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A network analysis of rumination on loneliness and the relationship with depression

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Previous literature has suggested a significant association between loneliness and depression. Importantly, research has shown that rumination can modulate the loneliness–depression relationship. However, most studies only treated loneliness, rumination or depression as unitary constructs. Considering the heterogeneity of the three concepts, we examined the relationship between specific loneliness, rumination items and depressive symptoms using the network analysis approach. In a large community adult sample ($N = 900$), we constructed the loneliness–depression and loneliness–rumination–depression network using a cross-sectional design. The results suggested that loneliness has no robust association with depressive symptoms. Instead, a connection between a specific ruminative thought ('think about how alone you are') and a specific loneliness item ('how often do you feel alone') is essential in maintaining the loneliness–rumination–depression network (partial $r = 0.307$). Our findings indicate that ruminating on the feeling of loneliness is the key underlying factor modulating the loneliness–depression relationship. Interventions for depression should focus on ameliorating ruminative thoughts, especially on loneliness feelings.

Depression is one of the most common mental health problems, affecting around 280 million of the population around the world[1]. During the COVID-19 pandemic in particular there has been a surge in the rate of depressive disorder, with an increase of over 25% within just the first year of the pandemic[2].

Loneliness has been identified as a critical risk factor for depression throughout the previous literature. Loneliness refers to a distressing state due to the unmet interpersonal needs stemming from a discrepancy between one's desired social connection and the actual social connection that one receives[3]. A close relationship between loneliness and depressive symptoms has been consistently supported in both theoretical works (for example, the 'evolutionary theory of loneliness' by Cacioppo and Cacioppo[4]) and multiple empirical studies, such as those reported in refs. 5,6. The *Diagnostic and Statistical Manual of Mental Disorders* fifth edition (DSM V) diagnostic criteria evaluate depression as the presence of five or more symptoms over two weeks for a major depressive episode. Anhedonia or a depressed mood must be among these symptoms, with others including changes in appetite, sleep disturbances, psychomotor issues, concentration difficulties, fatigue, feelings of worthlessness and suicidal thoughts. Given the widely reported high co-occurrence of loneliness and depression, it is of great importance and urgency to understand the

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underlying mechanism behind the relationship between loneliness and depression.

One possible way to explain the link between loneliness and depression is by exploring the role of rumination. Rumination is defined as a set of repetitive, intrusive and uncontrollable focuses on one's negative thoughts and feelings[7]. Rumination has multiple closely related psychological processes, such as worry, negative mind wandering, self-focus thoughts and so on. The definitions and clear cutoffs between these processes remain unclear in the current literature. However, the common feature shared by these processes is the prolonged and recurrent thinking process post certain stressors, the so-called perseverative cognition. The perseverative cognition hypothesis serves as an important theoretical model elucidating the crucial mediation role of rumination on the pathway between stressors (that is, loneliness) and mental disorders (that is, depression).

Perseverative cognition hypothesis

One important theoretical model, proposed by Brosschot and colleagues[8], is the 'perseverative cognition hypothesis'. In their theory, they state that perseverative cognition can serve as a mediator of the psychopathological pathways through which stressors (both physical and psychosocial stressors) impact health. More specifically, in combination with the theory of Tallis and Eysenck[9], worry and rumination, in response to stressors, can disrupt ongoing stressors and trigger the need to look for coping strategies, thus eliciting acute stress responses. However, under chronic stress, perseverative cognition can prolong stressor and stress responses, which continuously activate and maintain the unresolved threatening situations. Furthermore, perseverative cognition overly prepares an organism for action, keeping the individual in a hypervigilant state in preparation for potential threats, even without the actual existence of a stressor. The prolonged state of action readiness and vigilant state have long-term impacts on health through excessive activation of the cardiovascular system, immune functioning, the hypothalamic–pituitary–adrenal axis and other core life-supporting physiological systems[10]. The chronic pathogenic state can eventually develop into future organic diseases[8].

According to their theory, Brosschot and colleagues[8] hypothesized that a stressor would not have a direct impact on health if there was no perseverative cognition about the stressor that maintained the mental representation of it and prolonged the physiological activation. They thus state that perseverative cognition plays a critical part in mediating the way in which chronic stress becomes detrimental to our physical and mental health. In line with perseverative cognition theory, we can speculate that loneliness, as a specific stressor, can exert its impact by contributing to the development of depression indirectly through the prolonged cognitive representation of the loneliness feelings elicited by rumination.

Empirical evidence

Some studies have advocated that rumination and depression are highly associated with each other[11,12], and the relationship between rumination and loneliness has also been repeatedly supported across studies[12,13]. Furthermore, an increasing number of recent studies have proposed the potential transdiagnostic role of rumination in the loneliness–depression relationship. For example, researchers have demonstrated that loneliness is associated with depressive symptoms through the mediating effects of rumination[14–16]. However, other studies have found a moderating effect of rumination for specific types of loneliness (for example, parent-related loneliness), where individuals with a higher loneliness in terms of their relationships with parents, together with a higher level of rumination, are more vulnerable to depression development[15]. Altogether, previous studies have postulated that rumination can be critical in explaining the effects of loneliness on depression.

Multidimensionality issues

However, most of the studies only conceptualized the three concepts at an aggregate level. For example, studies usually operationalize depression as a single disorder using the sum of scores from a self-report questionnaire. However, the manifestation of depression is known to be heterogeneous, with varied symptom combinations across individuals. Park and colleagues[17] identified a total of 119 distinct depression patterns stemming from diverse depressive symptom combinations. Furthermore, the complexity of depression treatment was underscored by the work of Park and Kim[18], who identified 227 unique symptom combinations meeting DSM V diagnostic criteria. Studies have also suggested that different depressive symptoms are related to different cognitive risk factors, indicating that each specific depressive symptom can carry different characteristics[19,20]. Moreover, the contemporary psychopathological network paradigm proposes a causal system among symptoms causing each other to form a mental disorder[21]. Treating depression as a single disorder may ignore the potential causal relationships among depressive symptoms. As such, we propose to reconceptualize depression more at a symptom level, considering the unique contents carried by each depressive symptom and the causal relationships among them.

Similarly, studies have highlighted the multidimensionality of rumination. A recent study by Bernstein and colleagues[22] systematically explored the network structure of rumination. In the rumination network, they found that different items, even within the same subscales, interconnected differently with other items within or outside the subscales. Treating rumination as a unitary construct may mislead people that all the items within a scale or subscale are measuring the same things. However, only a few recent studies have begun to examine the effects of specific ruminative thoughts[23]. The existence of diverse potential subpatterns within each scale underscores the limitation of relying solely on the broader term, or these subfactors to capture the entirety of these complex constructs.

Researchers have also tried to consider the multifaced nature of loneliness. For example, studies have categorized loneliness into different facets, such as emotional versus social loneliness (two basic types of loneliness[24]), existential loneliness[25] or three-faceted constructs (intimate versus relational versus collective loneliness[26]). Although researchers have not yet reached agreement as to the structure of loneliness, this suggests a need to treat loneliness as a multifaceted construct. However, studies that included loneliness using more specific items are scarce[27]. The UCLA Loneliness Scale is one of the most widely used scales to measure loneliness. Previous factor analyses have shown that the scale can be factorized into three constructs of loneliness: intimate loneliness, relational loneliness and collective loneliness[26]. The absence of consensus on the precise factor structure of the UCLA Loneliness Scale indicates potential underlying subpatterns within the construct. We thus suggest treating the UCLA Loneliness Scale more at an item level to take into account the different loneliness constructs measured through the scale.

Admittedly, using total scores to describe the relationships between loneliness, rumination and depression can give us a general idea of their relationships. To better understand the complex psychological relationships in more detail, we should also look into the interconnections among variables at an item level. However, to the best of the our knowledge, no study has yet examined the relationship between individual items of loneliness and rumination and depressive symptoms all at once.

Considering the above literature review, the present study will take a first step to examine the relationship between specific loneliness items, rumination items and individual depressive symptoms using a network analysis approach in a cross-sectional study. Previous studies have suggested that there is a large gender difference in the prevalence of depression[28]. Studies have also shown mixed effects of gender differences in loneliness (for example ref. 29). According

to the previous literature, gender can be an important factor in influencing the behavior of the network structure (for example, the network may be more connected for women than for men). Therefore, a network comparison between women and men subsamples was conducted following the general network analysis. The aims of the present study are twofold. First, we aim to establish the relationship between loneliness, rumination and depression using their total scores to confirm the mediation effects of rumination, in line with previous research. Second, to achieve a more in-depth understanding of the relationship, we will construct a network of loneliness and depressive symptoms and a network of loneliness, rumination and depressive symptoms using more specific items. We hypothesize that rumination mediates the relationship between loneliness and depression, with a higher level of loneliness predicting more rumination, which will, in turn, predict a higher severity of depression. We also hypothesize that in the network analysis, specific loneliness items, rumination items and depressive symptoms will be positively related to each other.

Results

Sample characteristics

Two participants below the Montreal Cognitive Assessment (MoCA) cutoff score of 22 were excluded. Two participants were also excluded from the analyses due to voluntary withdrawal from the study or a large amount of missing data on the variables of interest. A final sample of 900 adults (68.3% women, M_{age} = 26.25 years, s.d.$_{age}$ = 13.35) were included in the analyses. Complete descriptive statistics are presented in Table 1.

Table 1 | Descriptive statistics

Variable	*N* (%) or mean (s.d.)
Age (years)	26.25 (13.35)
Gender	
Men	285 (31.67%)
Women	615 (68.33%)
Ethnicity	
Chinese	829 (92.11%)
Asian (except Chinese)	35
African	12
Other	24
Education level	
College and above	766 (85.11%)
Associate college/degree	40
High school	67
Middle school	19
Elementary school or below	8
Marital status	
Married	97
Cohabited	11
Separated	2
Divorced	10
Widowed	8
Unmarried and not cohabited	772 (85.78%)
UCLALS (total)	41.35 (10.65)
RRS (total)	45.48 (12.94)
PHQ-9 (total)	4.77 (4.20)

UCLALS, UCLA Loneliness Scale; RRS, Ruminative Responses Scale; PHQ-9, nine-item Patient Health Questionnaire.

Mediation model

Spearman's correlations suggest that loneliness, rumination and depression are significantly positively correlated with each other (Supplementary Table 1). Spearman's correlations were examined between loneliness and rumination ($\rho = 0.68, P < 2 \times 10^{-16}$), loneliness and depression ($\rho = 0.19, P < 2 \times 10^{-16}$) and rumination and depression ($\rho = 0.17, P < 2 \times 10^{-16}$).

Mediation analysis (Fig. 1) was performed to examine the role of rumination in the loneliness–depression relationship. The total effect of loneliness on depression was significant (bootstrapped total effect = 0.193, 95% confidence interval (CI) [0.169, 0.220]). Loneliness was significantly associated with rumination, and a higher level of loneliness statistically predicted more ruminative thoughts ($\rho = 0.680$, 95% CI [0.614, 0.744]). Rumination was significantly associated with depression, with more ruminative thoughts statistically predicting more depression ($\rho = 0.120$, 95% CI [0.092, 0.148]). The direct effects of loneliness on depression were significant (bootstrapped direct effect = 0.112, 95% CI [0.083, 0.141]) The indirect effects of loneliness on depression through rumination were significant (bootstrapped indirect effect = 0.081, 95% CI [0.061, 0.104]). Therefore, rumination mediated the loneliness–depression relationship.

Network robustness checks

The robustness check contains two components that support the credibility of the constructed networks. For network accuracy and stability, the non-parametric bootstrap procedure for the edge weights of both networks (Supplementary Fig. 1a,c) has a narrow 95% CI, indicating excellent accuracy. Case-dropping subset bootstrapping on the edge and centrality indices of both networks (Supplementary Fig. 2) suggests excellent stability for the edge weights and node expected influence (EI) over other centrality indices. As such, the present study reports the node EI for node centrality. The stability of the edge weights and node EI of the loneliness–depression network was excellent (both with a correlation stability (CS) coefficient of 0.75). The stability of the loneliness–rumination–depression network is excellent (CS-coefficient = 0.75) for node EI and good (CS-coefficient = 0.672) for edge weights. The bootstrapped difference test of the edge weights of the two networks suggests that most of the edges are significantly different from each other (Supplementary Fig. 3a,c).

The case-dropping bootstrap results of bridge centrality indices (bridge EI and bridge strength) are shown in Fig. 2b,d. The bridge centrality of the loneliness–depression network is not stable (CS-coefficient of bridge strength = 0.128; CS-coefficient of bridge EI = 0.128). The loneliness–rumination–depression network has stable bridge EI (CS-coefficient = 0.594) but unstable bridge strength (CS-coefficient = 0.206). The bridge EI of both networks indicates better network accuracy, with a narrower 95% CI after the non-parametric bootstrap, compared to bridge strength (Fig. 2a,c). Accordingly, the present study reports bridge EI as the indicator of bridge centrality. Supplementary Fig. 1b,d presents the non-parametric bootstrap results of the bridge strength of the two networks.

In terms of the network comparison test on the two subsamples randomly split from the original dataset, neither the network invariance test (*M* (maximum statistic) = 0.322, *P* = 0.0500) nor the global strength invariance test (*S* (distance) = 0.381, *P* = 0.707) suggests any substantially significant differences between the two network structures. Visual examination also supports a similar structure for the two networks (Supplementary Fig. 4a,b). For the networks of both subsamples, the most influential bridge symptoms are L4 ('how often do you feel alone') and R1 ('think about how alone you feel', partial *r* = 0.253 and 0.378, respectively, for the two subsamples), bridging the loneliness and rumination communities (Supplementary Fig. 4c,d). The network

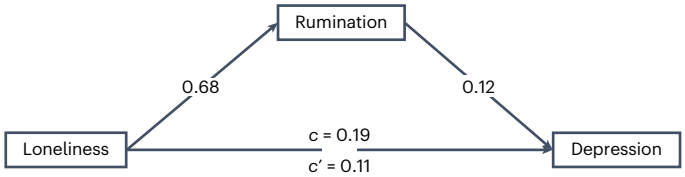

Fig. 1 | Mediation model between loneliness, rumination and depression as unitary constructs. Loneliness is the independent variable, rumination the mediating variable and depression the dependent variable. Total effects (*c*) and direct effects (*c*′) are also illustrated in the model.

structure and central bridge symptoms found in the two subsamples support the reliability and credibility of the network structure and bridge symptoms found in the original dataset and described in the following sections.

Bridge and node centrality

Figure 3 presents the network structures of the loneliness–depression and loneliness–rumination–depression networks. The bridge symptom with the highest bridge EI in the loneliness–depression network is D7 ('trouble concentrating on things'). The symptom of loneliness that D7 most strongly connected with is L11 ('how often do you feel left out', partial $r = 0.094$). However, the bridge centrality of the loneliness–depression network should be interpreted with caution, as the case-dropping bootstrap procedure indicated poor stability of the bridge centrality indices. In the loneliness–rumination–depression network, the bridge symptoms with the highest bridge EI, significantly different from other bridge symptoms, are L4 ('how often do you feel alone') and R1 ('think about how alone you feel'). L4 is most strongly connected to R1 (partial $r = 0.307$). Similarly, R1 is most strongly connected to L4 (partial $r = 0.307$). Supplementary Tables 2 and 3 present the edge weight matrices of the two networks. Illustrations of the full bridge EI plot and its bootstrapped difference test results are provided in Fig. 4b,d and Supplementary Fig. 5.

Figure 4a,c and Supplementary Fig. 3b,d illustrate the node EI plot and the bootstrap difference test results of the two networks. The central nodes with significantly higher node EI over the other nodes in the loneliness–depression network are L14 ('how often do you feel isolated from others') and D2 ('feeling down, depressed or hopelessness'). The nodes with significantly higher EI in the loneliness–rumination–depression network are R6 ('think about how passive and unmotivated you feel'), L4, L14 and R11 ('go away by yourself') and R17 ('think about how sad you feel').

Directed acyclic graph

Figure 5 presents directed acyclic graphs for the loneliness–depression and loneliness–rumination–depression networks. In the loneliness–depression graph, nodes of loneliness and depression are only connected to the nodes within their own communities, without any interconnection between the two communities. In the loneliness–rumination–depression graph, nodes from loneliness generally point to rumination nodes, which point to the depression community. Paths can be found linking the loneliness, depression and rumination communities through important bridge symptoms identified in the previous section. For example, R1 points to L4, which then points to D2. Other paths suggest a link between loneliness and depressive symptoms through rumination. For example, L7 ('no longer closer to others') and L12 ('relationships with others are meaningless') point to R19 ('not feel up to doing anything'), which points directly to R4 ('hard to concentrate') or indirectly through R18 ('think about shortcomings'), R16 ('think "Why can't I handle things better"') and R14 ('not able to concentrate') to R4. R4, in the end, points to D7 and other specific depressive symptoms.

Subsample network comparisons

To examine the effects that gender may have on a network, we constructed a loneliness–rumination–depression network for subsamples of women ($N = 615$) and men ($N = 285$), as illustrated in Supplementary Fig. 6. In particular, the women's network has good edge stability (CS-coefficient = 0.595) and excellent node EI stability (node EI = 0.75), but unstable bridge EI (bridge EI CS-coefficient = 0.439; Supplementary Figs. 7 and 9). In comparison, the men's network shows poor stability in either edge or bridge centrality indices (CS-coefficient edge = 0.361, bridge EI CS-coefficient = 0.126), but good stability in its node EI (CS-coefficient = 0.516; Supplementary Figs. 8 and 9). Supplementary Fig. 10 shows the full node centrality and bridge EI plots of both networks.

The network comparison test (NCT) with Holm–Bonferroni correction did not find significant differences in the network structure (network invariance test: $M = 0.294$, $P = 0.257$) or overall symptom connectivity (global strength invariance test: $S = 1.571$, $P = 0.146$).

Discussion

Going beyond traditional conceptualization and methodology, the present study utilizes network analysis to understand the relationship between specific loneliness items, rumination items and individual depressive symptoms. Specifically, we found no robust direct connection between individual loneliness items and depressive symptoms. Instead, ruminating on loneliness feelings was found to play an important role in mediating the loneliness–depression relationship.

Our two major hypotheses were satisfied by the study. First, in the mediation model, rumination indeed mediated the relationship between loneliness and depression. Our second hypothesis was also satisfied. In the loneliness–depression network, the present study did not reveal stable bridge symptoms due to the poor reliability of the bridge centrality indices. The instability of the loneliness–depression only network means that the two constructs are not the whole picture. Note that a high correlation between loneliness and depression does not equate to a causal relationship that loneliness will always trigger depression or vice versa. Therefore, in the present study, the loneliness–depression network indicated that the activation of the loneliness community alone is not stably associated with the manifestation of specific depressive symptoms. It explains, in real practice, why some individuals with a high level of loneliness may not necessarily connect to depressive symptoms.

In the loneliness–rumination–depression network, we found two influential bridge symptoms: L4 ('frequently feeling alone' thereafter) and R1 ('ruminating on loneliness' thereafter). In particular, 'frequently feeling alone' most strongly connects to other communities through the bridge symptom 'ruminating on loneliness'. Similarly, 'ruminating on loneliness' also has the strongest connection to 'frequently feeling alone'. The strong connection between the two nodes makes it the most influential pair of connections essential to the loneliness–rumination–depression network. In other words, frequently feeling loneliness and subsequently ruminating on the feeling of loneliness together can activate and sustain the close relationship between loneliness, rumination and depressive symptoms.

Our findings can be explained by previous theoretical works. In line with the Perseverative Cognition Hypothesis[8], the stressor (here, loneliness) leads to health damage (that is, depressive symptoms) through the effect of rumination. In our study, the maladaptive way of coping with the stressor—in this case, ruminating on the loneliness feelings—can be the reason why loneliness can result in the development of further depressive symptoms. Especially during the pandemic, due to the Chinese government's compulsory implementation of social distancing policies, people had less chance to gather with their socially significant others and form or maintain their social bonds in person. Social activities are especially important for younger adults (the primary participants of the present study), who require a larger amount of social connection with their friends and colleagues compared to

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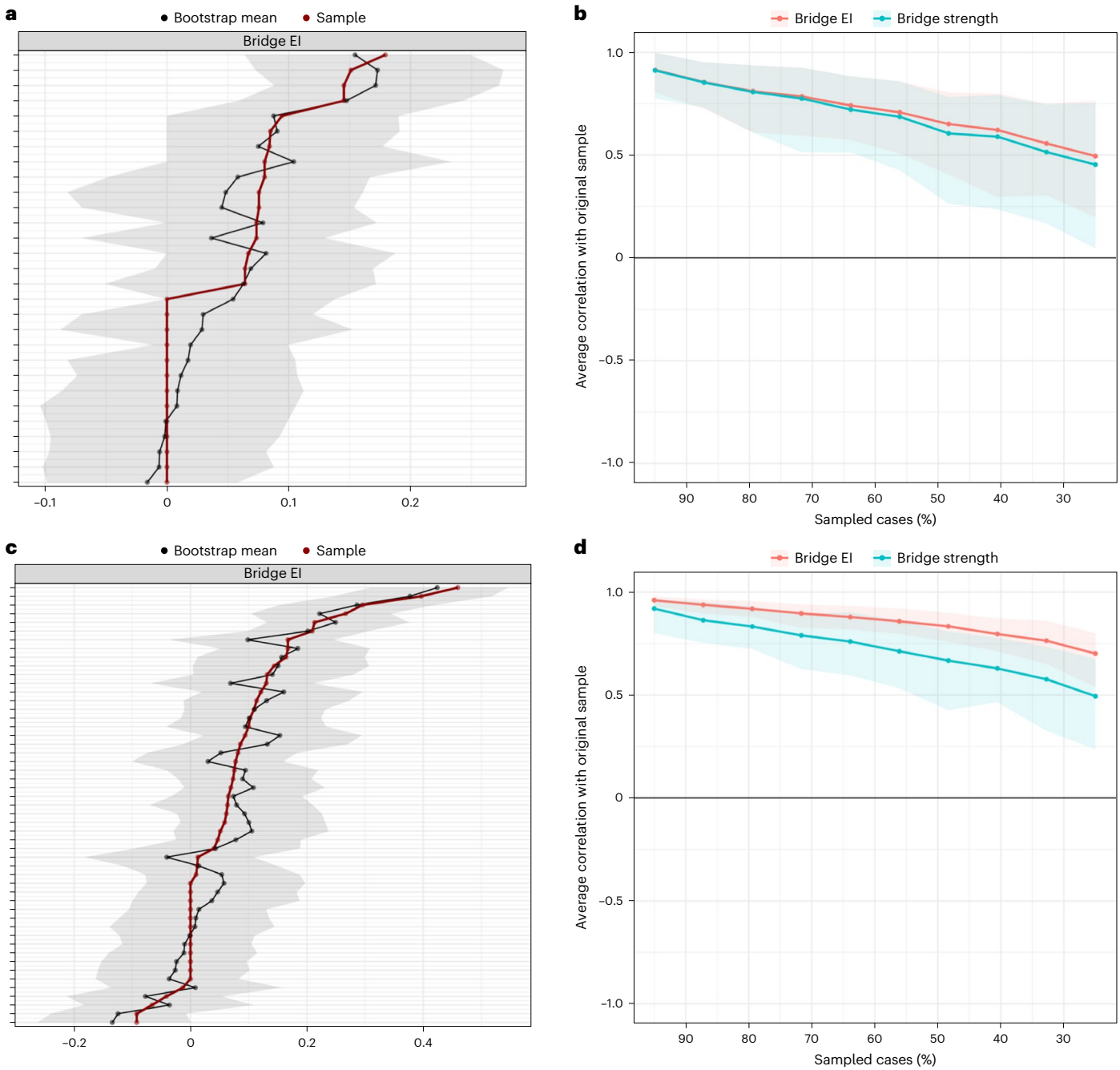

Fig. 2 | Accuracy and stability of bridge centrality indices using a non-parametric and case-dropping bootstrap approach. The non-parametric bootstrap method estimates the accuracy of the bridge EI. Red dots represent each node's corresponding bridge EI, from the highest to the lowest. Gray shading represents the 95% CI for the bridge EI. A narrower gray shadow means better accuracy for the bridge EI. The case-dropping bootstrap method increasingly dropped cases from the original sample and compared the centrality indices in the new versus the original dataset. The *x* axis indicates the proportion of the dataset that can be dropped. The *y* axis represents the correlation between the original bridge centrality indices and those after the cases were dropped with a 95% probability. The shades represent the 95% CI for the bridge centrality indices. **a**, Accuracy of the bridge EI of the loneliness–depression network. **b**, Stability of bridge centrality indices: bridge strength and bridge EI (one-step) of the loneliness–depression network. **c**, Accuracy of the bridge EI (one-step) of the loneliness–rumination–depression network. **d**, Stability of bridge centrality indices: bridge strength and bridge EI (one-step) of the loneliness–rumination–depression network.

other age groups. With the decrease in social activities, mismatches between the actual and desired social connections resulted in an elevation of loneliness levels among young adults. In response to chronic interpersonal stress, people started to ruminate the loneliness feelings repeatedly, maintaining the stressful responses in the long term. Furthermore, social distancing policies hindered lonely individuals from reconnecting with others and removing themselves from a fixation on loneliness, further exacerbating the negative impacts of rumination on mental health. This prolonged rumination in response to loneliness can, in turn, elicit sustained physiological responses to chronic stress, which eventually leads to negative impacts on health, such as developing depressive symptoms[30].

Our results are also consistent with previous empirical studies. A previous network analysis of rumination using the Ruminative

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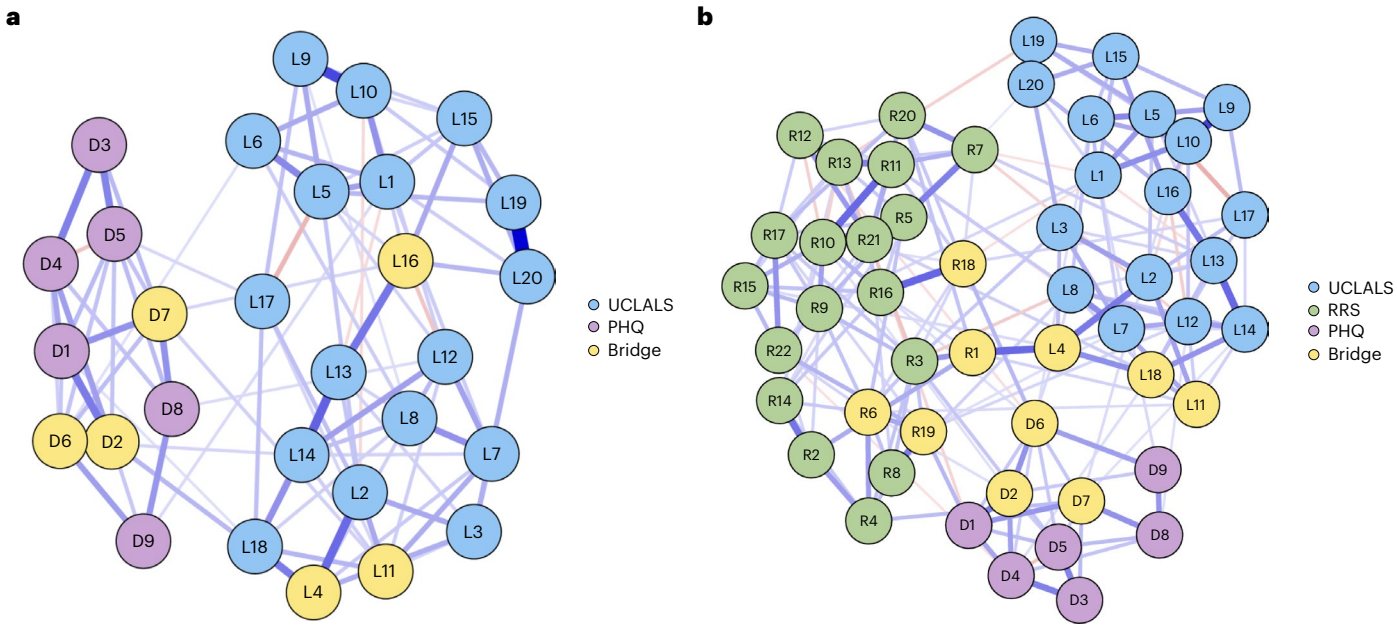

Fig. 3 | Estimated network structures. a,**b**, Network structures of loneliness and depressive symptoms (**a**) and loneliness, rumination and depressive symptoms (**b**) in 900 adults. Each community is colored to represent the variables of interest in this study (namely, loneliness, rumination and depression). The nodes belonging to the same community are assigned the same colors. Blue nodes represent individual items from the UCLA Loneliness Scale version 3. Green nodes represent individual items from the Ruminative Responses Scale (RRS). Purple nodes represent specific depressive symptoms from the Patient Health Questionnaire (PHQ). The thickness and length of the edges represent the strength of the partial correlation between the two nodes, with thicker or shorter edges representing a larger partial correlation between nodes. The colors of the edges represent the directionality of the partial correlation between nodes, where blue indicates a positive partial correlation and red a negative partial correlation. Bridge symptoms are highlighted in yellow, keeping the nodes above the 80% percentile of the bridge EI by convention[43].

Responses Scale (RRS) showed that thinking about how lonely one feels is among the most central nodes with the highest bridge EI in the rumination network[22]. Our study goes beyond previous works and elucidates how ruminating on loneliness contributes to explaining the association between loneliness and depressive symptoms. A recent study by Everaert and colleagues[23] revealed that ruminating on feelings of loneliness repeatedly and stably emerged as one of the best predictors of the central symptoms of depression. In line with these previous studies, we demonstrated that ruminating on loneliness is central in contributing to the loneliness–depression relationship. People may question whether our results are due to original overlaps between the content of the three questionnaires. In response to this, we confirm that our chosen questionnaires possess excellent face validity to assess the three constructs in the present study. Specifically, the UCLA Loneliness Scale focuses on subjective perceptions of social interactions, whereas RRS centers on the repetitive contemplation of past events. The UCLA Loneliness Scale and RRS distinctly measure separate constructs, with the former assessing subjective evaluations of interpersonal relationships and the latter addressing intrusive cognitive patterns concerning past feelings and events. In comparison, PHQ-9 targets depression, emphasizing maladaptive emotional and somatic states. The UCLA Loneliness Scale and PHQ-9 evaluate disparate aspects, with the former concentrating on subjective feelings specifically regarding interpersonal relationships and the latter scrutinizing individuals' historical and current mood states and somatic discomfort. Furthermore, the distinctions between RRS and PHQ-9 are evident, as RRS examines a maladaptive cognitive loop entailing repetitive recollections of past events, and PHQ-9 directly delineates abnormal mood states through various mood-related issues, cognitive challenges and somatic symptoms. These distinctions indicate that each questionnaire uniquely measures separate constructs. Therefore, the observed connections between items from the loneliness and rumination clusters in our results probably reflect meaningful associations bridging across distinct constructs rather than indicating content overlap among the scales.

Our findings also have some inconsistencies with the previous literature. For example, we did not find any depressive symptoms as influential bridge symptoms. This could be due to the characteristics of the current dataset, with most of the participants having minimal or lack of a clinical diagnosis of depressive disorders. It is possible that community participants were still at the early stage where rumination started to exacerbate the negative effects of loneliness on depressive symptoms, but they had not yet reached the full development of depression. As such, the connection between loneliness and rumination is more a determinant in the network at the current stage. This interpretation implies that focusing on reducing the ruminative thoughts on loneliness is essential in breaking the loneliness–depression association, especially for the community population at an earlier development stage of depression. Moreover, Everaert and colleagues[23] also worked on exploring the rumination–depression relationship at the item level and found that both thinking 'Why can't I get going' and rumination on loneliness feelings are among the cardinal items to predict future depressive symptoms. In our study, however, we only confirmed the important role of ruminating on loneliness. This could be due to methodology differences. For example, the unique contents covered by different questionnaires used in different studies may influence results.

The present study has multiple clinical implications. Researchers have suggested that deactivating bridge symptoms is the more effective way to deactivate the whole network compared to using symptoms based on other centrality indices[31]. As such, by removing or disrupting the connection between 'frequently feeling alone' and 'ruminating on loneliness', we may begin to deactivate the network of loneliness, rumination and depression and alleviate the adverse effects of loneliness on depression. Therefore, we suggest that ruminative thoughts on loneliness feelings can be a critical target for effective

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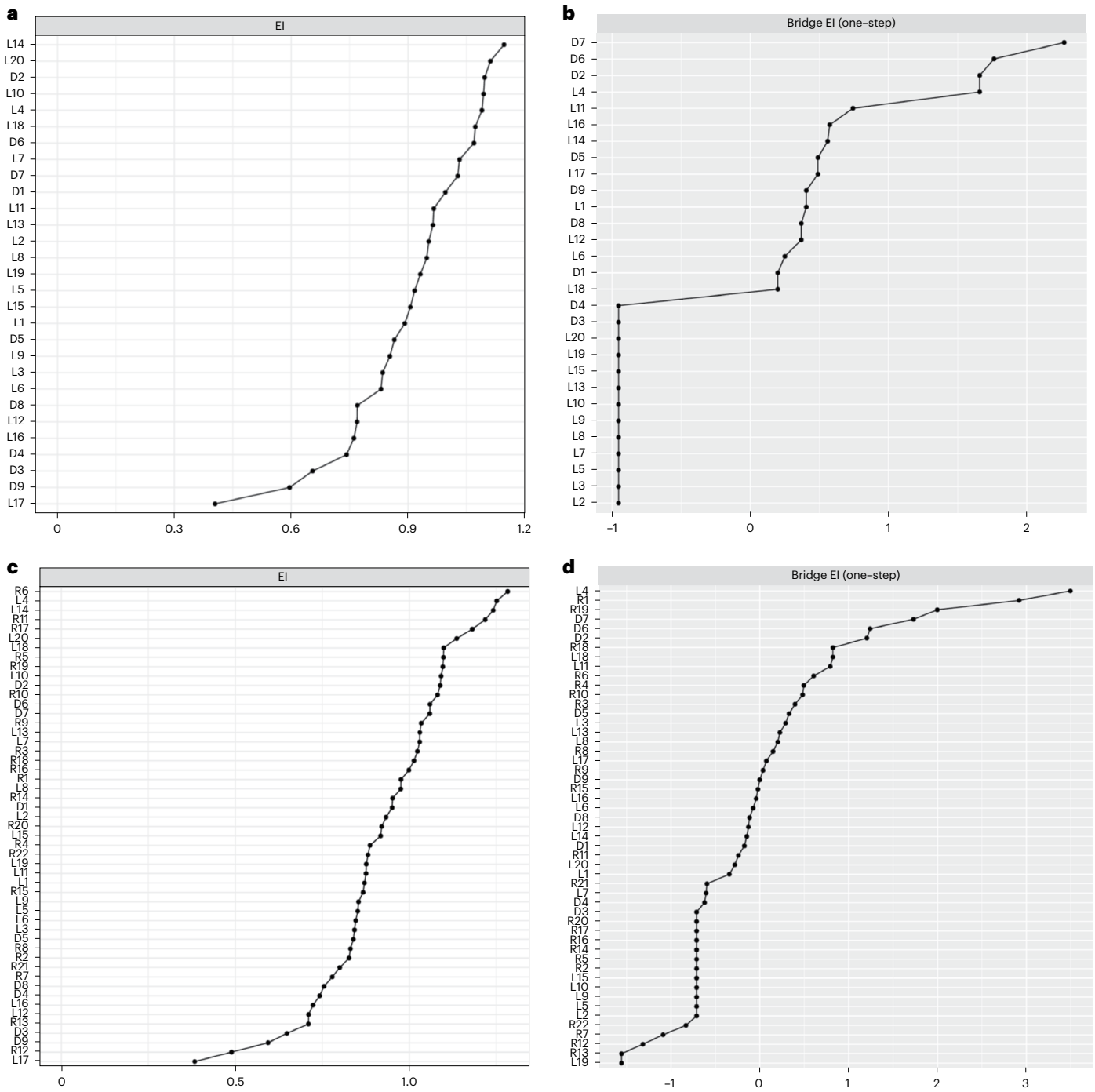

Fig. 4 | Node and bridge centrality indices. The EI (one-step) and bridge EI (one-step) were used in the present study. One-step EI is defined as the sum of all the edges extending from a node, including both negative and positive ones. One-step bridge EI is the sum of edge weights extending from one node to all nodes in other communities. **a**,**b**, EI (**a**) and bridge EI (**b**) of each node, from the highest to the lowest, of the loneliness–depression network. **c**,**d**, EI (**c**) and bridge EI (**d**) of each node, from the highest to the lowest, of the loneliness–rumination–depression network.

intervention preceding the full clinical development of depression for people with high loneliness. For example, psychotherapy such as cognitive behavioral therapy (CBT) could intentionally add cognitive training content targeting specific people with high loneliness to reappraise the negative feelings of rumination rather than ruminating on them. In addition, studies have found that rumination is a vital factor in explaining treatment resistance in depressive disorders[32]. As such, focusing on ruminative thoughts can also improve the treatment effects and decrease the treatment resistance of depressive disorders. However, identifying and targeting one specific kind of ruminative thought alone can be difficult in practice. Therefore, future studies should also consider how to specifically deactivate certain ruminative content for better practice.

The current study is not without limitations. First, the study recruited from a community population, with most participants being women. However, we have conducted network comparison tests to compare gender-stratified subsamples. The results suggest no significant difference between the two networks observed. This could be due to the characteristics of our dataset being mostly composed of women or due to the fact that our results were less likely driven by gender. In spite of

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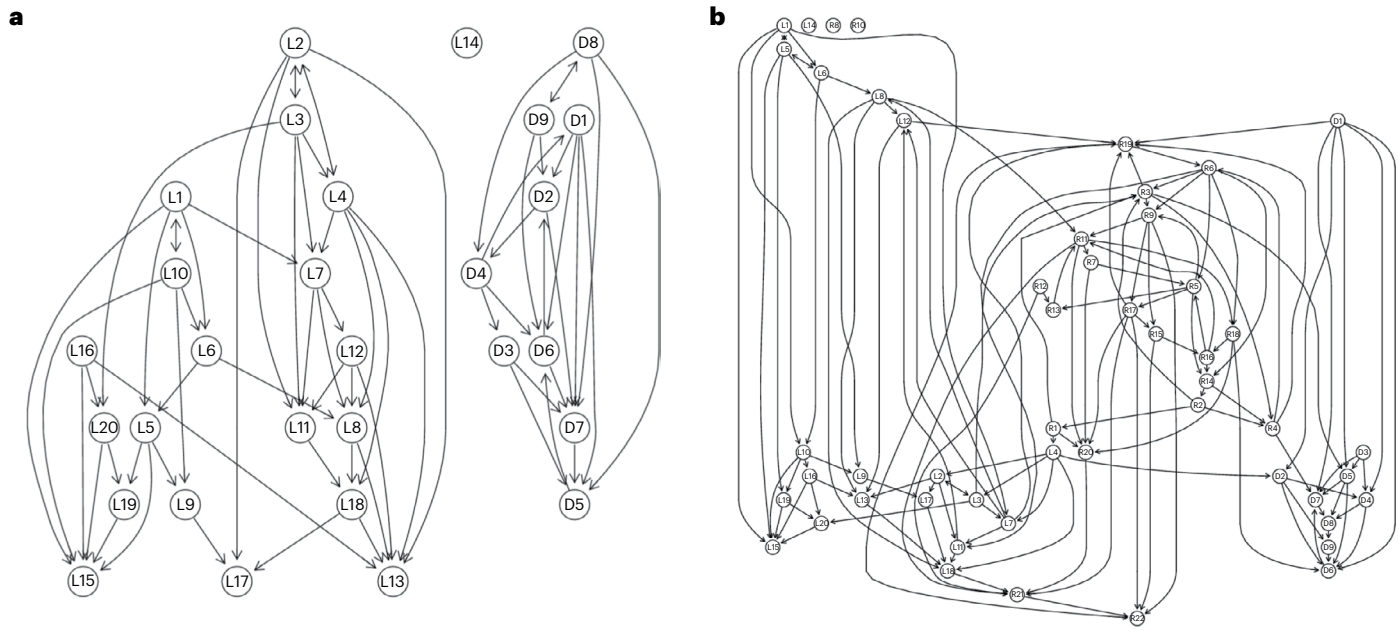

Fig. 5 | Completed partially directed acyclic graphs. a, Directed acyclic graph of the loneliness–depression network. **b**, Directed acyclic graph of the loneliness–rumination–depression network. This approach draws the possible directional links between individual items in the network by considering their conditional independence relationships.

this, future studies should try to use a more balanced sample to avoid the bias of the results and also try using clinical samples to see whether our results can be generalized to clinical settings as well. Second, this is a cross-sectional study that can only suggest correlations but not causations. However, we utilized the directed acyclic graph to infer putative causal links. The directional links drawn from loneliness to depression through rumination imply that loneliness can trigger specific ruminative thoughts, which eventually lead to more specific depressive symptoms. The findings form important first evidence of correlational relationships, and future studies are encouraged to validate our findings using a longitudinal design. Third, the scales we used to operationalize loneliness or rumination may not exhaustively capture the contents of the concept. For example, Maes and colleagues[33] reviewed the current conceptualization and measurements of loneliness, and suggested that most of the scales captured social and emotional loneliness but not other types (for example, existential or collective loneliness), which usually receive less attention. In terms of rumination, researchers have also discussed including the motivational, behavioral and metacognitive contents of rumination in addition to the cognitive construct[13]. Admittedly, the conceptualization and operationalization of the three constructs are not comprehensive enough. We are just tapping part of the construct based on widely accepted definitions and measurements we chose to use. By no means are we referring to our findings as thorough enough to explain every aspect of rumination, loneliness or depression. We acknowledge the inherent limitations of our study in fully capturing the complexity of rumination, loneliness and depression, and we understand that modifications to definitions or measures could impact our specific findings. Some may argue for a replication study. However, we may encounter practical challenges that necessitate our reliance on the UCLA Loneliness Scale and RRS in particular. Introducing lesser-known measures could hinder interpretability and comparability. Our study's specific definitions align with ongoing debates in the literature about loneliness, rumination and depression definitions. Although this may limit generalizability, we highlight the need for future research to refine construct definitions and develop comprehensive measurement tools. Despite these limitations, the chosen questionnaires demonstrate sufficient face validity and prior validity, supporting their use in our study and suggesting potential for further refinement in future studies. Fourth, the network structures and results should be interpreted or generalized with caution, as we only utilized one commonly used scale for each of the three concepts in a community population from China. Nevertheless, we have included a robustness check with an examination of network accuracy and stability and a split-halves network comparison test to increase the credibility of our results. Future studies are encouraged to replicate the current findings using other loneliness, rumination or depression scales or using different populations from different cultural backgrounds to increase the generalizability of the current findings.

Altogether, ruminating on the feeling of loneliness is the most influential factor that contributes to modulating the loneliness–depression relationship. This finding emphasizes the importance of considering the heterogeneity of depression and the multidimensionality of loneliness and rumination. Future studies are recommended to further replicate the current study and target resolving ruminative thoughts to alleviate the effects of loneliness on depressive symptoms.

Methods

Participants

A sample of 904 adult participants were recruited from the community population residing in Hong Kong, Guangzhou and Fuzhou, China, between 2021 and 2023 during the outbreak of the COVID-19 pandemic. A Montreal Cognitive Assessment (MoCA) was conducted during the screening. Any participants who scored below 22, a cutoff score validated in Chinese older populations[34], was regarded as having cognitive impairments and excluded from the final analysis.

Ethical approval of the project was obtained from the Human Research Ethics Committee of the affiliated institute of the first author and the last corresponding author (Human Research Ethics Committee ref. no. EA200161). All participants provided informed consent at the beginning of the study. They were notified of the potential harms and benefits of the study and their right to exit the study at any time. Participants who voluntarily gave their consent completed a series of questionnaires. Participants received no more than HK$80 for compensation.

Questionnaires

The questionnaires included measures of loneliness, rumination, depression, demographic characteristics and a variety of other individual features as part of a larger project.

Loneliness was measured through one of the most widely used scales, the UCLA Loneliness Scale version 3 (UCLA-3 Loneliness Scale[35]). The UCLA-3 Loneliness Scale includes 20 items with 11 positively worded items (for example, 'How often do you feel left out') and nine negatively worded items (for example, 'How often do you feel close to people'). Participants were instructed to indicate the frequency of their feelings of loneliness on a four-point Likert scale from 1 (never) to 4 (often). A higher score in positively worded items represents a higher level of loneliness. For negatively worded items, we reversely coded the items so that a higher score represented a higher level of loneliness. The UCLA Loneliness Scale has wide applicability. For instance, recent reviews on loneliness included studies that exclusively use the UCLA Loneliness Scale, suggesting the wide usage of the measure of loneliness[36]. Studies among parents of children with autism spectrum disorder (ASD), college students and older adults in China have repeatedly utilized the UCLA Loneliness Scale[37–39]. We adopted a validated Chinese version that has high internal consistency (Cronbach's $\alpha = 0.85$; ref. 40). The internal consistency of the items of the scale in the present sample is excellent (MacDonald's $\omega = 0.91$). Our factor analyses reveal strong internal validity of the UCLA Loneliness Scale, with high item loadings (above 0.5) across most items. Previous research consistently supports its external validity and reliability across various populations and settings (for example refs. 35,41). A recent review[42] confirmed the scale's good content validity and reliability, with widespread application in diverse contexts such as patients with diabetes[43] and COVID-19[44].

Rumination was evaluated using the 22-item RRS[45], derived from the Response Styles Theory of Nolen-Hoeksema[7]. The scale was scored on a four-point Likert scale from 1 (almost never) to 4 (almost always). The questionnaire asked participants how frequently they generally do or think as the statements in the questionnaire. An example of a questionnaire item is 'Think about how passive and unmotivated you feel'. A higher score indicates a higher level of ruminative response style. Recent reviews have utilized RRS as a measure of rumination, suggesting its wide usage (29 out of 58 studies in the review of Nagy and colleagues[46]; Stade and Ruscio[47]; exclusively for RRS, Stelmach-Lask and colleagues[48]). The RRS has also been extensively used in studies involving Chinese adolescents, individuals with mood disorders, and college students (for example, refs. 49,50). We adopted the Chinese version with good internal consistency reliabilities (Cronbach's $\alpha = 0.90$; ref. 51). The scale has excellent internal consistency for the present sample (MacDonald's $\omega = 0.95$). Our factor analysis for the RRS indicates strong internal validity, with most items showing high loadings on a single factor. Past research, including studies by Treynor and colleagues[45] and Liang and Lee[49], has demonstrated the good test–retest correlations and reliability of the RRS, particularly in Chinese samples across genders and in adolescents.

Depression was assessed by the PHQ-9[52]. The nine items from the PHQ-9 were designed based on the DSM-IV diagnostic criteria for depressive disorder[53]. Participants were asked about the frequency of suffering from depressive symptoms in the past two weeks. Examples of depressive symptoms are 'Feeling down, depressed or hopeless' and 'Feeling tired or having little energy'. The questionnaire utilized a four-point Likert scale, ranging from 0 (not at all) to 3 (nearly every day). A higher score for an item represents a higher severity of the specific depressive symptom. The PHQ-9 is a commonly utilized tool for measuring and tracking depression in large-scale samples given the short length of the questionnaire. Studies have systematically reviewed the wide use and good sensitivity and specificity of PHQ-9 in primary-care settings[54]. PHQ-9 has also been widely adopted in measuring depression among Chinese populations, as evidenced by its inclusion in various studies among Chinese college students[55]. The Chinese version adapted by Yu and colleagues[56] also suggests excellent internal consistency (Cronbach's $\alpha = 0.82$), comparable to the English version in a primary-care study (Cronbach's $\alpha = 0.89$). The internal consistency of the questionnaire in the present sample is good (MacDonald's $\omega = 0.87$). Our factor analysis suggests good factor loadings of all items on one factor. Research indicates strong reliability and test–retest correlations of the PHQ-9 with other depression scales and professional mental health diagnoses[52,54,57]. Recent reviews, such as by Levis and colleagues[57], underscore PHQ-9's exceptional sensitivity in screening major depression, surpassing semistructured diagnostic interviews, and highlighting its reliability in clinical contexts.

Data analysis

We first conducted Spearman correlations among loneliness, rumination and depression using their total scores to confirm the correlations between them as unitary constructs. We specifically chose to use the Spearman's correlation test because it is a non-parametric test that does not require the satisfaction of normality assumption, which is more suitable for the present dataset.

A mediation model was then drawn between loneliness, rumination and depression. The model defined loneliness as the independent variable, rumination as the mediating variable, and depression as the dependent variable. All paths, total effect, direct effect and indirect effect, were evaluated using bootstrapped 95% CIs with 5,000 bootstrap samples. The mediation effect of rumination was regarded as significant if the 95% CIs did not include zero.

The data were then analyzed using a network analysis approach following a cross-sectional design. Network analysis is an advanced statistical analytic strategy. Network analysis focuses on how individual items connect within and across the larger variables[58] and how these connections influence the behavior of the network to explain the larger phenomena[59]. Network analysis can help address the heterogeneity of larger concepts and thus contribute to better capturing how individual items play roles within and outside their own concept clusters. Specifically, the bridge symptoms in a network can be essential in linking the clusters of symptoms between different disorders or conditions and thus transferring the activation from one disorder or condition to another. Therefore, interventions or treatments targeting the most influential bridge symptoms in a network can be effective in ameliorating the co-occurrence of multiple maladaptive conditions. The whole analysis was performed in *R* version 4.1.3[60] using the psych version 2.3.3[61], lavaan version 0.6.15[62], bootnet version 1.5[63], qgraph version 1.9.3[64], networktools version 1.5.0[65], pcalg version 2.7.8[66] and NetworkComparisonTest version 2.2.1[67] packages.

Estimation of network structure. The graphical least absolute shrinkage and selection operator (LASSO) algorithm and the extended Bayesian information criterion (EBIC) were used to obtain the optimal partial correlation network structure using the bootnet package[63]. Spearman partial correlation was used as recommended and widely accepted across the literature[68]. The network was visualized with each item of the questionnaire depicted as a node and the line that interconnects between two nodes as an edge.

Network centrality indices. The centrality indices of the weighted networks were calculated and visualized using the CentralityPlot function from the qgraph package[64]. Traditional centrality indices, including strength, closeness, and betweenness, have all been used commonly in previous studies. However, recent research has pointed out the unreliability of using closeness and betweenness in assessing the centrality role of nodes[69]. In addition, studies argue that strength cannot accurately capture the centrality of nodes when one node has both negative and positive edges[69]. On the other hand, the one-step EI is defined as the sum of all the edges extending from the node, considering both negative and positive ones. Therefore, following the suggestions of

Robinaugh and colleagues[70], we focused on reporting the EI (one-step) as the indicator of centrality in the present analyses. For the sake of completeness, we also report other centrality indices (for example, strength, closeness and betweenness) in Supplementary Fig. 11.

Network robustness checks. The robustness checks contain two components. The first includes the estimation of network stability and accuracy. The second includes a network comparison test on two subsamples from the original larger sample randomly split into halves to examine the replicability of the loneliness–rumination–depression network structure.

Network stability and accuracy were evaluated by two bootstrap approaches using the bootnet package[63]. The non-parametric bootstrap procedure with 1,000 permutations was used to assess the accuracy of the edge weights by generating a 95% CI through random sampling of the original dataset. A narrower CI suggests good network accuracy. A case-dropping bootstrap method with 1,000 permutations was used to capture the stability of the centrality indices and edges. The CS-coefficient was obtained from the bootstrapping, and indicates the maximum proportion of the dataset that can be dropped while maintaining the correlation between the original centrality indices or edges and those after case-dropping above at least 0.7 (by default) with 95% probability. By convention, a CS-coefficient above 0.7 indicates excellent stability. A CS-coefficient above 0.5 but below 0.7 represents good stability. A CS-coefficient below 0.5 indicates poor stability[63]. The results from the case-dropping bootstrap test can also be used to support our selection of central indices in the present analyses (details are presented in the Results). Bootstrapped difference tests were performed at the end to evaluate the significance of the centrality indices of one node or edge compared to the others[71].

A network comparison test was carried out on the two randomly split halves from the original dataset using the 'NetworkComparisonTest' package[67]. The original dataset was randomly split into two datasets with 450 participants in each subsample. The network comparison test was performed on the loneliness–rumination–depression networks of the two subsamples using 1,000 iterations with two major tests: (1) network invariance test to examine whether any edges in the two networks are different and (2) global strength invariance test to examine any differences in the overall edge connectivity. Finally, the two subsample networks were compared for the parameters that are meaningful for the current studies (for example, the most influential bridge symptoms, the bridge connections between communities, and so on).

Bridge symptoms. To illustrate the nodes that play essential roles in bridging between clusters of items belonging to the same larger variable, or communities, we used the bridge function from the networktools package[65] to evaluate the bridge symptoms in the network. Similarly, we selected to report the bridge EI (one-step) for the centrality of the bridge symptoms[70]. One-step bridge EI is the sum of edge weights extending from one node to all nodes in other communities. Supplementary Fig. 12 presents other bridge indices (for example, bridge strength). Studies have suggested that activation of the nodes with the highest bridge EI are the most influential in activating other communities[65]. Non-parametric and case-dropping bootstrap procedures were also performed to evaluate the stability and accuracy of the bridge centrality indices.

Complete partially directed acyclic graph. To explore the potential directional influence between individual items in the network, a directed acyclic graph approach was applied to the estimated network using the 'pcalg' package[66]. A directed acyclic graph is a type of Bayesian network that draws the possible directional links between individual items in the network by considering their conditional independence relationships[71]. Such directed acyclic graphs can help reveal the most possible causal processes in cross-sectional observational datasets. The function of causal inference allows for identifying the potential risk factors or optimizing intervention targets preceding certain adverse processes[71].

Network comparison by gender. Finally, to understand whether the networks are different for women versus men, we also examined the potential gender differences in loneliness–rumination–depression networks by doing a network comparison test using the NetworkComparisonTest package[67]. We performed difference tests between the networks of subsamples (women versus men) using 1,000 iterations. Two general hypothesis tests were conducted for the two networks: (1) a network invariance test, whose null hypothesis states that all corresponding pairs of edges in two networks are the same, and (2) a global strength invariance test, which examines the overall edge connectivity in a network. Differences in each individual edge and centrality indices between the two subsamples' networks were also evaluated. Holm–Bonferroni correction was adopted to adjust the *P* value of the result for multiple comparisons.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this Article.

Data availability

The minimum anonymized data that support the findings of this study are available upon reasonable request from the corresponding authors. The participants did not consent to the sharing of the raw data to the public. Source data are provided with this paper.

Code availability

No custom code was used in this study.

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Author contributions

C.C.H.C. and T.M.C.L. conceived the research idea. N.M.L.W. and T.M.C.L. designed the study. N.M.L.W., R.Z. and J.W. collected the data. J.L. analyzed the data. All authors discussed the findings. J.L. produced the first draft of the manuscript. J.L., N.M.L.W., R.Z., J.W., R.S., C.C.H.C. and T.M.C.L. revised the manuscript. All authors approved the final version to be published and agreed to be accountable for the integrity and accuracy of all aspects of the work.

Competing interests

The authors declare no competing interests.

Additional information

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Peer review information *Nature Mental Health* thanks Juan Ramos-Cejudo and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

The research included local researchers in Guangzhou, Fuzhou and Hong Kong where local community populations were recruited for the current study. Roles and responsibilities were discussed and agreed among all collaborators ahead of the research. The research has also been approved by the University of Hong Kong Human Research Ethics Committee.

nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☐	☒ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	The behavioral data were collected with a laptop using online questionnaire platform.
Data analysis	The data analysis was performed in R v4.1.3 using the 'psych v2.3.3', 'lavaan v0.6.15', 'bootnet v1.5', 'qgraph v1.9.3', networktools v1.5.0', 'pcalg v2.7.8', and 'NetworkComparisonTest v2.2.1' packages. No custom code was used in this study.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The minimum anonymized data that support the findings of this study are available upon reasonable request from the corresponding authors. The participants did not consent to the sharing of the raw data to the public. Source data are provided with this study.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	For a total of 900 participants included in the final analysis, there are 285 men and 615 women.
Reporting on race, ethnicity, or other socially relevant groupings	For a total of 900 participants included in the final analysis, there are 829 Chinese, 35 Asian (except for Chinese), 12 African, and 24 others.
Population characteristics	A final sample of 900 adults (68.3% women, Mage = 26.25, SDage = 13.5) were recruited from the community population residing in Hong Kong, Guangzhou, and Fuzhou China.
Recruitment	Advertisements, posters. No potential biases were identified.
Ethics oversight	The University of Hong Kong Research Ethics Committee.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☒ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	Quantitative cross-sectional
Research sample	A final sample of 900 adults (68.3% women, Mage = 26.25, SDage = 13.5) were recruited from the community population residing in Hong Kong, Guangzhou, and Fuzhou China.
Sampling strategy	Random sampling.
Data collection	The behavioral data were collected with a laptop using online questionnaire platform.
Timing	Between February 2021 and 2023.
Data exclusions	Two participants below the Montreal Cognitive Assessment (MoCA) cut-off score of 22 were excluded.
Non-participation	Two participants were also excluded from the analyses due to a voluntary withdrawal from the study or a large amount of missing data on the variables of interest.
Randomization	Participants were not allocated into experimental groups.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☐ Antibodies
☐	☐ Eukaryotic cell lines
☐	☐ Palaeontology and archaeology
☐	☐ Animals and other organisms
☐	☐ Clinical data
☐	☐ Dual use research of concern
☐	☐ Plants

Methods

n/a	Involved in the study
☐	☐ ChIP-seq
☐	☐ Flow cytometry
☐	☐ MRI-based neuroimaging

Antibodies

Antibodies used — *Describe all antibodies used in the study; as applicable, provide supplier name, catalog number, clone name, and lot number.*

Validation — *Describe the validation of each primary antibody for the species and application, noting any validation statements on the manufacturer's website, relevant citations, antibody profiles in online databases, or data provided in the manuscript.*

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s) — *State the source of each cell line used and the sex of all primary cell lines and cells derived from human participants or vertebrate models.*

Authentication — *Describe the authentication procedures for each cell line used OR declare that none of the cell lines used were authenticated.*

Mycoplasma contamination — *Confirm that all cell lines tested negative for mycoplasma contamination OR describe the results of the testing for mycoplasma contamination OR declare that the cell lines were not tested for mycoplasma contamination.*

Commonly misidentified lines (See ICLAC register) — *Name any commonly misidentified cell lines used in the study and provide a rationale for their use.*

Palaeontology and Archaeology

Specimen provenance — *Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information). Permits should encompass collection and, where applicable, export.*

Specimen deposition — *Indicate where the specimens have been deposited to permit free access by other researchers.*

Dating methods — *If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.*

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight — *Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.*

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals — *For laboratory animals, report species, strain and age OR state that the study did not involve laboratory animals.*

Wild animals — *Provide details on animals observed in or captured in the field; report species and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.*

Reporting on sex — *Indicate if findings apply to only one sex; describe whether sex was considered in study design, methods used for assigning sex. Provide data disaggregated for sex where this information has been collected in the source data as appropriate; provide overall*

	numbers in this Reporting Summary. Please state if this information has not been collected. Report sex-based analyses where performed, justify reasons for lack of sex-based analysis.
Field-collected samples	*For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.*
Ethics oversight	*Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.*

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	*Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.*
Study protocol	*Note where the full trial protocol can be accessed OR if not available, explain why.*
Data collection	*Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.*
Outcomes	*Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.*

Dual use research of concern

Policy information about dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes	
☐	☐	Public health
☐	☐	National security
☐	☐	Crops and/or livestock
☐	☐	Ecosystems
☐	☐	Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes	
☐	☐	Demonstrate how to render a vaccine ineffective
☐	☐	Confer resistance to therapeutically useful antibiotics or antiviral agents
☐	☐	Enhance the virulence of a pathogen or render a nonpathogen virulent
☐	☐	Increase transmissibility of a pathogen
☐	☐	Alter the host range of a pathogen
☐	☐	Enable evasion of diagnostic/detection modalities
☐	☐	Enable the weaponization of a biological agent or toxin
☐	☐	Any other potentially harmful combination of experiments and agents

Plants

Seed stocks — *Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*

Novel plant genotypes — *Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*

Authentication — *Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*

ChIP-seq

Data deposition

☐ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links
May remain private before publication. — *For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.*

Files in database submission — *Provide a list of all files available in the database submission.*

Genome browser session
(e.g. UCSC) — *Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.*

Methodology

Replicates — *Describe the experimental replicates, specifying number, type and replicate agreement.*

Sequencing depth — *Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.*

Antibodies — *Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.*

Peak calling parameters — *Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.*

Data quality — *Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.*

Software — *Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.*

Flow Cytometry

Plots

Confirm that:

☐ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☐ All plots are contour plots with outliers or pseudocolor plots.

☐ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation — *Describe the sample preparation, detailing the biological source of the cells and any tissue processing steps used.*

Instrument — *Identify the instrument used for data collection, specifying make and model number.*

Software — *Describe the software used to collect and analyze the flow cytometry data. For custom code that has been deposited into a community repository, provide accession details.*

Cell population abundance

Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.

Gating strategy

Describe the gating strategy used for all relevant experiments, specifying the preliminary FSC/SSC gates of the starting cell population, indicating where boundaries between "positive" and "negative" staining cell populations are defined.

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type

Indicate task or resting state; event-related or block design.

Design specifications

Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.

Behavioral performance measures

State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).

Acquisition

Imaging type(s)

Specify: functional, structural, diffusion, perfusion.

Field strength

Specify in Tesla

Sequence & imaging parameters

Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.

Area of acquisition

State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software

Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).

Normalization

If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.

Normalization template

Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.

Noise and artifact removal

Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).

Volume censoring

Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

Statistical modeling & inference

Model type and settings

Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

(See Eklund et al. 2016)

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

Models & analysis

n/a	Involved in the study
☐	☐ Functional and/or effective connectivity
☐	☐ Graph analysis
☐	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.