Research Report

Aberrant neural network activation during reliving of autobiographical memories in adolescent depression

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Background: Adolescents with depression exhibit negative biases in autobiographical memory with detrimental consequences for their self-concept and well-being. Investigating how adolescents relive positive autobiographical memories and activate the underlying neural networks could reveal mechanisms that drive such biases. This study investigated neural networks when reliving positive and neutral memories, and how neural activity is modulated by valence and vividness in adolescents with and without depression.

Methods: Adolescents (\(N = 69; n = 17 \text{ with depression}\)) retrieved positive and neutral autobiographical memories. On a separate day, they relived these memories during fMRI scanning, and reported on pleasantness and vividness after reliving each memory. We used a multivariate, data-driven approach – event-related independent component analysis (eICA) – to characterize neural networks supporting autobiographical recollection.

Results: Adolescents with depression reported their positive memories as significantly less pleasant compared to healthy controls, while subjective vividness was unaffected. Using eICA, we identified a broad autobiographical memory network, and subnetworks related to reliving positive vs neutral memories. These subnetworks comprised a ‘self-referential processing network’ including medial prefrontal cortex, posterior cingulate cortex/pre-cuneus, and temporoparietal junction, anti-correlating with parts of the central executive network and salience network. Adolescents with depression exhibited aberrant activation in this self-referential network, but only when reliving relatively ‘low’ pleasant memories.

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Conclusions: Our findings provide first insights into how the quality of reliving autobiographical memories in adolescents with depression may relate to aberrant self-referential neural network activation, and underscore the potential of targeting memory reliving in therapeutic interventions to foster self-esteem and diminish depressive symptoms.

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1. Introduction

Adolescent-onset depression is a leading cause of illness and disability worldwide (World Health Organization, 2019), and a substantial proportion (50%) of adolescents do not respond to recommended treatment options (March et al., 2007). Depression is associated with impairments across the lifespan (Clayborne et al., 2019), including disturbances in how autobiographical memories are represented, recalled, and consolidated (Dalglish & Werner-Seidler, 2014; Hitchcock et al., 2014; Holmes et al., 2016). Novel autobiographical memory-based therapeutic interventions have been developed, such as memory specificity training, imagery re-scripting, and positive memory elaboration. These interventions show clinical potential (Dalglish & Werner-Seidler, 2014; Hitchcock et al., 2017; Holmes et al., 2016), also for adolescents with depression (Pile et al., 2020). To optimize such interventions it is important to elucidate underlying cognitive and neural mechanisms that drive memory deficits in adolescent depression. Therefore, this study examined how adolescents with and without depression relive positive autobiographical memories and identified the neural networks involved.

Autobiographical memories are central to a person’s identity and understanding of how one fits within the world (Harris et al., 2014; Harter & Leary, 2001). This narrative identity undergoes drastic development during adolescence, when adolescents acquire the capacity to connect one’s past experiences and sense of self with one’s present and future selves, establishing temporal continuity (Habermas & Reese, 2015; McAdams, 2011). As such, autobiographical memory is important for an individual’s self-concept and well-being. Recollecting positive autobiographical memories may boost self-esteem and work as an emotion regulation strategy, as it can bring about positive emotions and enhance well-being both in adults (Bower, 1981; Josephson, 1996; Speer et al., 2014; van Schie et al., 2019; Williams et al., 2007) and adolescents (Askelund et al., 2019). Reduced memory specificity and vividness in positive autobiographical memory retrieval and difficulties elaborating on positive memories are characteristic for adolescents with depression, even prior to depression-onset and after remission (Begovic et al., 2017). Hence, deficits in positive autobiographical memory processes might be fundamentally linked to the disturbances in self-concept and mood regulation that adolescents with depression experience.

Compromised autobiographical memory functioning may be reflected in aberrant neural activity within the so-called ‘autobiographical memory network’ (AMN) (Palmer et al., 2015; Rayner, 2019; Rayner et al., 2016; Sporns, 2011). This network includes medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), hippocampus, retrosplenial/posterior cingulate cortex (PCC), precuneus, ventrolateral PFC (vlPFC), anterior temporal cortex (ATC), temporoparietal junction (TPJ), and the cerebellum (Andrews-Hanna et al., 2014; Spreng et al., 2009; Svoboda et al., 2006; Tailby et al., 2017). The AMN substantially overlaps with the default mode network (DMN) as measured with resting-state techniques, which is implicated in self-related processing (Greicius et al., 2003). Neuro-imaging studies have demonstrated that individuals with depression show a hyperactive AMN/DMN and a hypoactive central executive network (CEN), which includes dorsolateral PFC (DLPFC) and posterior parietal cortex (PPC), and is involved in cognitive control and emotion regulation (Menon, 2011; Rayner et al., 2016). Depression has also been linked to aberrant functioning of regions important for salience processing, including the amygdala, ACC, and insula (Jameson et al., 2022; Menon, 2019; Menon & Uddin, 2010). While both potentiated memory for negative events and disrupted memory for positive events are characteristic for depression (Dillon & Pizzagalli, 2018), studies investigating the neural responses to positive autobiographical memory retrieval in individuals with depression are sparse. These few studies in adults found that patients with depression (vs healthy controls) showed hypo-activity in the amygdala and hypo-connectivity with dorsal ACC (dACC), PCC, and precuneus (Young et al., 2016), and hypo-activity in left AI and left parahippocampal gyrus during positive memory recall (Parlar et al., 2018).

Examining how neural (sub)networks support the processing of emotional valence, vividness, and self-referential processing in adolescents with and without depression, may advance the understanding of the specific disturbances in autobiographical memory recollection in adolescents with depression. The present study therefore examined alterations in spatiotemporal networks related to reliving positive autobiographical memories in adolescents with and without depression. To identify the spatiotemporal networks that adolescents recruit during the recollection of positive autobiographical memories, we used a relatively novel, multivariate, data-driven approach – event-related independent component analysis (eICA) (Masterton et al., 2013; Tailby et al., 2017).

More specifically, we first aimed to explore whether adolescents with depression experience reduced memory pleasantness and vividness during positive (vs neutral) autobiographical memory reliving compared to healthy controls. Second, within each of the components [i.e., spatial activation maps and associated time-courses of neural (sub) networks] recovered by eICA during reliving, we examined whether these time-courses were related to i) memory characteristics (i.e., valence and vividness) and ii) depression...
during reliving (Masterton et al., 2013; Tailby et al., 2017). We hypothesized that i) the response amplitude of distinct sub-networks, particularly within the AMN, co-very with emotional valence (e.g., mPFC, ACC; Piefke et al., 2003; Speer et al., 2014; van Schie et al., 2019) and vividness (e.g., hippocampus, insula [van Schie et al., 2019]) during memory reliving and ii) adolescent depression would modulate the degree to which subnetworks related to recollection processes are recruited during reliving, particularly self-referential thinking (e.g., PCC, precuneus) and emotional processing (e.g., amygdala, dACC, AI).

2. Methods and materials

We report all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. For sample size determination, see https://osf.io/yja3g.

2.1. Participants

Adolescents participated in RE-PAIR, a Dutch multi-method two-generation study investigating a bidirectional interplay between parent–adolescent interactions and adolescent well-being by comparing adolescents with depression (DEP) to healthy controls (HCs). DEP adolescents were primarily recruited via mental health clinics. Adolescents were also recruited via (social) media. Inclusion criteria for all adolescents were as follows: aged between 11 and 17 years when recruited during reliving, particularly self-referential thinking (e.g., mPFC, precuneus) and emotional processing (e.g., amygdala, dACC, AI).

To determine current and lifetime psychopathology based on DSM-IV criteria, adolescents were interviewed using the K-SADS-PL (Kaufman et al., 1996) by trained psychologists or graduate students of the Clinical Psychology unit of Leiden University prior to the lab session (DEP), or by graduate students during the lab session (HC). Final diagnoses were always discussed with a registered healthcare psychologist. Depressive symptoms were additionally measured using the Patient Health Questionnaire-9 (Kroenke & Spitzer, 2002) both during the initial lab session and after they came out the scanner. We tested whether adolescents’ levels of depressive symptoms changed over time, i.e., as measured during the lab session and during the MRI-scanning session (scheduled ≥ one week after the lab session: M = 7.21 weeks, SD = 5.59, range: 1–37.9). In general, depressive symptoms declined over time (b = −8.59, SE = .08, t(75) = 10.1, p < .001) [χ^2(1) = 9.65, p < .001]. However, we found a group*time interaction effect, indicating that this was particularly the case for DEP adolescents, whereas for HCs depressive symptoms remained stable over time (b = −3.13, SE = .80, t(67) = −3.92, p < .001) [χ^2(1) = 15.4, p < .001]. It should be noted though that DEP adolescents had significantly more depressive symptoms than HCs (p < .001), and on average still scored in the severe depression range during the fMRI scanning session (see also Table 1). Furthermore, depressive symptom scores over time were strongly correlated (r(67) = .917, p < .001).

2.3. Reliving autobiographical memories task

Adolescents performed a ‘reliving autobiographical memories’ (RAM)-task (van Schie et al., 2019). During the lab session (at least one week prior to the scanning session), adolescents retrieved four positive and four neutral autobiographical memories (i.e., retrieval phase) while being audio-recorded. Positive memories were defined as memories eliciting positive feelings, whereas neutral memories were defined as everyday memories not eliciting positive or negative feelings (e.g., brushing teeth, doing laundry), but still memorable (e.g., when something distinctive happened). We used a standardized text to introduce the task and to explain to participants what kind of memories we were looking for. We instructed participants to retrieve a specific moment with as much details as possible, from a first-person perspective and in the present tense. For positive memories we explicitly asked participants to come up with memories that made them feel good. For neutral memories, we asked for memories that did not necessarily make them feel good, but did not make them feel bad either. When participants did not come up with a memory, a memory example was given. When participants merely mentioned minor details of a memory, the researcher would ask standard questions to let adolescents elaborate more on the memory, e.g.: ‘Where was it? With whom were you? What did you do? What did you feel? What did you see? What did
you hear? What did you smell?’. After retrieving each memory, adolescents named the memory, specified the date, and rated memory pleasantness (i.e., ‘How pleasant was the memory?’ ranging from –10 ‘very unpleasant’ to 10 ‘very pleasant’) and vividness (i.e., ‘How vivid was the memory?’ ranging from 1 ‘not vivid at all’ to 7 ‘very vivid’). Memories could only serve as a positive memory when pleasantness was rated 7 or higher, and as a neutral memory when pleasantness was rated between 2 and 2. When ratings were outside these ranges, participants were asked to think of a new memory.

The memories were transcribed by researchers and prepared to use as stimuli for the RAM-task in the MRI scanner [i.e., when necessary: shortened (max 100 words per memory) and rewritten in present tense and from first-person perspective]. Positive memories (n = 58; DEP only: n = 14) had to be shortened more often than neutral memories (n = 27; DEP only: n = 2) for the scanning session [b = .11, SE = .03, t(68.5) = 3.85, p < .001] \( \chi^2(1) = 14.8, p < .001 \), but no group differences were found (main effect group: p = .296; group*valence interaction effect: p = .211). For each valence category, the four autobiographical memories were sorted in ascending order of pleasantness. In case of equal pleasantness, memories were ordered by date in months (most remote first), and then word count (shortest first).

On a later date, in the scanner, adolescents were instructed to read their memories on screen and to relive these memories as best as they could with their eyes open (i.e., reliving phase), see Fig. 1 for trial structure and timings of the RAM-task. The task consisted of two blocks in fixed order: first neutral memories and then positive memories. For each block, each trial started with a jittered black screen with a uniformly distributed duration varying between 1700 and 2300 msec. Next, the instruction screen ‘Please read the following memory carefully’ appeared for 2500 msec. Then, the memory was displayed on the screen for 20,000 msec, after which the text ‘Finished reading? Press any button to start reliving’ appeared below the memory for a maximum of 15,000 msec, as adolescents could press a button to terminate the reading part. After reading, a black screen was jittered with a duration of 1000 msec ± 0–100 msec. Next, the instruction screen ‘Please try to relive the moment that the event took place as well as you can’ was shown for 5000 msec, after which a fixation cross was shown for 30,000 msec. Following each memory, adolescents rated memory pleasantness (‘How pleasant was this memory?’ ranging from 1 ‘not pleasant at all’ to 7 ‘very pleasant’) and memory vividness (‘How vivid was this memory?’ ranging from 1 ‘not vivid at all’ to 7 ‘very vivid’) with MR-compatible button boxes. These questions were self-paced, with a maximum of 8000 msec. If adolescents did not respond within 8 sec, the message ‘Too late’ appeared (1 sec), and answer was excluded from analyses (pleasantness: n = 5, .91%; vividness: n = 1, .18%; HCIs only).

The RAM-task was programmed using E-Prime 2.0 (Psychological Software Tools, Pittsburgh, PA) and presented on a 32-inch BOLD-screen (Cambridge Research Systems, Cambridge, UK) placed at the end of the scanner bore, which participants could see via a mirror attached to the head coil.

Memories were coded on specificity [i.e., standard categories of the Autobiographical Memory Test (Williams & Broadbent, 1986): specific, extended, categorical], event type (e.g., wedding, birthday), and social context (e.g., with family, alone), with coders being blind to depression diagnosis and memory valence (Supplement).

2.4. Behavioral analysis

We analyzed whether pleasantness and vividness of both positive and neutral memories differed between groups using multilevel modeling (Hox et al., 2017) in R-4.0.4 (https://www.r-project.org). We specified memory valence on the first level
(including random effects), group (depression yes/no) on the second level, and adolescents’ pleasantness/vividness ratings as outcome, e.g.:

\[
\text{Memory pleasantness}_{ij} = \gamma_0 + \gamma_{10}(\text{Depression})_j + \gamma_{11}(\text{Depression})(\text{Positive}) + \nu_{ij} + \nu_i(\text{Positive})_j + \epsilon_{ij}
\]

\(\chi^2\)-tests were used to test for significance of effects.

### 2.5. fMRI data acquisition and analysis

MRI images were acquired using a Philips Achieva 3.0-T scanner (Philips Medical Systems, Best, NL) equipped with a SENSE-32 whole-head coil. We collected functional scans with T2*-weighted echo-planar imaging sequence [TR/TE: 2200/30 msec; flip angle: 80°; 38 transverse slices (anterior-to-posterior); FOV: 220 × 220 × 114.68 mm; voxel size: 2.75 mm\(^3\)], see Supplement for further details.

fMRI data were preprocessed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/), following standard procedures including spatial normalization using the DARTEL-toolbox (Ashburner, 2007) (Supplement). Next, we defined a general linear model (GLM) that included separate regressors for onsets of neutral and positive memory reliving, modeled as stick functions (i.e., duration = 0 sec). We used a Finite Impulse Response model (order = 13, window length = 13*2.2TR = 28.6 sec) to estimate BOLD-responses within the 30 sec reliving phase (i.e., 13 regressors per valence). The GLM further included 24 motion regressors (six realignment parameters, their square, their temporal derivative, and the square of their temporal derivative) to account for head motion (Friston et al., 1996), plus four WM and four CSF nuisance regressors (Supplement). Next, beta weights for each regressor were estimated using SPM’s first-level analysis. Furthermore, each subject’s mask generated during first-level model estimation was used to create an average mask using SPM’s ImCalc function. This mask was thresholded at .8 and binarized using FSL’s fslmaths function (www.fmrib.ox.ac.uk/fsl).

### 2.6. eICA

To reveal spatial activation maps and associated time-courses of neural (sub)networks (i.e., components), we used group-based eICA with temporally concatenated data of all

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**Fig. 1** – Trial structure and timings of reliving autobiographical memories (RAM)-task.
adolescents in line with (Tailby et al., 2017). In eICA – unlike applying ICA to the entire fMRI time-series data – ICA is only applied to the concatenated event-related time-courses at each voxel. We concatenated estimated beta weights of both neutral and positive memory regressors across time (i.e., 26 beta weights) per subject using SPM. Per subject, we used the created 4D NiFTI-file as input to conduct a multivariate group probabilistic ICA with MELODIC 3.15 in FSL 6.0.4 (Beckmann & Smith, 2004). First, we applied masking of non-brain voxels, and voxel-wise demeaning of the 4D-input data. Next, these data were whitened and projected into a 15-dimensional subspace using probabilistic principal component analysis. The dimensionality (n = 15 independent components) was estimated using Laplace approximation to the Bayesian model order (Beckmann & Smith, 2004; Minka, 2000). We decomposed the data into sets of vectors which describe signal variation across time, subjects, and memory valence, and across the spatial domain (i.e., maps) by optimizing for non-Gaussian spatial source distributions using a fixed-point iteration technique (Hyvärinen, 1999). To ensure stable ICA convergence, we performed the ICA 25 times (Poppe et al., 2013), with different randomized subject orders, followed by a meta-ICA using the concatenated spatial maps from all 25 ICAs as input (Wisner et al., 2013). The final ICA-output was chosen based on highest internal correlations of components across the 25 ICAs.

To test our hypotheses that these neural network components are modulated by i) memory valence/vividness, and ii) depression, we performed multilevel analyses for valence and vividness separately. We specified time, i.e., n TRs (13 levels) and memory valence/vividness on the first level, group on the second level, and adolescents’ estimated component time-courses as outcome, e.g.:

\[
\text{Network component time-course}_{ij} = \gamma_0 + \gamma_01(\text{Depression})_j + \gamma_{10}(\text{Time})_{ij} + \gamma_{01}(\text{Valence/Vividness})_{ij} + \gamma_{11}(\text{Depression})(\text{Time})_{ij} + \gamma_{02}(\text{Depression})(\text{Valence/Vividness})_{ij} + \gamma_{12}(\text{Depression})(\text{Time}*\text{Valence/Vividness})_{ij} + \epsilon_{ij}.
\]

First, we estimated the intra-class correlation coefficient (ICC) to assess the proportion of variance in estimated component time-courses explained by each adolescent separately. The null-model (Hox et al., 2017) per component (set as outcome) indicated that for each component, the ICC was zero. Therefore, ordinary linear regression analyses were used.

We applied Bonferroni correction to control for multiple comparisons [i.e., \(p = .05/(11 \text{ effects of interest} \times \text{all main and interaction effects with time, depression, and valence/vividness})^n \text{relevant components})].

To visualize relevant networks per moderator (i.e., valence, vividness, depression), we created a composite component map by combining spatial maps from relevant components per effect of interest. For instance, we combined all components with a main effect of valence into one composite map. For each voxel, we obtained the signed maximum absolute t-value across all relevant component spatial maps. These maximum absolute t-values per voxel were visualized in one final composite map.

3. Results

3.1. Memory characteristics in adolescents with vs without depression

During the retrieval phase performed during the lab session, across groups, positive (vs neutral) memories were rated as significantly more pleasant, vivid, remote, and were described with more words, and differed in event type, social context, and memory specificity (Supplement). No differences between DEP and HC adolescents during retrieval were found in memory pleasantness \([\chi^2(1) = .15, p = .696]\), vividness \([\chi^2(1) = .19, p = .667]\), remoteness \([\chi^2(1) = 1.43, p = .232]\), or number of words used \([\chi^2(1) = 2.63, p = .105]\). With regards to memory content, no differences were found between DEP and HC adolescents in the event type \([\chi^2(3) = 3.36, p = .339]\), social context \([\chi^2(6) = 3.53, p = .740]\), or memory specificity \([\chi^2(2) = 3.79, p = .151]\). For HCs, 11 memories were categorized as categorical (2.6%), and two as extended (.5%), while for DEP adolescents, only one memory was categorized as extended (.7%); see also Table S2. Furthermore, no depression status*memory valence interactions were found on these outcomes (all ps > .111).

Reliving positive (vs neutral) memories (i.e., during the scanning session) was rated as more pleasant \((b = 1.86, SE = .10, t(68.4) = 17.8, p < .001);\) main effect of memory valence \([\chi^2(1) = 316.0, p < .001]\). Furthermore, DEP adolescents (vs HCs) reported less pleasantness after reliving autobiographical memories \((b = -.31, SE = .15, t(68.4) = -2.14, p = .036);\) main effect of group \([\chi^2(1) = 4.58, p = .032]\). However, this was further specified by a group*valence effect on memory pleasantness \([\chi^2(1) = 3.85, p = .0499]\). Post-hoc pairwise Tukey-tests indicated that DEP adolescents (vs HCs) reported their positive memories as being less pleasant \([b = -.48, SE = .17, t(70.9) = -2.08, p = .007]\), while for neutral memories, pleasantness did not differ \([b = .02, SE = .21, t(70.6) = .08, p = .936]\) (Fig. 2A).

In terms of vividness, adolescents relived positive (vs neutral) memories more vividly \([b = .40, SE = .13, t(69.0) = 3.03, p = .003]);\) main effect of memory valence \([\chi^2(1) = 9.18, p = .002]\) (Fig. 2B). We did not find a main effect of group \([\chi^2(1) = 1.03, p = .311]\), or group*valence effect \([\chi^2(1) = .17, p = .678]\), indicating that memory vividness ratings did not differ between groups.

We additionally explored whether vividness was associated with memory pleasantness, in addition to valence and group. We found that reliving memories more vividly was related to increased pleasantness, above and beyond memory valence and/or group \([b = .25, SE = .04, t(62.1) = 5.71, p < .001];\) main effect of vividness \([\chi^2(1) = 32.6, p < .001]\).

3.2. Neural networks related to time, valence, and vividness

We identified neural network components as meaningful by assuming that these show an event-related response varying systematically across participants as a function of time, depression, and/or memory valence/vividness. Regression analyses showed that from the 15 components extracted by our eICA, 13 had a significant main effect of time. One component yielded activation in ventricles, and hence was
discarded, resulting in 12 relevant components, remaining significant after Bonferroni correction [i.e., p < .00038 (=.05/11 effects of interest×12 components)]. After visual inspection however, the significant time-courses of four components yielded no clear hemodynamic curve (Supplement) and were therefore not considered, resulting in eight components of interest. Five of these components also showed a significant main effect of valence. One of these five components had a significant valence×time effect. No memory vividness, or vividness×time effects were found.

We derived a composite map by combining the eight components displaying a main effect of time, to visualize neural activation patterns in response to memory reliving (Fig. 3A). This map shows activation in the AMN, with bilateral hubs in mPFC, retrosplenial cortex/PCC, precuneus, ACC, hippocampus, parahippocampal gyrus, amygdala, TPJ, ATC, auditory cortex, and somatosensory cortex. Task-related deactivation was primarily found in visual cortex, PPC, dIPFC, AI, inferior frontal gyrus (IFG), and superior temporal sulcus (STS).

Furthermore, we combined the four components with a main effect of valence into one composite map, to visualize neural activation patterns in response to positive vs neutral memory reliving (Fig. 3B). We found increased activation in hubs of the AMN/DMN, i.e., mPFC, pregenual ACC, subgenual ACC, PCC, precuneus, TPJ, hippocampus, parahippocampal gyrus, and temporal poles, as well as more deactivation in central parts of the CEN (PPC, dIPFC) and salience network (dACC, AI), and IFG, STS, and cerebellum.

Additionally, we found one component with a main effect of valence with increased activation for neutral vs positive memories, i.e., in auditory cortex, somatosensory cortex, supplementary motor cortex, insula, and amygdala (Fig. S2B–VIII). See Supplement for temporal dynamics of all components with a time, valence, and/or time×valence effect.

Taken together, eICA revealed networks that resemble the DMN/AMN while reliving memories, and reliving positive (vs neutral) memories was associated with stronger recruitment of a substantial part of these networks.

3.3. Neural networks related to adolescent depression

To examine how networks revealed by our eICA were modulated by adolescent depression, we performed regression analyses with depression and valence/vividness. These analyses revealed a significant group×vividness effect in one component [F(1, 1778) = 15.7, p < .001]. This component shows activation in a ‘self-referential processing subnetwork’ of the AMN/DMN, with major hubs in mPFC, PCC, precuneus, and TPJ (Fig. 4A). For DEP adolescents, lower memory vividness was related to increased network activation (b = −.01, SE = .00, t = −3.97, p < .001), while for HCs, activation was not dependent on vividness (b = .00, SE = .00, t = 1.61, p = .107) (Fig. 4B). No other effects related to depression were found (all p’s > .00057).

Affective results indicated that memory vividness is related to memory pleasantness. Therefore, we explored the role of memory pleasantness in activating this self-referential subnetwork related to depression and vividness. For DEP adolescents, activation of this subnetwork particularly depended on memory vividness when pleasantness ratings were reduced, while for HCs, activation was independent of memory vividness and pleasantness (group×vividness×pleasantness effect [F(1, 1774) = 14.2, p < .001]). As illustrated by Fig. 4C, for DEP adolescents, only memories low in pleasantness that were less vivid resulted in increased responses, while less pleasant, but more vivid memories resulted in decreased responses. However, when memory pleasantness was high, no group differences in this subnetwork were found.

3.4. Confound analyses

Results related to memory characteristics did not change when adding sex, age, or interval (days) between retrieval and reliving phase as covariate. When adding pubertal status, the depression group×valence effect on memory pleasantness was no longer significant (p = .0500); all other findings remained significant. Regarding the neural results, all
Fig. 3 – A: Composite map derived from eight components (I–VIII) with a significant main effect of time (for estimated time-courses per component, see Supplement). Regions with an initial increase/decrease in BOLD-signal while reliving positive and neutral autobiographical memories, are shown in red/blue, respectively. The network shown in red resembles the autobiographical memory network. B: Composite map derived from four components (IV–VI, VIII) with a significant main effect of valence. Red/blue colors show regions with an initial increase/decrease, respectively, in BOLD-signal while reliving positive compared to neutral autobiographical memories. The network shown in red resembles major hubs of the autobiographical memory network/default mode network.
outcomes remained significant when taking sex, age, pubertal status, interval, or left-handedness into account.

4. Discussion

The present study investigated: i) differences in memory characteristics and ii) neural (sub)networks related to memory valence, vividness and depression in a sample of adolescents with and without depression, while reliving positive and neutral autobiographical memories. Adolescents with depression (vs healthy controls) reported reduced pleasantness during positive memory reliving, while we found no differences in memory vividness. Using eICA, we identified a broad AMN while reliving memories, in line with prior research both in adults (Andrews-Hanna et al., 2014; Svoboda et al., 2006; Tailby et al., 2017) and children (McCrory et al., 2017). Moreover, we could distinguish subnetworks specifically related to memory valence, with positive memories being related to increased activation in a self-referential network with central nodes in mPFC, PCC, precuneus, and TPJ, as well as deactivation within the CEN and salience network. Finally, adolescents with depression (vs healthy controls) showed aberrant activation patterns in a ‘self-referential processing subnetwork’ while reliving less pleasant memories, being dependent on memory vividness. However,
when memories were highly pleasant, groups did not differ in activating this subnetwork.

Reliving autobiographical memories activated the AMN in adolescents, including mPFC, PCC, precuneus, hippocampus, amygdala, TPJ, and ATC. As expected, this broader AMN can be further delineated into subnetworks relevant for memory valence (Piefke et al., 2003; Speer et al., 2014; van Schie et al., 2019). Reliving positive (vs neutral) memories was related to increased activation in a self-referential subnetwork of the AMN/DMN (including mPFC, PCC, precuneus, TPJ) (Nohoff et al., 2006), together with more deactivation from the CEN (PFC, dIPFC) and salience network (dACC, AI), both involved in externally oriented attention (Menon & Uddin, 2010). The anti-correlating nature of these networks has been consistently found across a range of studies, although its functional significance is largely unknown (Buckner & DiNicola, 2019; Fox et al., 2005, 2009; Uddin et al., 2009). Activation in these networks may shift when extracting information from the external world versus constructing an internal mentally simulated world, such as remembering one’s past (Buckner & Carroll, 2007; Buckner & DiNicola, 2019). Reliving positive memories may involve a more internal focus (van Schie et al., 2019), reflecting deeper engagement in recollection, possibly explaining the increased (de)activation in these networks. Besides increased pleasantness and vividness, positive memories entailed more often life events with close others (e.g., birthdays), while neutral memories mainly involved daily activities (e.g., grocery shopping), alone, or with more distant others. Therefore, positive memory reliving may induce processing of self-relevant information more compared to neutral memories (Lind et al., 2019).

Interestingly, adolescents with depression showed increased activation in a self-referential subnetwork when both memory pleasantness and vividness were relatively low, while activation in healthy controls was independent of these memory characteristics. In our study, reduced pleasantness and vividness may be a proxy for reduced attention to the task, and increased self-focused attention, which is commonly observed in depression (Davey & Harrison, 2022; Ingram, 1990; Northoff, 2007). Possibly, adolescents with depression had difficulties to actively engage in these memories, resulting in more (negative) self-related thoughts. Adolescents with depression may also need to work disproportionately harder in an effort to retrieve these memories, because these memories are less forthcoming, resulting in greater activation. Yet, when memory pleasantness was relatively low, but vividness was high, adolescents with depression showed decreased activation within this subnetwork. Possibly, they experience more discrepancy between one’s past and present self when reliving these memories, resulting in a more distant way of reliving accompanied by less pleasantness (Libby & Eibach, 2011; Werner-Seidler et al., 2017). As parts of this subnetwork (PCC, vmPFC) are also involved in subjective value computation (Clithero & Rangel, 2014), these neural patterns could also indicate a ‘devalued self’ (Will et al., 2020). Both interpretations are consistent with our finding showing that adolescents with depression (vs healthy controls) reported reduced pleasantness, particularly after reliving positive memories.

Notably, when reliving highly pleasant memories, adolescents with depression did not differ from healthy controls in activating this self-referential subnetwork. Although adolescents with depression reported reduced pleasantness after positive memory reliving, these memories still induced pleasant feelings (vs neutral ones), and vividness was not affected. Also, no group differences were found in memory characteristics during the retrieval phase, indicating that adolescents with depression were able to generate specific and vivid positive memories after explicit instructions. Together, these findings support a growing body of evidence that positive autobiographical memory imagery has clinical potential (File et al., 2021). Adolescents with depression may think less spontaneously about positive aspects of the self, including past events. Actively instructing for positive memory recollection, especially memories validating a positive self, may be a powerful tool for mood-repair, and to positively enrich one’s narrative identity in adolescents with depression (Werner-Seidler et al., 2017).

Our study has several strengths. First, this study one of the first investigations of positive autobiographical memory reliving in adolescents with depression while in the scanner, using freely retrieved memories, instead of memory probes. Second, our extensive procedure yielded rich data about memory processing characteristics, being important for hands-on recommendations for clinical practice. Third, we applied eICA, a data-driven approach that is sensitive to capture spatiotemporal subdivisions of the brain explicitly related to memory reliving. However, this study is not without limitations. First, as we did not investigate negative memory reliving, it remains unknown whether networks are specifically related to positive autobiographical memories, or to generally salient memories. Also, positive (vs neutral) memories were more remote in time and described with more words. Prior research showed that increased memory remoteness is related to a third- vs first-person imagery perspective, which also can influence sensory and visual details (Rice & Rubin, 2009). Given that imagery perspectives and experiences were not assessed, we could not control for these possible confounding factors. It should also be noted that it remains uncertain whether adolescents were actually reliving their memories in the scanner, or if they were reliving the initial lab session where they generated these memories, or both. However, by using this method (i.e., explicitly asking to relive previously recalled memories being rated as either positive or neutral) instead of traditional methods (e.g., responding to emotional cue words with unknown reference to the participant), we had experimental control over the generation of positive (and neutral) memories, such that memories relived in the scanner were as similar as possible for each participant in terms of valence and other memory characteristics. Moreover, while reading memory descriptions, participants may have already started reliving, possibly resulting in differential time-courses of neural responses. Asking participants to press a button when starting with reliving may help disentangling these processes (Thome et al., 2020), but in turn may induce undesired motor and cognitive responses. Furthermore, quite some adolescents had comorbidities, such as posttraumatic stress disorder, possibly impacting memory recollection, which should be taken into account when interpreting our findings. Lastly, our depression sample was quite small due to i) difficulties
recruiting families with an adolescent with depression for an extensive study, and ii) COVID-19 pandemic disrupting data collection. Hence, future studies with larger sample sizes are essential to replicate our findings.

In conclusion, our results demonstrate that adolescents with depression can both retrieve and relive pleasant and vivid autobiographical memories, although subjective pleasantness of positive memories is blunted compared to healthy controls. Neuroimaging analyses showed that the AMN can be divided into subnetworks, with some subnetworks being sensitive to processing of positive versus neutral memories, and a self-referential subnetwork being affected in adolescent depression, especially when reliving relatively ‘low’ pleasant memories. Targeting quality of reliving memories in interventions, for instance with mental imagery-focused treatment (Blackwell, 2019), may be promising to diminish depressive symptoms.

Author contributions

Lisanne A.E.M. van Houtum: Conceptualization, Methodology, Software, Investigation, Formal analysis, Writing – Original Draft, Writing – Review & Editing, Visualization.
Charlotte C. van Schie: Conceptualization, Methodology, Software, Writing – Review & Editing, Supervision.
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Chris Talby: Methodology, Writing – Review & Editing, Supervision.
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Geert-Jan Will: Conceptualization, Investigation, Writing – Review & Editing, Supervision.
Marike S. Tollenaar: Conceptualization, Writing – Review & Editing, Supervision.
Bernet M. Elzinga: Conceptualization, Writing – Review & Editing, Supervision, Funding acquisition.

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Data/code availability and pre-registration statement

The de-identified processed group-level data, analysis scripts and materials for this study are available on DataverseNL (https://doi.org/10.34894/DHRHI1). The group-level MRI data are available on Neurovault (https://neurovault.org/collections/14102/). We are unable to make the raw and processed individual-level data publicly available, given that participants not explicitly consented for sharing their (coded) individual-level data on a public repository. To obtain these data, ethics committee approval and a data sharing agreement would be required. Legal copyright restrictions prevent public archiving of K-SADS, which can be obtained from the copyright holders in the cited references. For any questions or additional material, please contact the corresponding author. No part of the study procedures or analyses was pre-registered prior to the research being conducted.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary data

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References

Clayborne, Z. M., Varin, M., & Colman, I. (2019). Systematic review and meta-analysis: Adolescent depression and long-term...


