# Elevated cognitive rumination and adverse life events are associated with lower cortical surface area and suicidal ideation in adolescents with major depressive disorder

Dauvermann, M.R.; Schmaal, L.; Colic, L.; Velzen, L.S. van; Bellow, S.; Ford, T.J.; ... ; Harmelen, A.L. van

Journal of Affective Disorders 325 (2023) 93–101

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

# Elevated cognitive rumination and adverse life events are associated with lower cortical surface area and suicidal ideation in adolescents with major depressive disorder

Maria R. Dauvermann [a,b,c], Lianne Schmaal [d,e], Lejla Colic [f,g,h], Laura S. van Velzen [d,e], Sophie Bellow [c], Tamsin J. Ford [c], John Suckling [c], Ian M. Goodyer [c], IMPACT Consortium, Hilary P. Blumberg [f,i,j], Anne-Laura van Harmelen [c,k,*]

[a] Institute for Mental Health, School of Psychology, University of Birmingham, UK
[b] McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, MA, USA
[c] Department of Psychiatry, University of Cambridge, UK
[d] Orygen, Parkville, VIC, Australia
[e] Centre for Youth Mental Health, University of Melbourne, Melbourne, VIC, Australia
[f] Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA
[g] Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany
[h] Center for Intervention and Research on Adaptive and Maladaptive Brain Circuits Underlying Mental Health (CIRC), Jena, Germany
[i] Child Study Center, Yale School of Medicine, New Haven, CT, USA
[j] Department of Radiology and Biomedical Imaging, Yale School of Medicine, New Haven, CT, USA
[k] Institute of Education and Child Studies, Leiden University, the Netherlands

ARTICLE INFO

*Keywords:*
Suicidal ideation
Youth
Major depressive disorder
Rumination
Magnetic resonance imaging
Structural equation modeling

ABSTRACT

*Introduction:* Suicide is the second most common cause of death among young people. Structural brain alterations, rumination, and recent stressful experiences contribute to suicidal thoughts and behaviors (STBs).
*Methods:* Here, we employed structural equation modeling (SEM) to examine the unique and combined relationships of these risk factors with STBs in a sample of young people with major depressive disorder (MDD) from the Magnetic Resonance-Improving Mood with Psychoanalytic and Cognitive Therapies (MR-IMPACT) study ($N = 67$, mean age = 15.90; standard deviation ± 1.32).
*Results:* Whereas increased rumination and lower surface area of brain regions, that have been previously reported to be involved in both STBs and rumination, were associated with each other (Beta = −0.268, standard error (SE) = 0.114, Z = −2.346, $p = 0.019$), only increased rumination was related to greater severity of suicidal ideation (Beta = 0.281, SE = 0.132, Z = 2.134, $p = 0.033$). In addition, we observed that recent stress was associated with lower surface area in the suicidal ideation model without covariate only (Beta = −0.312, SE = 0.149, Z = −2.089, $p = 0.037$). For the attempt models, no associations were found between any of the risk factors and suicide attempts.
*Limitations:* We emphasize that these findings from this secondary analysis are hypothesis-forming and preliminary in nature given the small sample size for SEM analyses.
*Conclusion:* Our findings suggest that neither lower surface area nor recent stress are directly associated with youth suicidal ideation or attempt. However, lower surface area is related to recent stress and increased rumination, which predicted greater severity of suicidal ideation in young people with MDD.

## 1. Introduction

More than 800,000 individuals lose their lives by suicide annually worldwide (Centers for Disease Control and Prevention et al., 2012; World Health Organization, 2014). Among young people, suicide is the second most common cause of death (Curtin & Heron, 2019; Hawton et al., 2012) for which suicidal thoughts and behaviors (STBs) being major risk factors (Klonsky, May, & Saffer, 2016; Ribeiro et al., 2016), as

* Corresponding author at: Institute of Education and Child Studies, Leiden University, the Netherlands.
*E-mail address:* a.van.harmelen@fsw.leidenuniv.nl (A.-L. van Harmelen).

https://doi.org/10.1016/j.jad.2022.12.087
Received 26 March 2022; Received in revised form 25 August 2022; Accepted 18 December 2022
Available online 28 December 2022

are mental health conditions (Auerbach et al., 2019; Barzilay et al., 2020; de Beurs, Ten Have, Cuijpers, & de Graaf, 2019; Kasen & Chen, 2019; Lewinsohn, Clarke, Seeley, & P, 1994). In particular, major depressive disorder (MDD) is a mental health condition with one of the highest risks of suicide (Auerbach et al., 2019; de Beurs et al., 2019; Lewinsohn et al., 1994; Mullins et al., 2019; O'Rourke, Jamil, & Siddiqui, 2021). As such, a better understanding of the mechanisms that underlie this risk to STBs in young people suffering from MDD is critically important.

One of the potential mechanisms that underlies vulnerability to adolescent STBs is affective and behavioral dysregulation in the form of excessive and perseverative negative thinking, i.e., rumination (Barzilay et al., 2019; Crandall, Allsop, & Hanson, 2018; Harman et al., 2021; O'Reilly et al., 2020; Pu, Setoyama, & Noda, 2017). Rumination aids vulnerability to STBs, for instance, rumination has particularly strong links with STBs in individuals with MDD (i.e. suicidal ideation (Rogers & Joiner, 2018; Surrence, Miranda, Marroquín, & Chan, 2009); attempts (Horwitz, Czyz, Berona, & King, 2019; Rogers & Joiner, 2018; Surrence et al., 2009; Tang et al., 2021)).

STB risk in young people is further linked to alterations in brain structure and functioning (Schmaal et al., 2020). Convergence across neuroimaging research to date (Schmaal et al., 2020; van Harmelen, Schmaal, & Blumberg, 2021) suggests a theoretical model where suicidal ideation may be generated through structural and functional changes in ventral prefrontal regions and their major projection sites that underlie affective cognitive functions, such as rumination. The transition to suicidal behavior may then occur through the additional involvement of altered dorsal and lateral prefrontal systems and connections comprising top-down executive inhibition, suboptimal decision-making and planning processes (Schmaal et al., 2020). Complex interactions are thought to underlie the transition from suicidal thoughts to behaviors, which require further research. So far, only a limited number of neuroimaging studies examined young people with STBs, and reported altered functioning in frontal systems (Auerbach, Pagliaccio, Allison, Alqueza, & Alonso, 2021b; Johnston et al., 2017; van Harmelen et al., 2021) and reduced gray matter volumes in prefrontal and anterior cingulate cortices (Auerbach, Pagliaccio, et al., 2021b; Fan et al., 2019; Jabbi et al., 2020; Johnston et al., 2017; Lippard et al., 2019; van Harmelen et al., 2021). Therefore, risk for STBs may arise through increases in rumination presumably underpinned on a neural level by atypical brain structure and function linked to these regions. However, to date, the unique and contributing roles of rumination and its underpinning brain structure have not been examined together in STBs in young people with MDD.

Risk for STBs is also elevated after exposure to early-life stress such as trauma, abuse, neglect, or bullying experiences in childhood or adolescence (Barzilay et al., 2021; Chen et al., 2021; Duprey, Handley, Manly, Cicchetti, & Toth, 2021; Gonçalves Peter et al., 2020; Lebowitz, Blumberg, & Silverman, 2019; Roh et al., 2015; Saint Onge, Cepeda, Lee King, & Valdez, 2013; Sewall et al., 2020). Stress experiences during development are thought to shape brain development in multiple ways, including through alterations in synaptic pruning of neuronal networks (Johnson, Fields, & Bluett, 2020). In line with this, stressful experiences during childhood and adolescence have been linked with structural brain alterations in young people, including reduced corticostriatal-limbic gray matter volumes (Edmiston et al., 2011), that underpin cognitive flexibility associated with STBs (Spann et al., 2012). Therefore, stress during adolescence has been linked to mood and behavioral problems in young people (Green et al., 2010; McLaughlin et al., 2010a, 2010b). It is clear that stressful experiences, rumination, and related brain morphology contribute to STB risk in young people. To increase our understanding of mechanisms that contribute to STBs in young people with MDD, they need examining concurrently with each other such that any unique as well as joint effects can be revealed.

Here, we used structural equation modeling (SEM) in young people with MDD and STBs to investigate the relations and interrelations of self-reported ruminative responses and recent stressful experiences during adolescence together with their putative brain structural underpinnings. The Magnetic Resonance-Improving Mood with Psychoanalytic and Cognitive Therapies (MR-IMPACT) sample consisted of young people with a primary diagnosis of MDD. We specifically examined surface area (SA) of brain regions as this is the structural brain measure most clearly linked to STBs in a recent mega-analysis (Campos et al., 2020).

We hypothesized first, that higher levels of rumination, lower SA of related brain regions and exposure to one or more recent stressful events during adolescence would each be uniquely associated with STBs. We further expected that recent stress would be related to both lower SA of the brain and increased rumination. Furthermore, we assumed that lower SA and increased rumination would be associated with each other. We also hypothesized that lower SA may not be directly associated with youth STBs but lower SA will be related to increased rumination, with rumination predicting STBs directly. Similarly, we expected that recent stress may not directly predict STBs but rather recent stress will be associated with lower SA of the brain or rumination, with rumination predicting STBs instead.

## 2. Methods

### 2.1. Participants

Sixty-seven participants, aged between 11 and 17 years (mean = 15.90; standard deviation (SD) ± 1.32), 73 % females, were selected from the MR-IMPACT study based on complete data on the Columbia-Suicide Severity Rating Scale (C-SSRS) and the structural T1 scan, and represent a subsample of the MR-IMPACT study, and all had a diagnosis of MDD (Table 1). MR-IMPACT is a substudy of the IMPACT study, which is a larger clinical trial in adolescents with MDD (Goodyer et al., 2017). Full details of the MR-IMPACT protocol, including inclusion criteria, have been presented previously (Hagan et al., 2013a). Briefly, participants were recruited at 15 National Health Service child and adolescent mental health service (CAMHS) clinics in three regions in England. A current MDD diagnosis was established according to DSM-IV through child and parent interviews using the Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997). All participants in this sample of the MR-IMPACT study completed the short form of the Mood and Feelings Questionnaire (SMFQ) at the time of imaging (Sharp, Goodyer, & Croudace, 2006) (mean = 19.31; SD ± 6.76).

Exclusion criteria for MR-IMPACT included a diagnosis of primary or secondary comorbid disorders of bipolar type I, schizophrenia or eating disorders, alcohol or substance abuse or dependence, pervasive developmental disorder, generalized learning problems, current use of medication that may adversely interact with selective serotonin reuptake inhibitors, presence of a gross brain abnormality (T1 images screened by a neuroradiologist) and Magnetic Resonance Imaging (MRI) contraindications, including claustrophobia. Participants above 16 years provided written informed consent, while participants below 16 years and their parents/guardians provided written informed assent and informed permission, respectively. The study was approved by the National Research Ethics Service Committee East of England - Cambridge Central. Findings of these data have been published elsewhere, for example on age-related gray matter volume differences (Hagan et al., 2015) and cortical thickness (Villa et al., 2020) in adolescents with MDD compared to healthy controls. Findings on the full pragmatic superiority randomised controlled trial have been reported previously, including evidence that on average self-reported ruminative thinking dimished over the course of the longitudinal study regardless of which treament the patients received (Goodyer et al., 2017). However, SA and their relationship to STBs, rumination and recent stressful experiences have not been reported before.

**Table 1**
Characteristics for the MR-IMPACT sample ($N = 67$).

| | Number (percentage) | Mean (SD) | |
|---|---|---|---|
| Age | – | 15.90 (1.32) | |
| Sex (Female: Male) | 49: 18 (73 %: 27 %) | – | |
| Ethnicity | White<br>61 (91 %) | Mixed W/B/C/A/O[1]<br>6 (9 %) | |
| Antidepressant use[2] | 29 (43 %) | – | |
| Questionnaires | | | |
| Lifetime ideation | | | |
| Mild to severe lifetime ideation | 61 (91 %) | 3.4 (1.69) | |
| Lifetime attempt | | | |
| Presence of lifetime history of attempts (Yes: No) | 22: 45 (33 %: 67 %) | - | |
| SMFQ | – | 19.32 (6.76) | |
| RRS[3] | – | 16.18 (3.8) | |
| LEQ[4] | – | – | |
| Three questions | No event | One event | ≥ Two events |
| Lost touch with friends | 23 (57.5 %) | 10 (25 %) | 7 (17.5 %) |
| Problems with friends | 19 (47.5 %) | 14 (35 %) | 7 (17.5 %) |
| Lost people with personal significance | 18 (45 %) | 13 (32.5 %) | 9 (22.5 %) |
| Surface area of four regions of interest[5] | | | |
| Surface area | 67 (100 %) | | |
| IFG, Parsorbitalis | – | 788.93 (80.80) | |
| Precuneus | – | 4031.03 (489.07) | |
| Rostral anterior cingulate | – | 766.71 (146.38) | |
| Superior temporal | – | 3928.99 (410.23) | |

Abbreviations: IFG, inferior frontal gyrus; LEQ, Life Events Questionnaire; RRS, Ruminative Response Scale; SMFQ, Short Mood and Feelings Questionnaire; SD, standard deviation.
1 Mixed W/B/C/A/O = Mixed White, Black, Caribbean, African, or Other.
2 Including selective serotonin reuptake inhibitors.
3 Missing data in six participants (9 %).
4 Missing data in 27 participants (40 %).
5 Four regions of interests.

## 3. Measures

### 3.1. Suicidal thoughts and behaviors

STBs were assessed using the C-SSRS (Posner et al., 2011). The C-SSRS is an established interview to assess current and lifetime suicidal thoughts and actual attempts, which are defined as self-injurious acts committed with at least some intent to die. Ideation and attempt were assessed for lifetime period ('lifetime ideation/attempt'). Details on suicidal ideation and attempt are presented (Table 1).

Two STB groupings were generated based on the C-SSRS to provide for the systematic study considering potential overlap and differentiation between ideation and attempt:

(i) '*Lifetime suicidal ideation*' as a continuous variable (severity of ideation, based on the 5-point Likert scale from one to five with higher scores reflecting greater severity of ideation; see Table 1)
(ii) '*Lifetime suicidal attempt*' as a dichotomous variable (lifetime history of actual suicidal attempt scored '1' versus no lifetime history of attempt scored '0'; an actual attempt was defined as a self-injurious act committed with at least some intent to die).

### 3.2. Rumination

We assessed cognitive rumination with the Ruminative Response Scale (RRS), a 39-item measure derived from the Nolen-Hoeksema's Ruminative Depression Questionnaire (Nolen-Hoeksema, 2000). The RRS describes responses to low mood that are self-focused, symptom-focused and based on the possible consequences and causes of low mood using a 4-point Likert scale. Here, the shortened version of the RRS with 17 items was administered. The total RRS score is a sum score based on the subscales of reflection and brooding comprising responses to self-focus and ascertaining potential consequences and causes of low mood. Please see Table 1 and Supplementary Materials for more details.

### 3.3. Recent stress

Recent stress comprised an estimate of recent stressful events. A shortened version of the Life Events Questionnaire (LEQ; (Goodyer et al., 2011, Goodyer, Herbert, Tamplin, & Altham, 2000)) was used in which three questions were administered to assess undesirable stressful life events during the last twelve months. These three questions encompassed two friendship-based questions ('Lost touch with friends'; 'Problems with friends') and one general question ('Lost people of personal significance') to reflect peer and family relationship experiences of relevance to young people. The number of experienced events as well as the severity of these events were recorded. Scoring of severity was based on subjective rating on a Likert scale from '1' ('not at all') to '5' ('very stressful'). Moderate to severe recent undesirable life events were defined as scores between '3' to '5'. Briefly, 18 % of the young people had experienced two or more moderate to severe events when asked if they had lost touch with friends in the last year; 20 % reported to have had two or more moderate to severe events related to problems with friends; and 23 % said that they had lost people with personal significance. Please see Table 1 for details. In summary, the number of reported moderate to severe events across the three questions of the LEQ were recorded.

## 4. Structural MRI data

### 4.1. Structural MRI data acquisition

Neuroimaging data of all participants were acquired with a 3 Tesla Magnetom Trio Tim scanner (Siemens, Erlangen, Germany) at the Wolfson Brain Imaging Centre, University of Cambridge, UK. A high-resolution T1-weighted three-dimensional magnetically prepared rapid acquisition gradient echo sequence (3D-MPRAGE) was used to acquire date in the sagittal plane with the following parameters: 176 slices of 1 mm thickness without gap, repetition time (TR) = 2300 ms, echo time (TE) = 2.98 ms, inversion time (TI) = 900 ms, flip angle = 9°, matrix = 240 × 256, field of view (FOV) = 240 × 256 $mm^2$, voxel size = 1 $mm^3$.

### 4.2. Image preprocessing

T1-weighted MRI structural brain scans were analyzed using the validated and automated segmentation software FreeSurfer (Fischl et al., 2002) (version 6.0) (available at http://surfer.nmr.mgh.harvard.edu/). Here, we focused on SA of the 17 brain regions previously linked to STBs (Schmaal et al., 2020). Thus, the segmentation of cortical SA was visually inspected for accuracy following standardized protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols/). SA segmentations were excluded from the analyses if they were not properly segmented or outliers (> three SD away from the mean) were identified. The selection of brain markers followed these steps, which are summarized in the Supplemental Fig. S1 (first column). We extracted left and right hemispheric regional SA of the standard 68 Desikan-Killiany regions (Desikan et al., 2006) and averaged left and right hemispheric regional SA following the Passamonti and Malpetti approach (Malpetti et al., 2020; Passamonti et al., 2018, 2017). From these, we selected the 17 regions of interest (ROIs) that have been linked to STBs previously (please see Table S1) (Schmaal et al., 2020).

### 4.3. Overview of statistical analyses

We used SEM (Kline, 2016) in Lavaan (version 0.6–8; (Rosseel, 2012) in R version 4.0.5 (R Core Team, 2020)). To assess model fit, we report chi-square ($X^2$) fit statistics and the root mean squared error of approximation (RMSEA). RMSEA of less than 0.08 implies an acceptable model fit, and values of less than 0.05 imply a good fit (Kline, 2016). Furthermore, we report the comparative fit index (CFI), and the Tucker-Lewis index (TLI), for which the values of CFI and TLI > 0.95 represent good fit of the overall model (Kline, 2010). In addition, we also report the standardized root squared residual (SMRM). We note that all reported fit statistics and indices are over-identified. This means that our models were fully saturated and had perfect fit with 0 degrees of freedom, therefore we report and focus our discussion on the key associations within the models, and we will not interpret model fit indices. All 67 participants for this SEM analysis from the MR-IMPACT study were included because we employed the estimator maximum likelihood (ML) and we used full-information maximum likelihood (FIML), which is optimal for models that contain missing data that are assumed to be missing at random (Kline, 2016; Nash, 2014). Using FIML, the estimation assesses all parameters based on the cases that have available data. All variables were scaled to a standard normal distribution. Confirmatory Factor Analysis (CFA) and path analysis were run separately as the number of participants per parameter in the model would exceed the established rule of thumb of five parameters otherwise (Kline, 2005). Running CFA and path analysis separately (called structure after measurement) is an acceptable solution in smaller samples (Rosseel & Loh, 2022).

### 4.4. Calculation of latent rumination, stress and brain factors

We ran CFA to calculate latent factors for the three factors of interest: a 'rumination factor', a 'stress factor' and a 'brain factor'. Given the relatively modest sample size, factor scores for all latent factors were calculated using the Factor Score Regression approach for one-factor models (DiStefano, Zhu, & Mîndrilã, 2009; Lu, Kwan, Thomas, & Cedzynski, 2011) and utilized in SEM analyses to test their relationships and inter-relationships with STBs.

We created a latent 'rumination' factor based on total RRS score, which is a sum score based on the subscales of reflection and brooding responses to low mood (please see Supplementary Material for details).

The latent 'stress' factor has been built based on the total number of events that were rated as moderate or more severe for each of the three types of events from the LEQ ('Lost touch with friends'; 'Problems with friends'; 'Lost people of significance'). Specifically, for each of the three types of events, participants were asked to rate the severity of the event on a Likert scale from '1' ('not at all') to '5' ('very stressful'). Participants were also asked to provide the number of such events on a scale from '0' to '3', where 3 was used to indicate 3 or more events. From these answers, and in line with Goodyer et al., 2000, we selected only those experiences where the severity was rated as to be moderate or more severe (i.e. severity scores of '3', '4' or '5'), and used the *number* of those events for our analyses. As such, our latent stress factor was based on the number of moderate or more severe experiences that participants had reported.

For the calculation of the latent 'brain' factor and given the current uncertainty of what neural markers play a role in STBs in young people, we selected ROIs that have also been shown to be implicated in rumination (please see Supplemental Fig. S1 (second column)). Firstly, we chose SA from the 17 ROIs that are involved with suicidal ideation and attempt (Schmaal et al., 2020). In the next step, we reduced the number of ROIs to four regions that were implicated with rumination in a recent meta-analysis covering functional studies (Zhou et al., 2020): the inferior frontal gyrus (IFG; subregion parsorbitalis), precuneus, rostral anterior cingulate and the superior temporal cortex ((Zhou et al., 2020); Table S1). Finally, the latent 'brain' factor was created based on the selection of these four ROIs (Table 1).

### 4.5. Integrative models

After the calculation of these 'rumination', 'stress' and 'brain' factors using factor analyses, we used a path analysis (Kline, 2016) in Lavaan (Rosseel, 2012) to study the interrelations between these three latent factors and STBs in a stepwise manner. The first model predicted lifetime ideation and the second predicted lifetime actual attempt. In each model, the stress, brain and rumination factors were allowed to co-vary (Turecki, Ernst, Jollant, Labonté, & Mechawar, 2012; Van Harmelen, Schmaal, & Blumberg, 2019).

We previously reported that higher rumination scores at baseline were significantly reduced after treatment in IMPACT (Goodyer, Herbert, et al., 2017). Therefore, we investigated whether any association between rumination and suicidal ideation or suicidal attempt was explained by depression symptomatology in general. We examined whether all findings remained significant when adding depression severity (measured with the SMFQ sum score as a covariate) to the models.

Finally, we calculated the correlation matrix between all variables in the ideation and attempt models (i.e., rumination, stress and brain). Please see the supplementary material.

## 5. Results

### 5.1. Calculation of latent rumination, stress and brain factors

Factor loadings for all three latent factors were positive (see Supplementary Table S2 for details). This suggests that higher scores for the rumination factor reflect higher rumination scores. Similarly for the stress and brain factors, higher scores reflect more reporting of stress exposure and higher SA, respectively. Standardized estimates for relations among the three latent factors are shown in Table S3.

### 5.2. Integrative models

#### 5.2.1. Lifetime suicidal ideation

We first tested a model where rumination, stress and the ROIs brain factors together predicted lifetime suicidal ideation. Rumination was positively associated with lifetime suicidal ideation (Fig. 1A) with regression estimates reported in Table S4). In addition, rumination was negatively associated with the brain factor, suggesting increased rumination was related to lower SA in the ROIs that underlie rumination processes in the brain (i.e. IFG (parsorbitalis), precuneus, rostral anterior cingulate and the superior temporal cortex). Additionally, stress was negatively associated with the brain factor, indicating that a greater number of recent stressful events were related to lower SA in those ROIs.

In the next step, we re-ran this model for suicidal ideation by using the sum score of the SMFQ as a covariate. We observed a significant relationship between the SMFQ and severity of ideation. However, SMFQ was not significantly related to rumination, stress or the brain factor. The positive association between rumination and severity of ideation remained significant as did the negative relationship between rumination and the brain factor (Fig. 1B, Table S4).

#### 5.2.2. Lifetime suicidal attempt

In a model testing the relations and interrelations between the rumination, stress and brain factors on lifetime suicidal attempt, we found that recent stress was negatively associated with the brain factor. In addition, reduced SA was significantly related to rumination. However, none of the three latent factors predicted suicidal attempts (Fig. 2A) with regression estimates reported in Table S5).

Then we re-ran this model by covarying for the SMFQ sum score. We found that SMFQ was not significantly related to any of the latent factors or history of attempt. Only the negative association between rumination

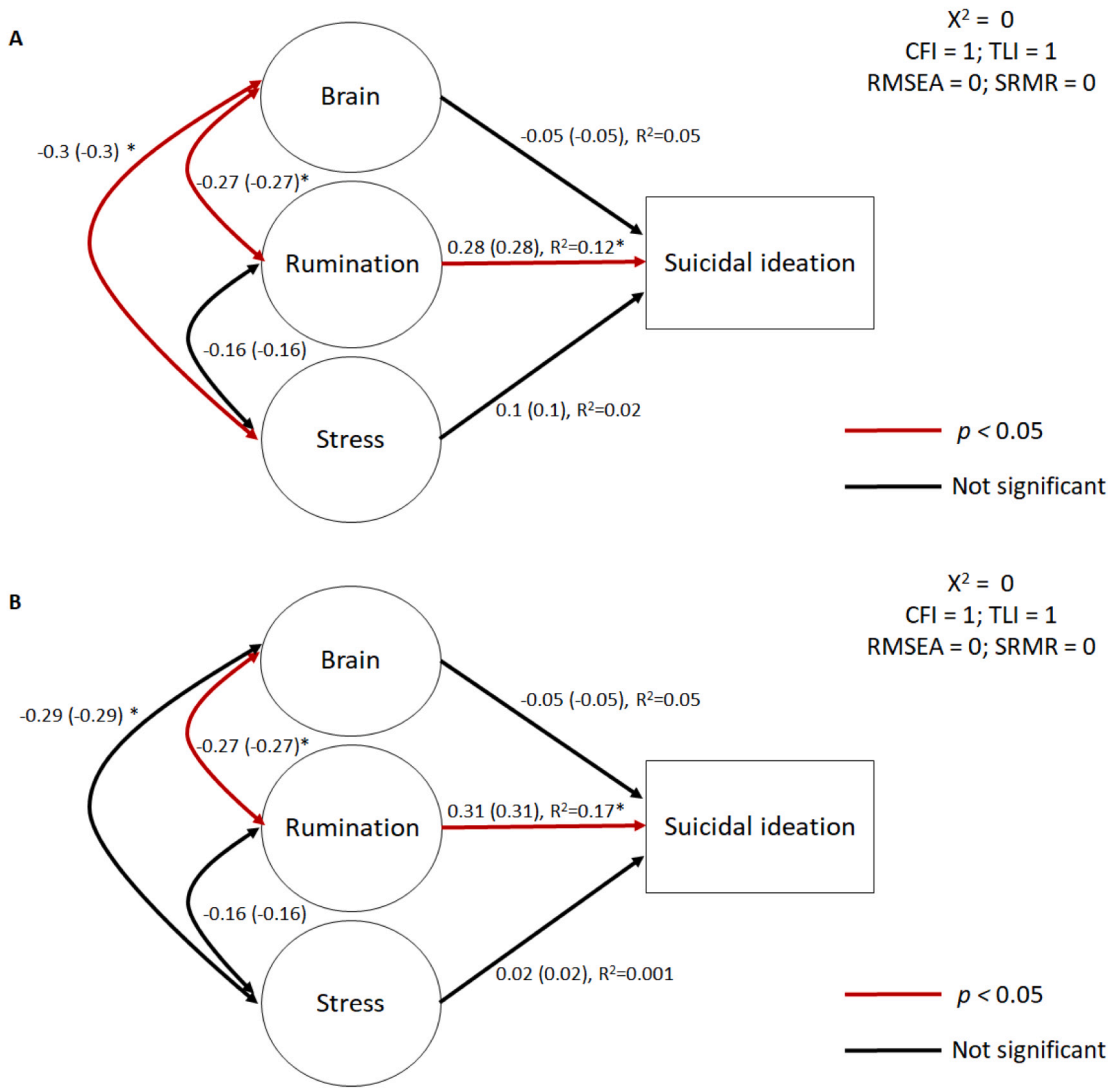


**Fig. 1.** Integrative ideation models.
A. Suicidal ideation - without SMFQ as covariate.
B. Suicidal ideation - with SMFQ as covariate.
Brain alterations were based on selected brain regions of inferior frontal gyrus (pars orbitalis), precuneus, rostral anterior cingulate and the superior temporal cortex. Estimates are unstandardized (standardized) path coefficients. Single-headed arrows represent regression paths. Double-headed arrows depict covariances between the three endogenous variables. Red arrows denote significant associations. Black arrows represent non-significant associations.* $p < 0.05$.
B. SMFQ was specified as covariate for all latent factors and the dependent variable in this model, but is not depicted for simplicity. The relationship between the sum score of SMFQ and ideation was significant at $p < 0.001$.
Abbreviations. SMFQ, Short Mood and Feelings Questionnaire; ROI, region of interest; STB, suicidal thoughts and behaviors.

and the lower SA of the brain remained significant (Fig. 2B, Table S5).

## 6. Discussion

We investigated the relationships and inter-relationships of rumination, recent stressful experiences during adolescence and brain structural alterations on STBs in young people with MDD. We observed that rumination was associated with greater severity of lifetime suicidal ideation, but not with suicide attempt history. A greater number of recent stressful experiences and higher rumination scores were independently related to lower SA of the brain regions (i.e., IFG (pars orbitalis), precuneus, rostral anterior cingulate and the superior temporal cortex regions) previously implicated in STBs among other regions (Schmaal et al., 2020). In addition, these regions have also been shown to underlie rumination (Zhou et al., 2020). These findings suggest that both recent stress and these brain regions may contribute to suicidal ideation through their effect on ruminative responses in young people with MDD, while recent stress was not associated with rumination. Indeed, after covarying for depressive symptoms, we observed that the relation between rumination and severity of ideation was not explained by depression severity. The strong relation between the brain and rumination factors, in addition to the strong relation between rumination and suicidal ideation from the correlation matrix findings, further support our tentative interpretation that lower surface area is associated with increased rumination, which predicted greater severity of suicidal ideation. Furthermore, this tentative conclusion was based on the fact that the brain regions selected for our analyses were chosen because of their suggested role in suicidal ideation (Schmaal et al., 2020) and rumination (Zhou et al., 2020). Unfortunately, our sample size did not meet the requirements to test this suggested mediation, as such, future studies with larger samples will be able to fully test this suggested mediation. We propose that these findings from this secondary analysis

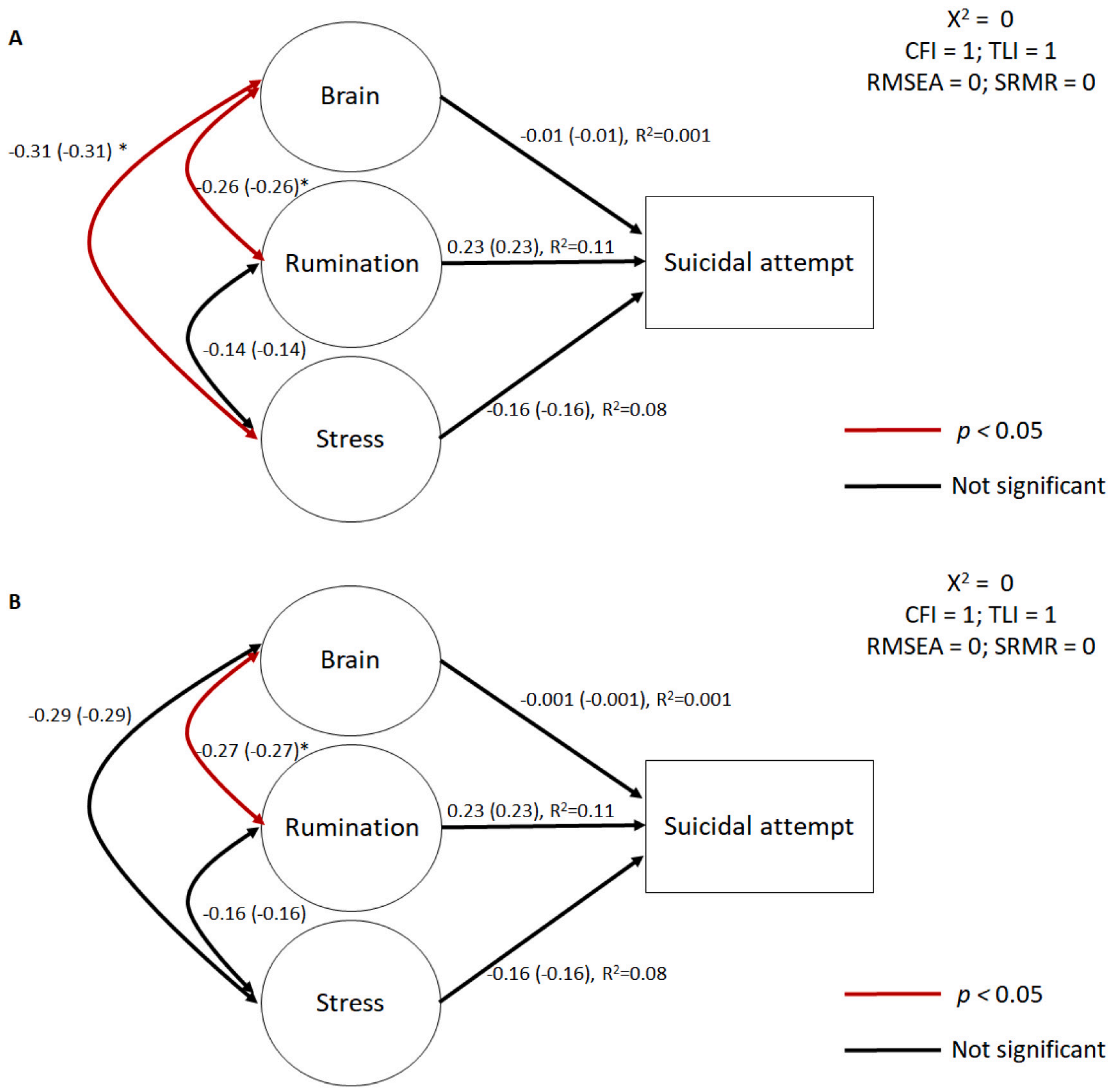


**Fig. 2.** Integrative attempt models.
A. Suicide attempt - without SMFQ as covariate.
B. Suicide attempt - with SMFQ as covariate.
Brain alterations were based on selected brain regions of inferior frontal gyrus (pars orbitalis), precuneus, rostral anterior cingulate and the superior temporal cortex. Estimates are unstandardized (standardized) path coefficients. Single-headed arrows represent regression paths. Double-headed arrows depict covariances between the three endogenous variables. Red arrows denote significant associations. Black arrows represent non-significant associations.
B. SMFQ was specified as covariate for all latent factors and the dependent variable in this model, but is not depicted for simplicity. No signficiant relationships were observed.
Abbreviations. SMFQ, Short Mood and Feelings Questionnaire; ROI, Region of interest; STB, suicidal thoughts and behaviors.

suggest a new hypothesis of a potential role of increased rumination in amplifying suicidal ideation in adolescents with MDD.

We found that more recent stressful life events were associated with lower SA of ROIs previously implicated in STBs (Schmaal et al., 2020) and rumination (Zhou et al., 2020) (i.e., the IFG (parsorbitalis), precuneus, rostral anterior cingulate and the superior temporal region) when not covaried by depressive symptoms. In addition, we further observed that lower SA was related to higher rumination factor scores, and that rumination was linked to greater severity of suicidal ideation. We suggest that these findings are in keeping with latent stress calibration models (McCrory & Viding, 2015) that propose recent stress may shape brain development and related cognitive functioning making individuals more vulnerable to mental illness (Puetz et al., 2020). Furthermore, these findings are in line with a STBs model proposed by Schmaal et al. (Schmaal et al., 2020) indicating that the brain factor representing lower SA of the IFG (parsorbitalis), precuneus, rostral anterior cingulate and the superior temporal region may support the generation of suicidal ideation via their function in rumination. Finally, our finding of the relationship between rumination and elevated suicidal ideation in young people with MDD is in keeping with the literature (Rogers & Joiner, 2018; Surrence et al., 2009).

The findings from the IMPACT study and the prior ADAPT study (Goodyer et al., 2008; Goodyer, Herbert, et al., 2017) have both shown that all treatments for adolescents with MDD that result in decreased depressive symptoms also decrease low mood-related ruminations at the same rate. This may explain why, in the IMPACT study, suicidal ideation remains lower in successfully treated cases regardless of the treatment they received. Therapeutic methods to decrease suicidal ideation in adolescents with MDD and higher ruminative thinking scores exist already. Finally, we note the lack of associations between ruminations, recent stress and SA of brain regions on suicidal behavior. Whilst this may be of potential interest, we advise caution as recent neurobiological studies on STBs report very small effect sizes (Auerbach et al., 2021a, 2021b; van Harmelen et al., 2021; Vidal-Ribas et al., 2021), which may explain these null findings on the direct association between the brain factor and STBs.

Our study has some limitations. Firstly, our findings are based on a small sample size for latent factor analyses. To overcome this issue, we used the Factor Score Regression approach, however, this method has some drawbacks (DiStefano et al., 2009; Lu et al., 2011). In addition, our SEM models are exactly equalling the recommended guideline of N > five per estimated path (Nunnally, 1967). This indicates that it was not feasible for us to test the models for gender differences or medication effects. We emphasize the preliminary nature of the findings given the small sample size for SEM analyses. As such, large datasets like the Adolescent Brain Cognitive Development (ABCD) dataset (Vidal-Ribas et al., 2021) and the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) STBs (Rentería et al., 2017) are needed to conclusively investigate the relations and interrelations of rumination and other functions, such as impulsivity, on youth STBs. Secondly, a further limitation is that recent stressful experiences during adolescence were assessed with only three questions that encompassed two friendship-based and one general relationship questions. Therefore, the available data in this study excludes the experience of a range of potential traumatic events, such as childhood trauma, and should be interpreted carefully. Moreover, missing data of the LEQ and rumination further limit the interpretation. Thirdly, the cross-sectional study design does not allow the interpretation of directionality of the hypothesized associations (e.g., that an increased number of recent stressful experiences and lower SA of the brain affect rumination), where it is also possible that increased rumination may lead to greater exposure of stressful experiences and may contribute to lower area during brain development. Fourthly, studies seeking to replicate the presented findings may consider including a group of clinical controls (i.e., individuals with a mental health condition who do not have a history of ideation and/or attempt) and healthy controls (i.e., individuals without a mental health condition or STBs) to further characterize the effects of biopsychosocial factors on young people developing STBs. Additionally, a future follow-up period is recommended given the known risk period for the development of mental health conditions, including STBs, until the age of approximately 30 years (Lee et al., 2014).

We aimed to advance our understanding of the relations and interrelations of biological, psychological, and social risk factors for youth STBs. We found that suicidal ideation may be related to rumination in young people with MDD, which is associated with lower SA in these four brain regions. These hypothesis-forming findings are preliminary in nature and need to be proven and replicated. However, our findings offer new pathways for further research to improve our understanding of biological, psychological, and social risk correlates of developing STBs in adolescents with MDD.

## Funding

This work was supported by the MQ Brighter Futures Award MQBFC/2 (A-LvH, HPB, and LS) and by the National Institute of Mental Health of the National Institutes of Health under Award Number R01MH117601 (LS), RC1MH088366 (HPB), R01MH113230 (HPB), R61MH111929 (HPB). MRD, LvV and LC were supported by the MQ Brighter Futures Award MQBFC/2. ALvH is funded by the Leiden Social Safety and Resilience Programme. L.S. is supported by a NHMRC Career Development Fellowship (1140764). ALvH was supported by a Royal Society Dorothy Hodgkin Fellowship (DH15017), and an MRC MRF emerging leaders award. HPB is supported by the American Foundation for Suicide Prevention, International Bipolar Foundation, For the Love of Travis Foundation, and Women's Health Research at Yale and Women's Health Access Matters. LvV is supported by the Australian National Suicide Prevention Research Fund, managed by Suicide Prevention Australia. LC is supported by the Interdisciplinary Center of Clinical Research of the Medical Faculty Jena.

## Contributions

Conceptualization, MRD and A-LvH; Methodology, MRD, IMG, LvV, LC, LS, HPB and A-LvH.; Formal analysis, MRD; Project administration, SB; Funding acquisition, LS, HPB and A-LvH. All authors co-wrote and approved the final manuscript.

## Declaration of Competing Interest

HPB received an honorarium for a talk at Aetna. The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

## Acknowledgments

We thank our participants for their time and interest in the study.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.12.087.

## References

Auerbach, R.P., Chase, H.W., Brent, D.A., 2021a. The elusive phenotype of preadolescent suicidal thoughts and behaviors: can neuroimaging deliver on its promise? Am. J. Psychiatry. https://doi.org/10.1176/appi.ajp.2020.21010022.

Auerbach, R.P., Mortier, P., Bruffaerts, R., Alonso, J., Benjet, C., Cuijpers, P., Demyttenaere, K., Ebert, D.D., Green, J.G., Hasking, P., Lee, S., Lochner, C., McLafferty, M., Nock, M.K., Petukhova, M.V., Pinder-Amaker, S., Rosellini, A.J., Sampson, N.A., Vilagut, G., Zaslavsky, A.M., Kessler, R.C., 2019. Mental disorder comorbidity and suicidal thoughts and behaviors in the World Health Organization world mental health surveys international college student initiative. Int. J. Methods Psychiatr. Res. 28, e1752 https://doi.org/10.1002/mpr.1752.

Auerbach, R.P., Pagliaccio, D., Allison, G.O., Alqueza, K.L., Alonso, M.F., 2021b. Neural correlates associated with suicide and nonsuicidal self-injury in youth. Biol. Psychiatry 89, 119–133. https://doi.org/10.1016/j.biopsych.2020.06.002.

Barzilay, R., Calkins, M.E., Moore, T.M., Wolf, D.H., Satterthwaite, T.D., Cobb Scott, J., Jones, J.D., Benton, T.D., Gur, R.C., Gur, R.E., 2019. Association between traumatic stress load, psychopathology, and cognition in the Philadelphia neurodevelopmental cohort. Psychol. Med. 49, 325–334. https://doi.org/10.1017/S0033291718000880.

Barzilay, R., Moore, T.M., Calkins, M.E., Maliackel, L., Jones, J.D., Boyd, R.C., Warrier, V., Benton, T.D., Oquendo, M.A., Gur, R.C., Gur, R.E., 2021. Deconstructing the role of the exposome in youth suicidal ideation: trauma, neighborhood environment, developmental and gender effects. Neurobiol. Stress 14, 100314. https://doi.org/10.1016/j.ynstr.2021.100314.

Barzilay, R., White, L.K., Moore, T.M., Calkins, M.E., Taylor, J.H., Patrick, A., Huque, Z. M., Young, J.F., Ruparel, K., Pine, D.S., Gur, R.C., Gur, R.E., 2020. Association of anxiety phenotypes with risk of depression and suicidal ideation in community youth. Depress. Anxiety 37, 851–861. https://doi.org/10.1002/da.23060.

de Beurs, D., Ten Have, M., Cuijpers, P., de Graaf, R., 2019. The longitudinal association between lifetime mental disorders and first onset or recurrent suicide ideation. BMC Psychiatry 19, 345. https://doi.org/10.1186/s12888-019-2328-8.

Campos, A.I., Thompson, P.M., Veltman, D.J., Pozzi, E., van Veltzen, L.S., Jahanshad, N., Adams, M.J., Baune, B.T., Berger, K., Brosch, K., Bülow, R., Connolly, C.G., Dannlowski, U., Davey, C.G., de Zubicaray, G.I., Dima, D., Erwin-Grabner, T., Evans, J.W., Fu, C.H.Y., Gotlib, I.H., Goya-Maldonado, R., Grabe, H.J., Grotegerd, D., Harris, M.A., Harrison, B.J., Hatton, S.N., Hermesdorf, M., Hickie, I.B., Ho, T.C., Kircher, T., Krug, A., Lagopoulos, J., Lemke, H., McMahon, K., MacMaster, F.P., Martin, N.G., McIntosh, A.M., Medland, S.E., Meinert, S., Meller, T., Nenadic, I., Opel, N., Redlich, R., Reneman, L., Repple, J., Sacchet, M.D., Schmitt, S., Schrantee, A., Sim, K., Singh, A., Stein, F., Strike, L.T., van der Wee, N.J.A., van der Werff, S.J.A., Völzke, H., Waltemate, L., Whalley, H.C., Wittfeld, K., Wright, M.J., Yang, T.T., Zarate, C.A., Schmaal, L., Rentería, M.E., 2020. Brain correlates of suicide attempt in 18,925 participants across 18 international cohorts. medRxiv. https://doi.org/10.1101/2020.05.06.20090191.

Centers for Disease Control and Prevention, Eaton, D.K., Kann, L., Kinchen, S., Shanklin, S., Flint, K.H., Hawkins, J., Lowry, R., McManus, T., Chyen, D., Whittle, L., Lim, C., Wechsler, H., Harris, W.A., 2012. Youth risk behavior surveillance - United States, 2011. MMWR. Surveill. Summ. 61, 1–162.

Chen, L.-R., Wang, G.-F., Xie, G.-D., He, Y., Chen, S.-S., Yuan, M.-Y., Chang, J.-J., Li, Y.-H., Su, P.-Y., 2021. Association between sexual abuse victimization during the life course and suicidal behaviors in male and female college students in China: timing, duration, types and patterns. J. Affect. Disord. 280, 30–38. https://doi.org/10.1016/j.jad.2020.11.048.

Crandall, A., Allsop, Y., Hanson, C.L., 2018. The longitudinal association between cognitive control capacities, suicidality, and depression during late adolescence and young adulthood. J. Adolesc. 65, 167–176. https://doi.org/10.1016/j.adolescence.2018.03.009.

Curtin, S.C., Heron, M., 2019. In: Death Rates Due to Suicide and Homicide Among Persons Aged 10-24: United States, 2000-2017. NCHS Data Brief, pp. 1–8.

Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage 31, 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021.

DiStefano, C., Zhu, M., Mîndrilã, D., 2009. Understanding and Using Factor Scores: Considerations for the Applied Researcher, 14. https://doi.org/10.7275/da8t-4g52.

Duprey, E.B., Handley, E.D., Manly, J.T., Cicchetti, D., Toth, S.L., 2021. Child maltreatment, recent stressful life events, and suicide ideation: a test of the stress sensitivity hypothesis. Child Abuse Negl. 113, 104926 https://doi.org/10.1016/j.chiabu.2020.104926.

Edmiston, E.E., Wang, F., Mazure, C.M., Guiney, J., Sinha, R., Mayes, L.C., Blumberg, H.P., 2011. Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. Arch. Pediatr. Adolesc. Med. 165, 1069–1077. https://doi.org/10.1001/archpediatrics.2011.565.

Fan, S., Lippard, E.T.C., Sankar, A., Wallace, A., Johnston, J.A.Y., Wang, F., Pittman, B., Spencer, L., Oquendo, M.A., Blumberg, H.P., 2019. Gray and white matter differences in adolescents and young adults with prior suicide attempts across bipolar and major depressive disorders. J. Affect. Disord. 245, 1089–1097. https://doi.org/10.1016/j.jad.2018.11.095.

Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33, 341–355. https://doi.org/10.1016/s0896-6273(02)00569-x.

Gonçalves Peter, A., Lopez Molina, M., de Azevedo Cardoso, T., Campos Mondin, T., Azevedo da Silva, R., Jansen, K., Dornellas de Barros, M.M., Nobre Dos Santos, É., Rodrigues de Aguiar, K., de Mattos, Dias, Souza, L., 2020. Incidence and risk factors for suicide attempts in patients diagnosed with major depressive disorder. Psychol. Res. Behav. Manag. 13, 1147–1157. https://doi.org/10.2147/PRBM.S274769.

Goodyer, I.M., Dubicka, B., Wilkinson, P., Kelvin, R., Roberts, C., Byford, S., Breen, S., Ford, C., Barrett, B., Leech, A., Rothwell, J., White, L., Harrington, R., 2008. A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial. Health Technol. Assess. 12 (iii–iv) https://doi.org/10.3310/hta12140 ix–60.

Goodyer, I.M., Herbert, J., Tamplin, A., Altham, P.M.E., 2000. First-episode major depression in adolescents: affective, cognitive and endocrine characteristics of risk status and predictors of onset. Br. J. Psychiatry 176, 142–149. https://doi.org/10.1192/bjp.176.2.142.

Goodyer, I.M., Tsancheva, S., Byford, S., Dubicka, B., Hill, J., Kelvin, R., Reynolds, S., Roberts, C., Senior, R., Suckling, J., Wilkinson, P., Target, M., Fonagy, P., 2011. Improving mood with psychoanalytic and cognitive therapies (IMPACT): a pragmatic effectiveness superiority trial to investigate whether specialised psychological treatment reduces the risk for relapse in adolescents with moderate to severe unipolar depres. Trials 12, 175. https://doi.org/10.1186/1745-6215-12-175.

Goodyer, Ian M., Herbert, J., Tamplin, A., Altham, P.M.E., Reynolds, S., Barrett, B., Byford, S., Dubicka, B., Hill, J., Holland, F., Kelvin, R., Midgley, N., Roberts, C., Senior, R., Target, M., Widmer, B., Wilkinson, P., Fonagy, P., 2017. Cognitive-behavioural therapy and short-term psychoanalytic psychotherapy versus brief psychosocial intervention in adolescents with unipolar major depression (IMPACT): a multicentre, pragmatic, observer-blind, randomised controlled trial. Health Technol. Assess. (Rockv) 176, 1–93. https://doi.org/10.3310/hta21120.

Goodyer, Ian M., Reynolds, S., Barrett, B., Byford, S., Dubicka, B., Hill, J., Holland, F., Kelvin, R., Midgley, N., Roberts, C., Senior, R., Target, M., Widmer, B., Wilkinson, P., Fonagy, P., 2017. 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 superior. Lancet Psychiatry 4, 109–119. https://doi.org/10.1016/S2215-0366(16)30378-9.

Green, J.G., McLaughlin, K.A., Berglund, P.A., Gruber, M.J., Sampson, N.A., Zaslavsky, A.M., Kessler, R.C., 2010. 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. https://doi.org/10.1001/archgenpsychiatry.2009.186.

Hagan, C.C., Graham, J.M.E., Tait, R., Widmer, B., van Nieuwenhuizen, A.O., Ooi, C., Whitaker, K.J., Simas, T., Bullmore, E.T., Lennox, B.R., Sahakian, B.J., Goodyer, I.M., Suckling, J., 2015. Adolescents with current major depressive disorder show dissimilar patterns of age-related differences in ACC and thalamus. NeuroImage Clin. 7, 391–399. https://doi.org/10.1016/j.nicl.2014.12.019.

Hagan, Cindy C., Graham, J.M., Widmer, B., Holt, R.J., Ooi, C., van Nieuwenhuizen, A.O., Fonagy, P., Reynolds, S., Target, M., Kelvin, R., Wilkinson, P.O., Bullmore, E.T., Lennox, B.R., Sahakian, B.J., Goodyer, I., Suckling, J., 2013. Magnetic resonance imaging of a randomized controlled trial investigating predictors of recovery following psychological treatment in adolescents with moderate to severe unipolar depression: study protocol for magnetic resonance-improving mood with psych. BMC Psychiatry 13, 247. https://doi.org/10.1186/1471-244X-13-247.

Harman, G., Kliamovich, D., Morales, A.M., Gilbert, S., Barch, D.M., Mooney, M.A., Feldstein Ewing, S.W., Fair, D.A., Nagel, B.J., 2021. Prediction of suicidal ideation and attempt in 9 and 10 year-old children using transdiagnostic risk features. PLoS One 16, e0252114. https://doi.org/10.1371/journal.pone.0252114.

van Harmelen, A.-L., Schmaal, L., Blumberg, H.P., 2021. Imaging suicidal thoughts and behavior: the promise of computational models. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. https://doi.org/10.1038/s41386-020-00841-2.

Hawton, K., Bergen, H., Waters, K., Ness, J., Cooper, J., Steeg, S., Kapur, N., 2012. Epidemiology and nature of self-harm in children and adolescents: findings from the multicentre study of self-harm in England. Eur. Child Adolesc. Psychiatry 21, 369–377. https://doi.org/10.1007/s00787-012-0269-6.

Horwitz, A.G., Czyz, E.K., Berona, J., King, C.A., 2019. Rumination, brooding, and reflection: prospective associations with suicide ideation and suicide attempts. Suicide Life. Threat. Behav. 49, 1085–1093. https://doi.org/10.1111/sltb.12507.

Jabbi, M., Weber, W., Welge, J., Nery, F., Tallman, M., Gable, A., Fleck, D.E., Lippard, E.T.C., DelBello, M., Adler, C., Strakowski, S.M., 2020. Frontolimbic brain volume abnormalities in bipolar disorder with suicide attempts. Psychiatry Res. 294, 113516 https://doi.org/10.1016/j.psychres.2020.113516.

Johnson, W.M., Fields, S.A., Bluett, E., 2020. Bipolar disorder: managing the peaks and valleys. Int. J. Psychiatry Med. 55, 349–356. https://doi.org/10.1177/0091217420952573.

Johnston, J.A.Y., Wang, F., Liu, Jie, Blond, B.N., Wallace, A., Liu, Jiacheng, Spencer, L., Cox Lippard, E.T., Purves, K.L., Landeros-Weisenberger, A., Hermes, E., Pittman, B., Zhang, S., King, R., Martin, A., Oquendo, M.A., Blumberg, H.P., 2017. Multimodal neuroimaging of frontolimbic structure and function associated with suicide attempts in adolescents and young adults with bipolar disorder. Am. J. Psychiatry 174, 667–675. https://doi.org/10.1176/appi.ajp.2016.15050652.

Kasen, S., Chen, H., 2019. Social context and change in suicide ideation in a community sample of youths. Soc. Psychiatry Psychiatr. Epidemiol. 55, 319–327. https://doi.org/10.1007/s00127-019-01772-0.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., Ryan, N., 1997. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J. Am. Acad. Child Adolesc. Psychiatry 36, 980–988. https://doi.org/10.1097/00004583-199707000-00021.

Kline, R.B., 2005. Principlesand Practice of Structural Equation Modeling, 2nd ed. Guilford Press, New York.

Kline, R.B., 2010. Principles and Practice of Structural Equation Modeling, 3rd Inter. ed. The Guilford Press.

Kline, R.B., 2016. Methodology in the social sciences. In: Principlesand Practice of Structural Equation Modeling, 4th ed. Guilford Press.

Klonsky, E.D., May, A.M., Saffer, B.Y., 2016. Suicide, suicide attempts, and suicidal ideation. Annu. Rev. Clin. Psychol. 12, 307–330. https://doi.org/10.1146/annurev-clinpsy-021815-093204.

Lebowitz, E.R., Blumberg, H.P., Silverman, W.K., 2019. Negative peer social interactions and oxytocin levels linked to suicidal ideation in anxious youth. J. Affect. Disord. 245, 806–811. https://doi.org/10.1016/j.jad.2018.11.070.

Lee, F.S., Heimer, H., Giedd, J.N., Lein, E.S., Šestan, N., Weinberger, D.R., Casey, B.J., 2014. Mental health. Adolescent mental health–opportunity and obligation. Science 346, 547–549. https://doi.org/10.1126/science.1260497.

Lewinsohn, P.M., Clarke, G.N., Seeley, J.R., P, R., 1994. Major depression in community adolescents: age at onset, episode duration, and time to recurrence. J Am Acad Child Adolesc Psychiatry 33, 809–818.

Lippard, E.T.C., Johnston, J.A.Y., Spencer, L., Quatrano, S., Fan, S., Sankar, A., Weathers, J., Pittman, B., Oquendo, M.A., Blumberg, H.P., 2019. Preliminary examination of gray and white matter structure and longitudinal structural changes in frontal systems associated with future suicide attempts in adolescents and young adults with mood disorders. J. Affect. Disord. 245, 1139–1148. https://doi.org/10.1016/j.jad.2018.11.097.

Lu, I.R., Kwan, E., Thomas, D.R., Cedzynski, M., 2011. Two new methods for estimating structural equation models: an illustration and a comparison with two established methods. Int. J. Res. Mark. 28, 2580268. https://doi.org/10.1016/j.ijresmar.2011.03.006.

Malpetti, M., Kievit, R.A., Passamonti, L., Jones, P.S., Tsvetanov, K.A., Rittman, T., Mak, E., Nicastro, N., Bevan-Jones, W.R., Su, L., Hong, Y.T., Fryer, T.D., Aigbirhio, F.I., O'Brien, J.T., Rowe, J.B., 2020. Microglial activation and tau burden predict cognitive decline in Alzheimer's disease. Brain 143, 1588–1602. https://doi.org/10.1093/brain/awaa088.

McCrory, E.J., Viding, E., 2015. The theory of latent vulnerability: reconceptualizing the link between childhood maltreatment and psychiatric disorder. Dev. Psychopathol. 27, 493–505. https://doi.org/10.1017/S0954579415000115.

McLaughlin, K.A., Green, J.G., Gruber, M.J., Sampson, N.A., Zaslavsky, A.M., Kessler, R.C., 2010. Childhood adversities and adult psychopathology in the National Comorbidity Survey Replication (NCS-R) III: associations with functional impairment related to DSM-IV disorders. Psychol. Med. 40, 847–859. https://doi.org/10.1017/S0033291709991115.

McLaughlin, Katie A., Green, J.G., Gruber, M.J., Sampson, N.A., Zaslavsky, A.M., Kessler, R.C., 2010. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication II: associations with persistence of DSM-IV disorders. Arch. Gen. Psychiatry 67, 124–132. https://doi.org/10.1001/archgenpsychiatry.2009.187.

Mullins, N., Bigdeli, T.B., Børglum, A.D., Coleman, J.R.I., Demontis, D., Mehta, D., Power, R.A., Ripke, S., Stahl, E.A., Starnawska, A., Anjorin, A., Corvin, A., Sanders, A.R., Forstner, A.J., Reif, A., Koller, A.C., Świątkowska, B., Baune, B.T., Müller-Myhsok, B., Penninx, B.W.J.H., Pato, C., Zai, C., Rujescu, D., Hougaard, D.M., Quested, D., Levinson, D.F., Binder, E.B., Byrne, E.M., Agerbo, E., Streit, F., Mayoral, F., Bellivier, F., Degenhardt, F., Breen, G., Morken, G., Turecki, G., Rouleau, G.A., Grabe, H.J., Völzke, H., Jones, I., Giegling, I., Agartz, I., Melle, I., Lawrence, J., Walters, J.T.R., Strohmaier, J., Shi, J., Hauser, J., Biernacka, J.M., Vincent, J.B., Kelsoe, J., Strauss, J.S., Lissowska, J., Pimm, J., Smoller, J.W., Guzman-Parra, J., Berger, K., Scott, L.J., Jones, L.A., Azevedo, M.H., Trzaskowski, M., Kogevinas, M., Rietschel, M., Boks, M., Ising, M., Grigoroiu-Serbanescu, M., Hamshere, M.L., Leboyer, M., Frye, M., Nöthen, M.M., Alda, M., Preisig, M., Nordentoft, M., Boehnke, M., O'Donovan, M.C., Owen, M.J., Pato, M.T., Renteria, M.E., Budde, M., Weissman, M.M., Wray, N.R., Bass, N., Craddock, N., Smeland, O.B., Andreassen, O.A., Mors, O., Gejman, P.V., Sklar, P., McGrath, P., Hoffmann, P., McGuffin, P., Lee, P.H., Mortensen, P.B., Kahn, R.S., Ophoff, R.A., Adolfsson, R., Van der Auwera, S., Djurovic, S., Kloiber, S., Heilmann-Heimbach, S., Jamain, S., Hamilton, S.P., McElroy, S.L., Lucae, S., Cichon, S., Schulze, T.G., Hansen, T., Werge, T., Air, T.M., Nimgaonkar, V., Appadurai, V., Cahn, W., Milaneschi, Y., Fanous, A.H., Kendler, K.S., McQuillin, A., Lewis, C.M., 2019. GWAS of suicide attempt in psychiatric disorders and association with major depression polygenic risk scores. Am. J. Psychiatry 176, 651–660. https://doi.org/10.1176/appi.ajp.2019.18080957.

Nash, J.C., 2014. On best practice optimization methods in Ro title. J. Stat. Softw. 60, 1–14.

Nolen-Hoeksema, S., 2000. The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. J. Abnorm. Psychol. 109, 504–511.

Nunnally, J.C., 1967. Psychometric Theory. McGraw-Hill, New York.

O'Reilly, L.M., Pettersson, E., Quinn, P.D., Klonsky, E.D., Lundström, S., Larsson, H., Lichtenstein, P., D'Onofrio, B.M., 2020. The association between general childhood psychopathology and adolescent suicide attempt and self-harm: a prospective, population-based twin study. J. Abnorm. Psychol. 129, 364–375. https://doi.org/10.1037/abn0000512.

O'Rourke, M.C., Jamil, R.T., Siddiqui, W., 2021. Washington State Suicide Prevention and Awareness. Treasure Island (FL).

Passamonti, L., Rodríguez, P.V., Hong, Y.T., Allinson, K.S.J., Bevan-Jones, W.R., Williamson, D., Jones, P.S., Arnold, R., Borchert, R.J., Surendranathan, A., Mak, E., Su, L., Fryer, T.D., Aigbirhio, F.I., O'Brien, J.T., Rowe, J.B., 2018. [(11)C]PK11195 binding in alzheimer disease and progressive supranuclear palsy. Neurology 90, e1989–e1996. https://doi.org/10.1212/WNL.0000000000005610.

Passamonti, L., Vázquez Rodríguez, P., Hong, Y.T., Allinson, K.S.J., Williamson, D., Borchert, R.J., Sami, S., Cope, T.E., Bevan-Jones, W.R., Jones, P.S., Arnold, R., Surendranathan, A., Mak, E., Su, L., Fryer, T.D., Aigbirhio, F.I., O'Brien, J.T., Rowe, J.B., 2017. 18F-AV-1451 positron emission tomography in Alzheimer's disease and progressive supranuclear palsy. Brain 140, 781–791. https://doi.org/10.1093/brain/aww340.

Posner, K., Brown, G.K., Stanley, B., Brent, D.A., Yershova, K.V., Oquendo, M.A., Currier, G.W., Melvin, G.A., Greenhill, L., Shen, S., Mann, J.J., 2011. The Columbia-suicide severity rating scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am. J. Psychiatry 168, 1266–1277. https://doi.org/10.1176/appi.ajp.2011.10111704.

Pu, S., Setoyama, S., Noda, T., 2017. Association between cognitive deficits and suicidal ideation in patients with major depressive disorder. Sci. Rep. 7 https://doi.org/10.1038/s41598-017-12142-8.

Puetz, V.B., Viding, E., Gerin, M.I., Pingault, J.-B., Sethi, A., Knodt, A.R., Radtke, S.R., Brigidi, B.D., Hariri, A.R., McCrory, E., 2020. Investigating patterns of neural response associated with childhood abuse v. Childhood neglect. Psychol. Med. 50, 1398–1407. https://doi.org/10.1017/S003329171900134X.

R Core Team, 2020. R:A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.

Rentería, M.E., Schmaal, L., Hibar, D.P., Couvy-Duchesne, B., Strike, L.T., Mills, N.T., De Zubicaray, G.I., McMahon, K.L., Medland, S.E., Gillespie, N.A., Hatton, S.N., Lagopoulos, J., Veltman, D.J., Van Der Wee, N., Van Erp, T.G.M., Wittfeld, K., Grabe, H.J., Block, A., Hegenscheid, K., Völzke, H., Veer, I.M., Walter, H., Schnell, K., Schramm, E., Normann, C., Schoepf, D., Konrad, C., Zurowski, B., Godlewska, B.R., Cowen, P.J., Penninx, B.W.J.H., Jahanshad, N., Thompson, P.M., Wright, M.J., Martin, N.G., Christensen, H., Hickie, I.B., 2017. Subcortical brain structure and suicidal behaviour in major depressive disorder: a meta-analysis from the ENIGMA-MDD working group. Transl. Psychiatry 7. https://doi.org/10.1038/tp.2017.84.

Ribeiro, J.D., Franklin, J.C., Fox, K.R., Bentley, K.H., Kleiman, E.M., Chang, B.P., Nock, M.K., 2016. Self-injurious thoughts and behaviors as risk factors for future suicide ideation, attempts, and death: a meta-analysis of longitudinal studies. Psychol. Med. 46, 225–236. https://doi.org/10.1017/S0033291715001804.

Rogers, M.L., Joiner, T.E., 2018. Suicide-specific rumination relates to lifetime suicide attempts above and beyond a variety of other suicide risk factors. J. Psychiatr. Res. 98, 78–86. https://doi.org/10.1016/j.jpsychires.2017.12.017.

Roh, B.-R., Yoon, Y., Kwon, A., Oh, S., Lee, S.I., Ha, K., Shin, Y.M., Song, J., Park, E.J., Yoo, H., Hong, H.J., 2015. The structure of co-occurring bullying experiences and associations with suicidal behaviors in Korean adolescents. PLoS One 10, e0143517. https://doi.org/10.1371/journal.pone.0143517.

Rosseel, Y., 2012. Lavaan: an R package for structural equation modeling. J. Stat. Softw. 48, 1–36.

Rosseel, Y., Loh, W.W., 2022. A Structural After Measurement (SAM) Approach to Structural Equation Modeling. https://osf.io/pekbm/.

Saint Onge, J.M., Cepeda, A., Lee King, P.A., Valdez, A., 2013. The relationship between trajectories of family/cultural stressors and depression and suicidal ideation among substance using Mexican-American adults. Am. J. Community Psychol. 52, 263–272. https://doi.org/10.1007/s10464-013-9592-4.

Schmaal, L., van Harmelen, A.L., Chatzi, V., Lippard, E.T.C., Toenders, Y.J., Averill, L.A., Mazure, C.M., Blumberg, H.P., 2020. Imaging suicidal thoughts and behaviors: a comprehensive review of 2 decades of neuroimaging studies. Mol. Psychiatry 25, 408–427. https://doi.org/10.1038/s41380-019-0587-x.

Sewall, C.J.R., Girard, J.M., Merranko, J., Hafeman, D., Goldstein, B.I., Strober, M., Hower, H., Weinstock, L.M., Yen, S., Ryan, N.D., Keller, M.B., Liao, F., Diler, R.S., Kay Gill, M., Axelson, D., Birmaher, B., Goldstein, T.R., 2020. A bayesian multilevel analysis of the longitudinal associations between relationship quality and suicidal ideation and attempts among youth with bipolar disorder. J. Child Psychol. Psychiatry. https://doi.org/10.1111/jcpp.13343.

Sharp, C., Goodyer, I.M., Croudace, T.J., 2006. The short mood and feelings questionnaire (SMFQ): a unidimensional item response theory and categorical data factor analysis of self-report ratings from a community sample of 7-through 11-year-old children. J. Abnorm. Child Psychol. 34, 379–391. https://doi.org/10.1007/s10802-006-9027-x.

Spann, M.N., Mayes, L.C., Kalmar, J.H., Guiney, J., Womer, F.Y., Pittman, B., Mazure, C. M., Sinha, R., Blumberg, H.P., 2012. Childhood abuse and neglect and cognitive flexibility in adolescents. Child Neuropsychol. J. Norm. Abnorm. Dev. Child. Adolesc. 18, 182–189. https://doi.org/10.1080/09297049.2011.595400.

Surrence, K., Miranda, R., Marroquín, B.M., Chan, S., 2009. Brooding and reflective rumination among suicide attempters: cognitive vulnerability to suicidal ideation. Behav. Res. Ther. 47, 803–808. https://doi.org/10.1016/j.brat.2009.06.001.

Tang, H., Xiong, T., Shi, J., Chen, Y., Liu, X., Zhang, S., Wang, H., Lu, Q., Yao, Z., 2021. Global and reflective rumination are related to suicide attempts among patients experiencing major depressive episodes. BMC Psychiatry 21, 117. https://doi.org/10.1186/s12888-021-03119-z.

Turecki, G., Ernst, C., Jollant, F., Labonté, B., Mechawar, N., 2012. The neurodevelopmental origins of suicidal behavior. Trends Neurosci. 35, 14–23. https://doi.org/10.1016/j.tins.2011.11.008.

Van Harmelen, A.-L., Schmaal, L., Blumberg, H.P., 2019. Journal of Affective Disorders Special Issue on Suicide-Related Research: hopeful progress but much research urgently needed. J. Affect. Disord. https://doi.org/10.1016/j.jad.2019.03.054.

Vidal-Ribas, P., Janiri, D., Doucet, G.E., Pornpattananangkul, N., Nielson, D.M., Frangou, S., Stringaris, A., 2021. Multimodal neuroimaging of suicidal thoughts and behaviors in a U.S. population-based sample of school-age children. Am. J. Psychiatry 178, 321–332. https://doi.org/10.1176/appi.ajp.2020.20020120.

Villa, L.M., Goodyer, I.M., Tait, R., Kelvin, R., Reynolds, S., Wilkinson, P.O., Suckling, J., 2020. Cognitive behavioral therapy may have a rehabilitative, not normalizing, effect on functional connectivity in adolescent depression. J. Affect. Disord. 268, 1–11. https://doi.org/10.1016/j.jad.2020.01.103.

World Health Organization, 2014. PreventingSuicide Suicide. A Global Imperative. WHO Press.

Zhou, H.-X., Chen, X., Shen, Y.-Q., Li, L., Chen, N.-X., Zhu, Z.-C., Castellanos, F.X., Yan, C.-G., 2020. Rumination and the default mode network: meta-analysis of brain imaging studies and implications for depression. NeuroImage 206, 116287. https://doi.org/10.1016/j.neuroimage.2019.116287.