 1 to compare odds ratios across different attentional bias

conditions and different diagnostic groups. Using SPSS 25.0 (IBM Corp., Armonk, NY), we performed a series of logistic regression analyses to test the hypotheses that decreased engagement toward expected reward and non-punishment and increased disengagement from expected reward and non-punishment at 16 years of age would predict onset of depression between 16 and 25 years of age. Because the 2 hypotheses concern effects in a specific direction, 1-sided tests were used[29,30]; that is, for effects in the expected direction, 1-sided p = 2-sided p from SPSS output/2, and for effects in the unexpected direction, 1-sided p = 1 − (2-sided p/2). (The original output is available at https://osf.io/zvw5d/.) First, separate models were tested for reward and non-punishment games, followed by a model including both games. All effects were adjusted for gender, age at time of the SOT, and family socioeconomic position. To correct for multiple tests, we used the classic false discovery rate (FDR) method, resulting in an FDR-derived significance threshold of .0125.[31] (For further details, see Supplement 1 and Table S6, available online.) Results were interpreted as significant only for p values below this threshold.

Sensitivity Analyses. Because depression is highly comorbid with other psychiatric problems, differences between depressed and non-depressed individuals may be explained by other psychiatric problems. We tested whether the effects found were specific to depression by repeating the analyses after excluding all individuals with a lifetime separation anxiety disorder, agoraphobia, generalized anxiety disorder, obsessive compulsive disorder, panic disorder, social phobia, specific phobia, attention-deficit disorder, oppositional defiant disorder, or conduct disorder (sensitivity check 1). Furthermore, although we already excluded participants with clinical depression before or during the SOT, our findings could still be driven by subclinical depressive symptoms at the time of the SOT (T3) rather than by a prospective association. Therefore, analyses were repeated while adjusting for scores on the YSR depression scale assessed at T3 (sensitivity check 2). In addition, for 89 participants without onset of depressive disorder at T4, it was unknown whether they developed depression from T4 to T6. We checked whether the findings still held after excluding this subsample (sensitivity check 3). Then, we repeated the main analyses without adjusting for gender, age, and socioeconomic position (sensitivity check 4) and tested each of the 8 effects in separate univariate models (sensitivity check 5).

Open Science
The data and syntax have been made publicly available through the Open Science Framework and can be accessed at https://osf.io/zvw5d/.

RESULTS
Descriptive Statistics
Adolescents who developed a depressive disorder between 16 and 25 years of age were more likely to be female, have a lower socioeconomic family status, and report more (sub-clinical) depressive symptoms and other lifetime psychiatric problems at 16 years than their peers who did not develop a depressive disorder (Table 1).

Task Attributes
As presented in Table 1, engagement to reward and non-punishment had a positive value for all groups, which means that all groups showed more engagement to reward than to non-reward and more engagement to non-punishment than to punishment. In voluntary trials, difficulty to disengage from reward and non-punishment also showed positive values for all groups, that is, participants in general had more difficulties disengaging from expected reward and non-punishment than from expected non-reward and punishment in trials in which they could voluntarily control their attention. On a more automatic level of processing, the depression groups showed negative values on disengagement from reward and non-punishment, that is, less difficulties in disengaging from reward and non-punishment than in disengaging from non-reward and punishment, whereas the control groups showed virtually no difference. For other task-related descriptive statistics, see Tables S7 and S8, available online.

Reward-Related Attentional Biases and Onset of Depression
Faster disengagement from expected reward and non-punishment during automatic trials predicted onset of depressive disorder (p < FDR-derived significance threshold; Table 2; 95% confidence intervals of odds ratios are presented in Table S9, available online). No other tests reached statistical significance.

Sensitivity Analyses. Excluding participants with comorbid diagnoses did not weaken the effect of faster disengagement from expected reward; if anything, the effect became stronger. The effect of faster disengagement from expected non-punishment became slightly weaker and no longer reached statistical significance (sensitivity check 1; Table 2, right panel). Adjusting for depressive symptoms at T3 (sensitivity check 2; Table S10, available online), exclusion of participants without onset of depressive disorder at T4 for whom T6 information was missing (sensitivity check 3; Table S11, available online), and repeating the main analyses without adjusting for gender, age, and socioeconomic position (sensitivity check 4; Table S12, available online)

TABLE 1 Descriptive Statistics of Demographics and Attentional Engagement to and Disengagement From Expected Reward and Non-Punishment, Presented Separately for Each Prospective Diagnostic Group

	Mean (SD) or Count (%)			
	Depression (n = 81)	No Depression (n = 450)	Depression, No Other Diagnoses (n = 41)	No Psychiatric Diagnosis (n = 305)
Demographics and psychiatric problems				
Socioeconomic family status (n = 80, n = 449)	0.05 (0.84)	0.15 (0.73)	0.00 (0.82)	0.17 (0.72)
Age at time of SOT	16.0 (0.6)	16.2 (0.6)	15.9 (0.7)	16.1 (0.6)
Age at first onset of depression	20.0 (3.2)	—	20.4 (3.3)	—
Women	55 (68%)	216 (48%)	28 (68%)	150 (49%)
Psychiatric diagnoses other than depression[a]	40 (49%)	145 (32%)	—	—
Depressive symptoms at time of SOT[b] (n = 80, n = 444)	0.31 (0.25)	0.23 (0.22)	0.32 (0.25)	0.20 (0.20)
Attentional engagement to and disengagement from expected reward and non-punishment (SOT)				
Engagement to reward, automatic	30.28 (27.94)	29.54 (33.15)	30.29 (28.81)	29.57 (33.67)
Difficulty to disengage from reward, automatic	−19.78 (69.08)	2.24 (61.13)	−29.42 (74.85)	0.57 (59.95)
Engagement to reward, voluntary control	40.80 (41.35)	36.76 (50.99)	50.01 (36.65)	37.59 (50.65)
Difficulty to disengage from reward, voluntary control	8.93 (52.72)	5.30 (51.35)	11.16 (45.36)	2.95 (52.01)
Engagement to non-punishment, automatic	24.35 (29.53)	28.54 (34.90)	27.75 (28.36)	28.51 (34.37)
Difficulty to disengage from non-punishment, automatic	−20.02 (71.74)	1.51 (61.83)	−19.63 (77.58)	1.36 (61.44)
Engagement to non-punishment, voluntary control	32.16 (51.17)	34.95 (50.47)	32.84 (49.01)	34.36 (51.31)
Difficulty to disengage from non-punishment, voluntary control	12.03 (70.63)	4.11 (59.56)	20.76 (63.75)	1.54 (59.42)

Note: SOT = spatial orienting task.
[a]Lifetime separation anxiety disorder, agoraphobia, generalized anxiety disorder, obsessive compulsive disorder, panic disorder, social phobia, specific phobia, attention-deficit disorder, oppositional defiant disorder, or conduct disorder.
[b]Mean score on the Youth Self-Report affective problems scale: 0 = "not true"; 1 = "somewhat or sometimes true"; 2 = "very or often true"; higher scores reflect more depressive symptoms.

TABLE 2 Results of Logistic Regression Analyses of Onset of Depression between 16 and 25 Years of Age on Reward-Related Attentional Biases at 16 Years

	Depression[a] (n = 529)		Depression Without Other Diagnoses[b] (n = 346)	
	OR	p	OR	p
Reward model				
Engagement to reward, automatic	0.980	.439	0.918	.319
Difficulty to disengage from reward, automatic	**0.670**	**<.001**	**0.571**	**<.001**
Engagement to reward, voluntary control	1.107	.789	1.248	.888
Difficulty to disengage from reward, voluntary control	1.055	.671	1.181	.824
Non-punishment model				
Engagement to non-punishment, automatic	0.887	.182	0.948	.383
Difficulty to disengage from non-punishment, automatic	**0.734**	**.007**	0.740	.043
Engagement to non-punishment, voluntary control	0.939	.313	0.907	.292
Difficulty to disengage from non-punishment, voluntary control	1.132	.841	1.333	.945
Full model				
Engagement to reward, automatic	1.009	.525	0.926	.345
Difficulty to disengage from reward, automatic	**0.679**	**.001**	**0.591**	**.002**
Engagement to reward, voluntary control	1.127	.822	1.299	.921
Difficulty to disengage from reward, voluntary control	1.061	.689	1.194	.839
Engagement to non-punishment, automatic	0.867	.148	0.906	.301
Difficulty to disengage from non-punishment, automatic	**0.751**	**.011**	0.780	.080
Engagement to non-punishment, voluntary control	0.931	.295	0.923	.335
Difficulty to disengage from non-punishment, voluntary control	1.141	.849	1.361	.947

Note: All variables were standardized (Z-values) before analysis. All effects were adjusted for gender, age at time of the attentional reward bias task, and socioeconomic family status (unadjusted effects are presented in Table S12, available online). One-sided p values are reported. Boldface type indicates p values below the false discovery rate (FDR)-derived significance threshold (.0125). OR = odds ratio.
[a]DSM-IV diagnosis of major depressive disorder or dysthymia between 16 and 25 years of age.
[b]Sensitivity check 1: similar to a, but without other diagnoses (ie, depressed only versus super-healthy).

yielded results comparable to the main analyses. Testing each of the 8 effects in separate univariate models (sensitivity check 5) resulted in the same patterns (exact odds ratios and p values are available from the authors upon request).

Additional Post Hoc Check. The disengagement scores were computed by difference scores; therefore, the disengagement effects we found could be explained by the fact that participants who later developed depression disengaged more easily from locations of expected reward (or non-punishment) to locations of expected non-reward (or punishment), by the fact that they showed more difficulties in disengaging from locations of expected non-reward (or punishment) to locations of expected reward (or non-punishment), or by both. Figure 1 and Table S8, available online, indicate that the differences between individuals with and without onset of depression were due mainly to difficulties in shifting from a location of expected non-reward or punishment to a location of expected reward or non-punishment, that is, the main group differences were

found in un-cued hard automatic response trials (Table S8, available online).

DISCUSSION

This study showed that decreased reward responsiveness predicts future onset of depression. Our results provide evidence in favor of the hypothesis that easier disengagement from expected reward than from expected non-reward and easier disengagement from expected non-punishment than from expected punishment at 16 years of age predicted depressive disorder between 16 and 25 years of age. This was found at the more automatic level and not at the more voluntary level of information processing. Adolescents who would later develop depression had more difficulties than their never-depressed peers in disengaging from locations of expected negative outcomes (ie, non-reward and punishment) and subsequently shifting to locations of expected positive outcomes (ie, reward and non-punishment). Contrary to expectations, we found no evidence that decreased initial engagement toward reward

FIGURE 1 Automatic Disengagement From Locations of Expected Reward Versus Non-Reward
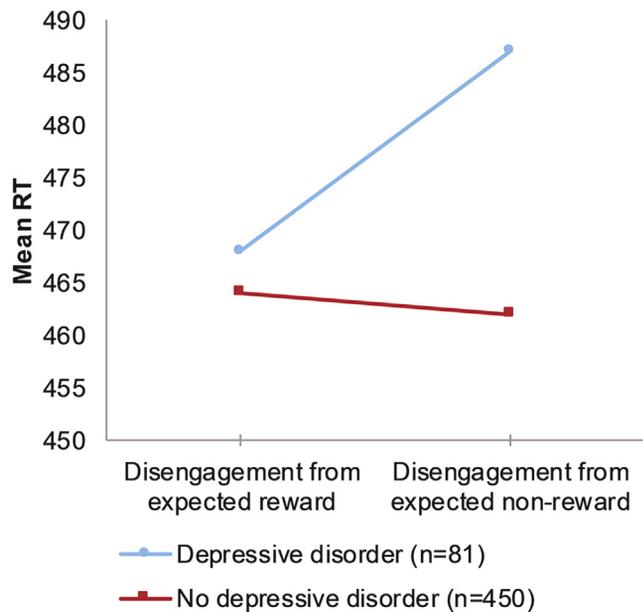
Note: Mean reaction times (RTs) of automatic disengagement from locations of expected reward to locations of expected non-reward and automatic disengagement from locations of expected non-reward to locations of expected reward are presented separately for adolescents with and without later onset of depression. Patterns are similar for automatic disengagement from locations of expected non-punishment compared with expected punishment (not presented here). Please note color figures are available online.

or non-punishment predicts onset of depressive disorder. Effects were not driven by co-occurring anxiety or other psychiatric problems and therefore seem specific to depression, and they were not driven by subclinical depressive symptoms at 16 years of age.

Engagement to expected reward in our task should be interpreted as engagement to expected reward when the target actually appears where the reward is expected, that is, when shifting attention from one location to the other is not required. Disengagement from expected non-reward is to be interpreted as a shift toward expected reward after the initial expectation that the target would appear in a different location and would be non-rewarding, that is, when shifting attention from one location to the other is required. The fact that we found a disengagement effect but not an engagement effect suggests that adolescents with vulnerability to depression respond similarly to expected reward, non-reward, non-punishment, and punishment when there is no need to shift attention, but specifically show decreased reward responsiveness in situations in which they are initially focused on negative information.

Our general finding that low reward responsiveness predicts onset of depression is consistent with preliminary

prospective evidence from most previous studies.[6,7,10,11,13] Two studies found opposite effects. In one study, increased activity in reward-related brain areas during selfish rewards predicted an increase in depressive symptoms[9]; in the other, increased node strength for resting-state reward-related brain networks predicted onset of depression.[12] The latter finding might be less contradictory than it seems, because it has been argued that increased resting-state node strength could imply a blunted responsiveness to rewards.[12] Our findings also are consistent with cognitive neuropsychological models of depression according to which biases toward negative and away from positive information have a central causal role in the development of depression[32] and with earlier suggestions that these biases might be driven by a difficulty to disengage from negative stimuli rather than by more initial engagement toward negative stimuli.[33] That we did not find the hypothesized effect of decreased engagement toward expected reward and non-punishment tentatively suggests that vulnerability to future depression is not characterized by problems with engaging in rewarding situations when they present themselves, but more with the incapability to let go of negative situations and redirect attention to situations that might potentially result in reward. This could ultimately result in the overall bias toward negative and away from positive information that characterizes depressed individuals.

Participants who did not develop depression showed no difference in automatic disengagement from expected reward (or non-punishment) versus non-reward (or punishment), whereas one would possibly expect them to show more difficulties in disengaging from expected reward than the other way around.[34] This lack of an automatic disengagement effect is consistent with previous studies in which the same task was used,[14,25,34] but so far no plausible explanation has been given. We propose that the perceived safety of the conditions in which reward and non-punishment were expected and the perceived threat of the conditions in which non-reward and punishment were expected might have moderated participants' attentional scope. Because safe environments have been found to broaden attentional scope and threatening environments have been found to narrow attentional scope,[35] individuals might find it easier to redirect their broader focus away from a safe environment (ie, a location of expected reward or non-punishment) than to redirect their narrow focus away from a threatening environment (ie, a location of expected non-reward or punishment). This could have masked the difficulties healthy adolescents can have with disengaging from expected reward (or non-punishment), particularly on more automatic levels of information processing, because these are associated with a more narrow attentional scope

than voluntary levels.[14] In a task containing a neutral condition, not part of the present task, it might be better evaluated if healthy adolescents have more difficulties in disengaging from expected reward than in disengaging from an expected neutral condition.

Reflection that our findings pertain to automatic rather than voluntary levels of information processing is required. It has been suggested that depressed individuals are characterized particularly by voluntary higher-order top-down information-processing biases, because previous studies using behavioral reaction time tasks have found results on voluntary but not on automatic levels of information processing.[36] It is important to emphasize that our prospective approach of investigating information-processing biases in individuals who were healthy at the time of assessment is novel and an important difference from the existing literature. We propose that although voluntary processes might indeed largely explain information-processing biases for individuals who already have depression, automatic processes could constitute a vulnerability to depression in not-yet-depressed individuals. Adolescents with an automatic tendency to remain focused on negative situations and a diminished capability to redirect attention to potentially rewarding situations might process disproportionally more negative information,[14] which might gradually trigger the more voluntary top-down negative biases that characterize patients who are depressed. A plausible explanation of why no automatic attentional biases have been found in patients who are depressed is that they in general perform slower on reaction time tasks, which could mask existing automatic biases. That is, automatic versus voluntary processing tends to be operationalized in the same way for everyone without taking into account individual differences in processing time. Because patients who are depressed process information slowly, they might not show automatic reward-related differences on a behavioral reaction times task when the reward-related information is presented only briefly.

The findings of the present study suggest that enhancement of reward responsiveness, particularly in situations in which adolescents are focused on negative information, could benefit adolescents who are vulnerable to depression. Whether enhancement of reward responsiveness can actually lower risk of depression can be tested only in an experimental setting, but if it could, the potential gain would be substantial. Assuming that our effect sizes reflect un-confounded causal relations, we estimated that increasing reward-related attentional bias in adolescents with low reward responsiveness by 1 SD could prevent 5.3 depression onsets per 100 adolescents treated (see Table S13 for details). Previous attempts to modify attentional biases toward negative information in currently depressed individuals suggest that an increase of 1 SD is feasible.[37,38] However, note that these interventions did not focus on training reward responsiveness specifically in situations in which people are focused on negative information, did not target the specific automatic processes of attention our results apply to (ie, 250 ms between cue and target), and were aimed at lowering depressive symptoms in already depressed individuals rather than at lowering the risk at first onset of depression.

Our study has notable strengths. We investigated whether reward-related attentional bias predicts onset of depression with a large sample and a long follow-up period (9 years). Our large sample allowed excluding participants with an onset of depression at the time of or before the assessment of the attention task, which was necessary for disentangling contemporaneous from prospective associations. This led to confirmation of previously reported preliminary evidence[6,7,10,11,13] that biased processing of reward-related information might represent a vulnerability marker for depression, which has important implications for early treatment and prevention. Depressive disorder was assessed by standardized diagnostic interviews at 19 years of age and by a validated depression self-report diagnostic assessment at 25 years. Because depression is commonly characterized by high comorbidity with other psychiatric disorders, we started by comparing adolescents with and without a depressive disorder between 16 and 25 years of age regardless of other psychiatric problems, because this best represents depression in the population, and assessed the specificity of these findings for depression by repeating the analyses after excluding adolescents with lifetime psychiatric problems other than depression.

Our study is not without limitations. First, because of the lack of a neutral condition in the SOT, it was impossible to distinguish between difficulties with disengaging from negative information and decreased responsiveness to positive information after an initial focus on negative information. A neutral condition also could have helped to explain the absence of a disengagement effect in healthy controls. Second, the retrospective assessments of the CIDI and the LIDAS at 19 and 25 years of age increased the risk for recall bias, especially for psychiatric problems with a young age at onset. Third, our sample size was sufficiently large to find effect sizes with an odds ratio approximately equal to 0.65, but not for finding more subtle effects that also could play a role in

vulnerability to depression. Fourth, the conclusions of this study are limited to depression onset from mid-adolescence up to early adulthood; they might not generalize to populations with an early or later onset. Fifth, it might have been interesting to compare the reward responsiveness of the group with future depression with the reward responsiveness of a group with past depression, but because of the heterogeneity of the group with past depression (ie, adolescents could have remitted from depression or not, and might or might not have experienced several episodes since the first onset of depression), we were not convinced that the results of such a comparison could be interpreted adequately.

To conclude, we found that difficulties in shifting attention from expected non-reward to expected reward and from expected punishment to expected non-punishment at 16 years of age predicted depression during 9 years of follow-up. This was found only at an automatic level of information processing. Our findings suggest that decreased reward responsiveness at 16 years marks vulnerability for depression. Prevention programs may aim at increasing at-risk adolescents' responsiveness to cues for potential rewards, particularly in situations in which they are focused on negative experiences.

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