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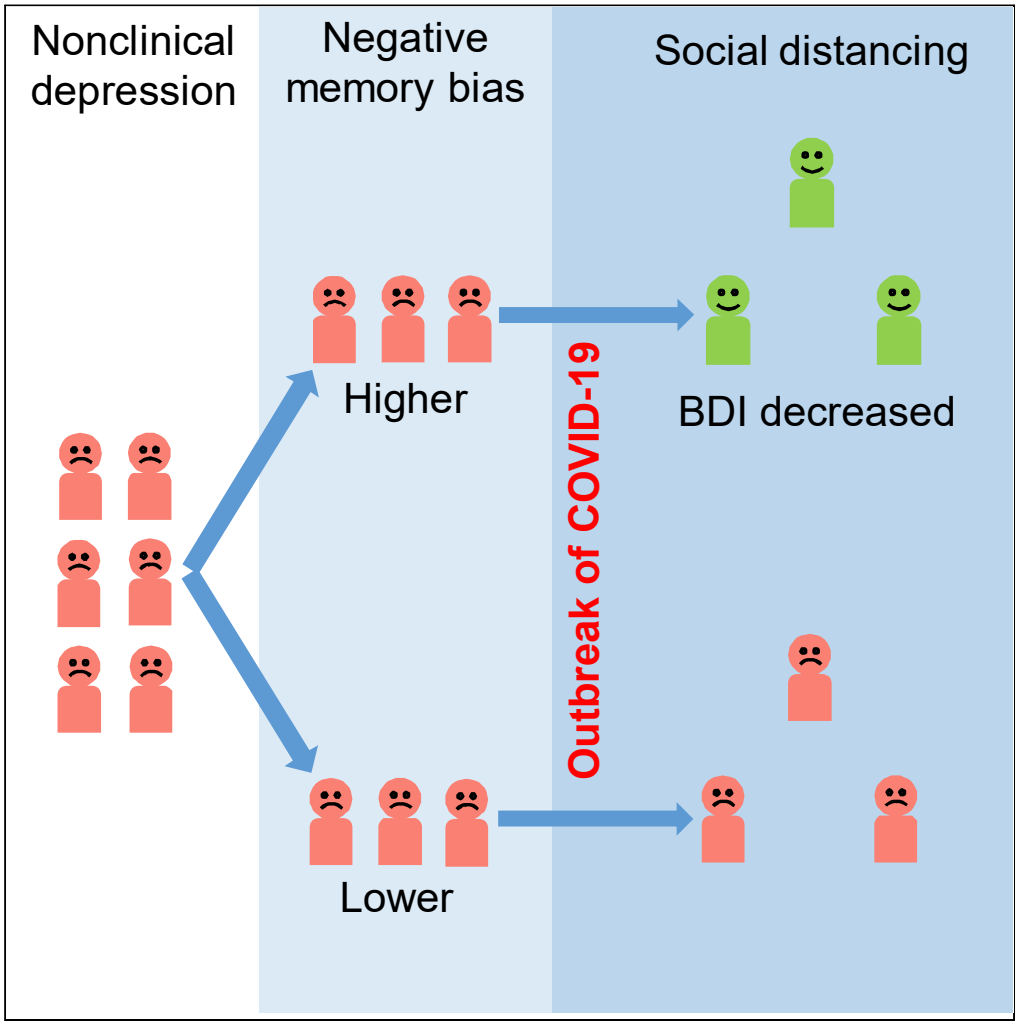

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HIGHLIGHTS

We collected depressive degree before and during the COVID-19 pandemic

Depressive degree negatively correlated with memory bias during the pandemic

Reduced social stress during the pandemic might lead to the altered relationship

Results provide extra support for social distancing policies during the pandemic

Zhang et al., iScience 24, 102081
February 19, 2021
https://doi.org/10.1016/j.isci.2021.102081

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Outbreak of COVID-19 altered the relationship between memory bias and depressive degree in nonclinical depression

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SUMMARY

The outbreak of the novel coronavirus disease 2019 (COVID-19) has increased concern about people's mental health under such serious stressful situation, especially depressive symptoms. Cognitive biases have been related to depression degree in previous studies. Here, we used behavioral and brain imaging analysis, to determine if and how the COVID-19 pandemic affects the relationship between current cognitive biases and future depression degree and the underlying neural basis in a nonclinical depressed population. An out-expectation result showed that a more negative memory bias was associated with a greater decrease in future depressive indices in nonclinical depressed participants during the COVID-19 pandemic, which might be due to decreased social stress. These data enhance our understanding of how the depressive degree of nonclinical depressed populations will change during the COVID-19 pandemic and also provide support for social distancing policies from a psychological perspective.

INTRODUCTION

The outbreak of the novel coronavirus disease 2019 (COVID-19) is a major emergency that people around the world are facing. Until now, the virus has rapidly spread in most countries, with more than 60 million cases reported (https://covid19.who.int/). This serious stressful situation has increased concern about people's mental health, especially depressive symptoms (Adhanom Ghebreyesus, 2020; Shi et al., 2020). In addition to the possible direct impact of the pandemic on mental health, recent studies have argued that governments' policies for the prevention of viral spread (for example, social distancing policies) may also have an impact on psychological distress and cause mental disorders (Galea et al., 2020; Orben et al., 2020; Venkatesh and Edirappuli, 2020). Nonclinical depressed individuals, who are associated with depressive symptoms but do not meet the criteria for clinical depression, are widely distributed around the world and are at high risk of depression (Ayuso-Mateos et al., 2010; Ronald C. Kessler et al., 1997). Therefore, it is important to investigate how the depressive degree changes during the COVID-19 pandemic in the nonclinical depressed population.

The cognitive model of depression proposed by Beck clarified the cognitive factors that are associated with depressive degree (Beck, 2008). According to this model, biased attention, interpretation, and memory play primary roles in the development and maintenance of depression (Disner et al., 2011). Current negative cognitive biases have been related to future depressive symptoms (Gotlib and Joormann, 2010; Kleim et al., 2014; Romero et al., 2014; Rude et al., 2003; Smith et al., 2018). Therefore, to understand how the depressive degree will change during the COVID-19 pandemic in the nonclinical depressed population, it is important to investigate how the outbreak of COVID-19 may affect the relationship between current cognitive biases and future depression.

Two possible effects of the COVID-19 pandemic on the relationship between current cognitive biases and future depression in the nonclinical depressed population can be put forward. On the one hand, the COVID-19 pandemic is a threat to life. Fear and anxiety about a new disease and what could happen can be a powerful source of stress and increase the depressive degree. Recent studies have also found significant increased symptoms and a high prevalence of depression during the COVID-19 pandemic (Bauerle et al., 2020; Chen et al., 2020; Choi et al., 2020; Corbett et al., 2020). Therefore, in nonclinical depressed

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https://doi.org/10.1016/j.isci.2021.102081

individuals, those with more negative biased cognition might become more depressed when facing elevated stress during the COVID-19 pandemic. Thus, the outbreak of COVID-19 may promote a positive correlation between negative cognitive biases and future depressive degree. On the other hand, some measures (for example, social distancing policies) have been carried out by governments to prevent the spread of the virus. These measures have caused significant changes in social habits. Although recent studies have argued that these prevention measures may cause psychological distress, we propose that these measures may result in decreased social stress in the nonclinical depressed population, which has been reported to be a crucial risk factor for depression (Pinquart and Sorensen, 2003; Schuster et al., 1990; Slavich et al., 2009). In addition, negative cognitive biases play a key role in the causing and maintaining of social stress (Clark and McManus, 2002; Heinrichs and Hofmann, 2001; Hirsch and Clark, 2004; Ledley and Heimberg, 2006; Musa and Lepine, 2000). Therefore, in nonclinical depressed individuals, those with more negative biased cognition may experience more social stress before the pandemic and thus show more relief of depression when facing reduced stress during the COVID-19 pandemic. Thus, the outbreak of COVID-19 may change the relationship between current cognitive biases and future depressive degree and promote a negative correlation between them.

According to a previous meta-analysis of functional neuroimaging of depression (Miller et al., 2015), ten brain areas were highlighted in youth with depression. These areas were the subgenual anterior cingulate cortex (ACC), ventrolateral prefrontal cortex (vlPFC), caudate, thalamus, parahippocampal gyrus, cuneus, dorsal cingulate cortex (DCC), insula, dorsolateral prefrontal cortex and superior temporal cortex (Miller et al., 2015). The roles of these areas in cognitive biases have also been discussed in previous studies (Disner et al., 2011; Sakaki et al., 2020; Wiers and Wiers, 2017). For example, the DCC functions in the inhibitory processing and cognitive control of emotion and its greater activation when inhibiting attention to negative stimuli in individuals with depression has been considered to be associated with the cognitive biases of depression (Disner et al., 2011). The cognitive biases associated with depression have been proposed to be particularly prominent for emotional faces (Stuhrmann et al., 2011). Greater brain response to sad faces in the depressed population was interpreted as neurobiological evidence of negative cognitive biases (Stuhrmann et al., 2011; Suslow et al., 2010). Attenuated response to happy faces has also been reported as an evidence of impaired processing of happy expressions (Fu et al., 2007).

Based on what has been discussed above, we hypothesize that the outbreak of COVID-19 may alter the relationship between current cognitive biases and future depression degree in the nonclinical depressed population. In the present study, nonclinical depressed participants' current depressive indices, cognitive biases, brain response to emotional faces, and future depressive indices were assessed. Some of the nonclinical depressed participants' future depressive indices were assessed before the outbreak of COVID-19, and some were assessed during the COVID-19 pandemic. We also included a group of nondepressed participants to ensure the results were specific to the effect of the COVID-19 pandemic. All of the nondepressed participants' future depressive indices were assessed before the COVID-19 pandemic. We compared the correlations between negative cognitive biases and future depressive indices between samples whose future depressive indices were assessed before or during the COVID-19 pandemic. Regions of interest (ROI) analysis was also carried out to test whether the relationship between brain activity in the cognitive bias-related regions and future depressive indices also showed the same pattern under the effect of the COVID-19 pandemic as that between cognitive biases and future depressive indices.

RESULTS

A total of 98 adults participated in our study. Three participants were excluded because two quit the study after the behavior tests and the other slept during the experiment. The participants attended a present depressive indices assessment session, a cognitive biases assessment session (see Figure S1), an fMRI scan session, a future depressive indices assessment session, and a socializing information collection session (Figure 1). The participants' present (measured no more than 1 week before the day of the experiment) and future (measured 3 month later) depressive indices were assessed using the Beck Depression Inventory-II (BDI) (Beck et al., 1996). The participants were classified as the healthy group (HG, n = 34, BDI cutoff range: 0–13) or the nonclinical depressed group (NDG, n = 61, BDI cutoff range: 14–63) based on their present BDI score (Everaert et al., 2014). Members of the NDG whose future depressive indices were assessed before the pandemic were further classified as the before the pandemic group (BG, n = 31), and those whose future depressive indices were assessed during the pandemic were further classified as during the pandemic group (DG, n = 30). For detailed experimental design and analysis method, see Transparent methods.

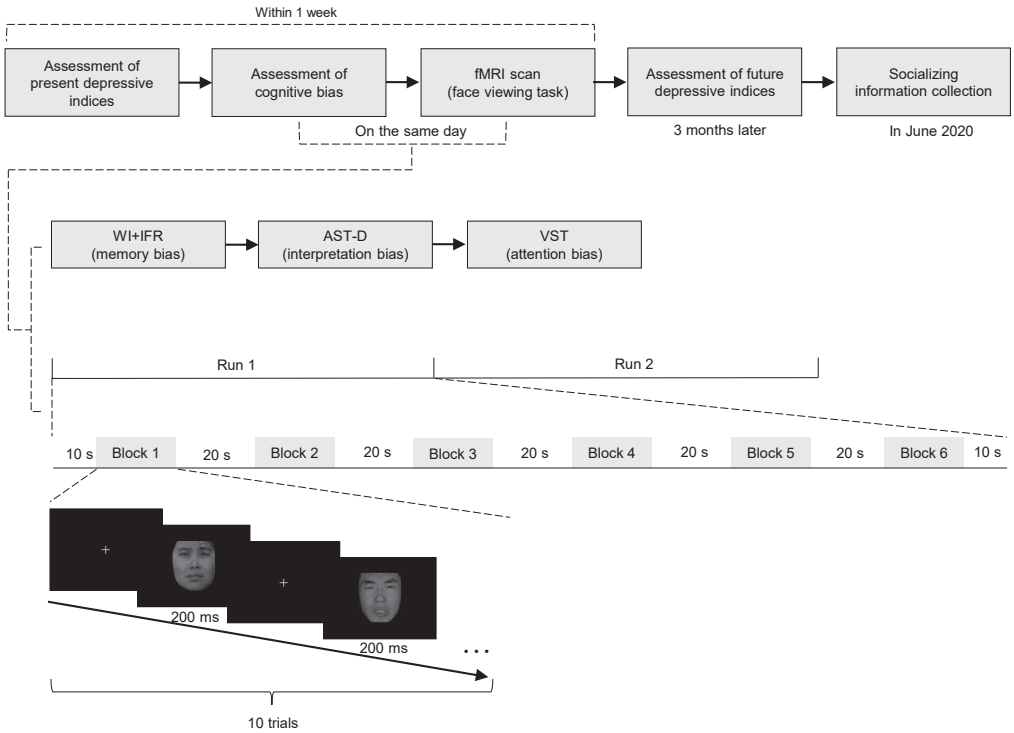

Figure 1. Procedure. The procedures of the experiments are shown in a flow chart

A word identification task (WI) plus incidental free recall (IFR) task was used to assess memory biases. Interpretation biases were evaluated using the ambiguous scenarios test for depressed mood (AST-D). A visual search task (VST) was used to investigate attentional biases to sad faces. The fMRI experiment was a face viewing task composed of 2 runs, each with 6 blocks. The facial stimuli in each run consisted of grayscale normalized sad, happy, and neutral expressions of 30 men and 30 women. In each block, 5 trials of male faces and 5 trials of female faces were shown. In each trial, a face was shown in the center of the screen for 200 ms, followed by a black screen. Each trial lasted for 2 s. Then, the next face appeared. A fixation cross was presented for 20 s between two blocks and for 10 s before the first block and after the last block of each session. Prior to the experiment, the subjects were instructed to attentively watch the faces and recognize the corresponding expressions.

Demographics and BDI scores

There were no significant differences among the three groups in regard to age, gender, or years of education ($p > 0.1$, Table 1). Moreover, the present BDI of the HG was significantly lower than that of the BG and DG ($F(2, 92) = 69.48$, $p < 0.001$, Table 1), but there was no significant difference between the BG and DG ($t(59) = 1.31$, $p = 0.19$). In addition, the future BDI of the HG was also significantly lower than that of the BG and DG ($F(2, 92) = 12.32$, $p < 0.001$, Table 1), and there was no significant difference between the BG and DG ($t(59) = 0.84$, $p = 0.40$).

Cognitive biases comparison

For memory biases, no significant difference was found among the three groups in regard to the percentage of negative ($F(2, 88) = 2.17$, $p = 0.12$) or positive ($F(2, 88) = 1.63$, $p = 0.20$) words recalled. However, for interpretation biases, the pleasantness ratings in the HG were significantly higher than those in the other two groups ($F(2, 92) = 9.12$, $p < 0.001$; compared with the BG, $t(63) = 3.74$, $p < 0.001$; compared with the DG, $t(62) = 3.67$, $p < 0.001$), with no significant difference found between the BG and DG ($t(59) = 0.60$, $p = 0.55$). For attention biases, the accuracy and reaction time (RT) of the sad targets among the neutral distractors condition in the visual search task (VST) were analyzed, and no significant differences were found among the three groups (accuracy: $F(2, 92) = 1.09$, $p = 0.34$; RT: $F(2, 92) = 0.18$, $p = 0.84$).

Comparison of changes in future BDI scores

There was no significant change in future BDI in the HG ($t(33) = 0.73$, $p = 0.47$). A significant decrease in the future BDI was found in both BG ($t(30) = -3.03$, $p < 0.01$) and DG ($t(29) = -4.70$, $p < 0.0001$). However, there was no significant difference in the change in future BDI between the BG and DG ($t(59) = 0.20$, $p = 0.84$).

Table 1. Sample demographics and BDI scores

Sample group	HG (n = 34)	BG (n = 31)	DG (n = 30)	F/χ^2	p Value
Age (mean ± SD, year)	21.59 ± 1.88	21.32 ± 1.81	20.70 ± 1.70	2.01	0.14
Gender (M/F, n)	24/10	16/15	15/15	3.52	0.17
Education (mean ± SD, year)	15.74 ± 1.71	15.26 ± 1.59	15.03 ± 1.16	1.81	0.17
Present BDI (mean ± SD)	6.74 ± 3.71	19.10 ± 6.44	21.13 ± 5.64	69.48	<0.001
Future BDI (mean ± SD)	7.29 ± 5.80	13.65 ± 8.22	15.23 ± 6.31	12.32	<0.001

For continuous variables, one-way analysis of variance was carried out. For categorical variables, χ^2 tests were carried out.

The COVID-19 pandemic altered the ability of negative memory biases to predict future BDI scores

Regarding memory biases, there was no significant difference among the three groups in the correlation between the percentage of negative (for the HG and BG, $z = 0.80$, $p = 0.42$; for the HG and DG, $z = 0.93$, $p = 0.35$; for the BG and DG, $z = 0.13$, $p = 0.89$) or positive (for the HG and BG, $z = 0.0077$, $p = 0.99$; for the HG and DG, $z = 1.22$, $p = 0.22$; for the BG and DG, $z = 1.18$, $p = 0.24$) words recalled and present depressive indices. However, the correlation coefficients between the percentage of negative words recalled and future depressive indices in the DG were significantly different than those in the HG ($z = 2.58$, $p < 0.01$) and BG ($z = 2.87$, $p < 0.005$), with the percentage of negative words recalled significantly predicting future depressive indices in the DG ($r = -0.63$, $p < 0.001$, Figure 2A) but not in the BG ($r = 0.057$, $p = 0.77$, Figure 2A) or the HG ($r = -0.052$, $p = 0.77$, Figure 2A). The correlation coefficients were not significantly different between the HG and BG ($z = 0.41$, $p = 0.68$). Moreover, the correlation coefficients between the negative words recalled and future or present depressive indices in the DG were also significantly different ($z = 2.74$, $p < 0.01$), and no significant correlation was found between the negative words recalled and present depressive indices ($r = -0.076$, $p = 0.70$). In addition, we also found that the percentage of negative words recalled also significantly predicted changes in depressive indices in the DG ($r = -0.50$, $p < 0.01$, Figure 2B) but not in the BG ($r = 0.081$, $p = 0.68$, Figure 2B) or HG ($r = -0.21$, $p = 0.24$, Figure 2B). The results of the comparisons of correlations were consistent when using analysis of variance (ANOVA) (Table S1). No significant differences were found among the three groups in the correlation between the percentage of positive words recalled and future depressive indices (for the HG and BG, $z = 0.73$, $p = 0.47$; for the HG and DG, $z = 0.14$, $p = 0.89$; for the BG and DG, $z = 0.82$, $p = 0.41$).

Regarding interpretation biases, there were no significant differences among the three groups in the correlation coefficients between the pleasantness ratings and the present depressive indices (for the HG and BG, $z = 0.067$, $p = 0.95$; for the HG and DG, $z = 0.37$, $p = 0.71$; for the BG and DG, $z = 0.43$, $p = 0.67$), with the pleasantness ratings significantly or nearly significantly correlated with the present BDI in the DG ($r = -0.32$, $p = 0.083$), BG ($r = -0.42$, $p = 0.019$), and HG ($r = -0.41$, $p = 0.017$). Moreover, the pleasantness ratings also significantly predicted future depressive indices in all three groups (for the DG, $r = -0.53$, $p < 0.005$; for the BG, $r = -0.37$, $p = 0.038$; for the HG, $r = -0.43$, $p = 0.011$).

Regarding attention biases, there were no significant correlations between the present depressive indices and accuracy (for the DG, $r = -0.15$, $p = 0.41$; for the BG, $r = 0.26$, $p = 0.16$; for the HG, $r = -0.23$, $p = 0.19$) or the average RT for correct responses (for the DG, $r = 0.17$, $p = 0.38$; for the BG, $r = -0.0094$, $p = 0.96$; for the HG, $r = -0.15$, $p = 0.41$) in the sad target condition. Moreover, no significant differences were found among the three groups for the correlation coefficients between future depressive indices and accuracy (for the HG and BG, $z = 0.72$, $p = 0.47$; for the HG and DG, $z = 1.67$, $p = 0.10$; for the BG and DG, $z = 0.94$, $p = 0.35$) or the average RT for correct responses (for the HG and BG, $z = 0.44$, $p = 0.66$; for the HG and DG, $z = 1.06$, $p = 0.29$; for the BG and DG, $z = 0.61$, $p = 0.54$) in the sad target condition.

Correlations between the brain response to sad faces and negative memory biases

ROI were defined as the areas proposed in the introduction section (see Figure 3A). We calculated the correlations between the responses of those areas to sad faces and negative memory biases. The results showed that the response to sad faces was significantly correlated with negative memory biases in the bilateral DCC (left: $r = 0.29$, $p = 0.049$, FDR adjusted, Figure 3B; right: $r = 0.33$, $p = 0.045$, FDR adjusted, Figure 3B), and right vlPFC (right: $r = 0.31$, $p = 0.049$, FDR adjusted, Figure 3B). No significant correlation

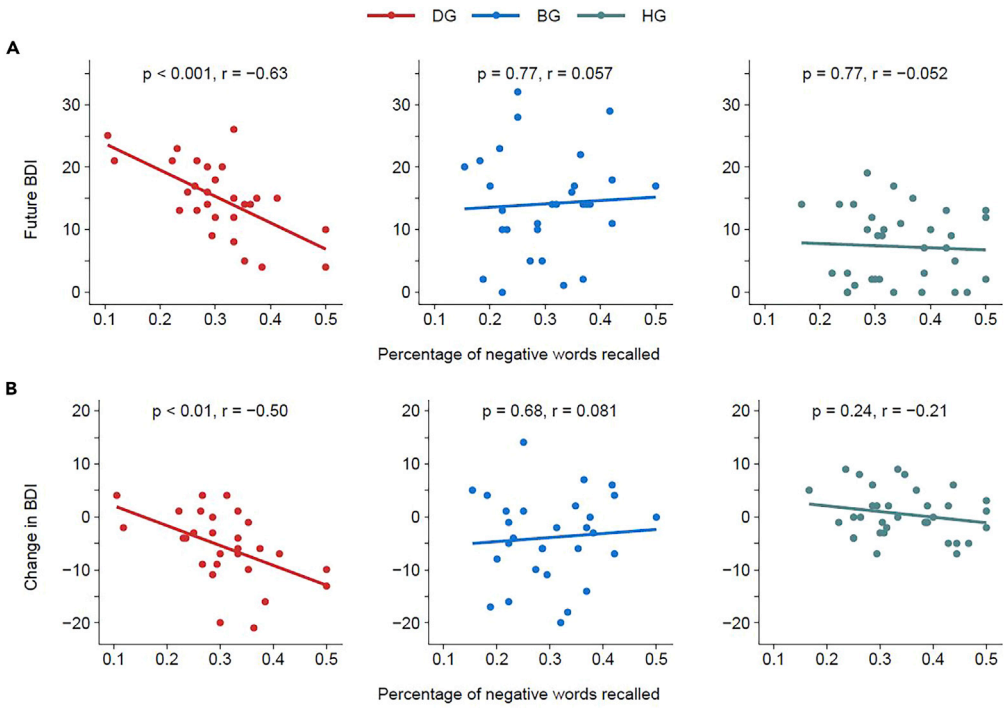

Figure 2. Correlations between negative memory biases and future BDI or change in BDI

(A) Correlations between negative memory biases and future BDI in the DG, BG, and HG. Future BDI scores were plotted against the percentage of negative words recalled in the IFR task.

(B) Correlations between negative memory biases and changes in BDI in the DG, BG, and HG. Changes in the BDI scores were plotted against the percentage of negative words recalled in the IFR task.

was found in the other areas after the correction for multiple comparisons (all $p > 0.1$, FDR adjusted). The areas (left insula, left STG, left thalamus, left vlPFC, right cuneus, right dlPFC, right insula) in which the response to sad faces was significant ($p < 0.05$) or nearly significant ($p < 0.1$) correlated with negative memory biases but didn't survive the correction for multiple comparisons were shown in Table S2.

The COVID-19 pandemic altered the ability of the brain response to sad faces to predict future BDI scores

We further investigated whether the COVID-19 pandemic altered the ability of the response to sad faces in the bilateral DCC, and right vlPFC to predict future depressive indices. The response to sad faces in the left DCC significantly predicted future depressive indices in the DG ($r = -0.41$, $p = 0.026$, Figure 4A) but not in the BG ($r = 0.035$, $p = 0.86$) or the HG ($r = 0.10$, $p = 0.60$). The correlation coefficients in the DG were also significantly more negative than those in the BG ($z = 1.68$, $p = 0.047$, one side) and the HG ($z = 1.97$, $p = 0.025$, one side). Although the correlations between the future BDI and response to sad faces in the right DCC were not significant in the DG, the trend was the same as that in the contralateral region ($r = -0.31$, $p = 0.10$, Figure 4A). Moreover, the response to sad faces in the DCC were also negatively correlated with the change in depressive indices in the DG (left: $r = -0.35$, $p = 0.065$, Figure 4B; right: $r = -0.40$, $p = 0.032$, Figure 4B), and no significant correlation was found between the response to sad faces in the bilateral DCC and present BDI (left: $r = -0.052$, $p = 0.79$; right: $r = 0.13$, $p = 0.51$). No significant correlation was found between the response to sad faces in the right vlPFC and future depressive indices ($r = -0.16$, $p = 0.41$) or change in future depressive indices in the DG ($r = -0.021$, $p = 0.91$). And the correlation coefficients between the response to sad faces in the right vlPFC and future depressive indices ($z = 0.79$, $p = 0.43$) or change in depressive indices ($z = 0.71$, $p = 0.48$) were not significantly different between the BG and DG. For the left insula, left STG, left thalamus, and right cuneus, although their correlation with negative memory biases did not survive the correction for multiple comparisons, the correlation between their responses to sad faces and future BDI scores were also significantly (or nearly significantly) changed during

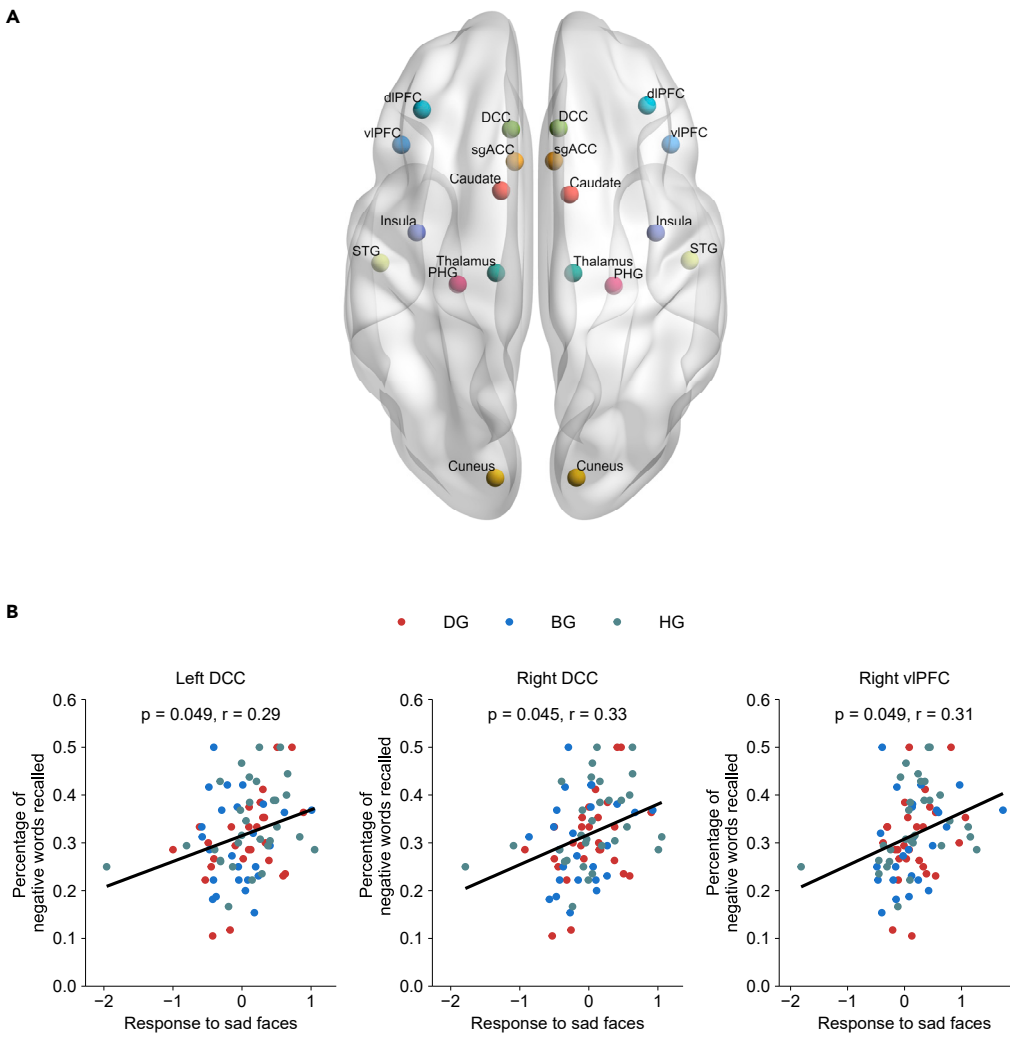

Figure 3. Correlations between the brain response to sad faces and negative memory biases

(A) Locations of ROIs. The location of the spheres in the figure represent the average coordinates of the corresponding ROIs.

(B) Correlations between brain activity and negative memory biases during the emotional face viewing task. Percentage of negative words recalled in the IFR task were plotted against the average beta values (activation of sad faces minus neutral faces) of each voxel in the left and right DCC and right vlPFC. Corrected p values were shown.

the pandemic compared with the correlation between their responses to sad faces and present BDI scores, with their responses to sad faces more negatively correlated with future BDI scores (see Table S1).

Comparison of changes in future BDI scores in high or low memory biases subgroups

We further compared the changes in future BDI scores between the BG and DG in the higher and lower negative memory biases subgroups separately. We calculated the quartiles of the percentage of negative words recalled in the incidental free recall (IFR) task in the SDG and defined those with a memory bias higher than the 75% quantile or lower than the 25% quantile as the high bias group and the low bias group, respectively. Two-way ANOVA was carried out, with changes in future BDI as the response variable and pandemic (the BG or DG) and memory bias (high or low bias) as two factors. Significant interactions were found between pandemic and memory bias factors ($F(1, 25) = 8.62$, $p < 0.01$, Figure 5), with changes in future BDI in the high bias subgroup of the DG being significantly lower than those in the high bias subgroup of the BG ($t(13) = 3.37$, $p < 0.005$, Figure 5). No significant difference was found between the low bias subgroups of the DG and BG ($t(12) = 0.94$, $p = 0.37$, Figure 5).

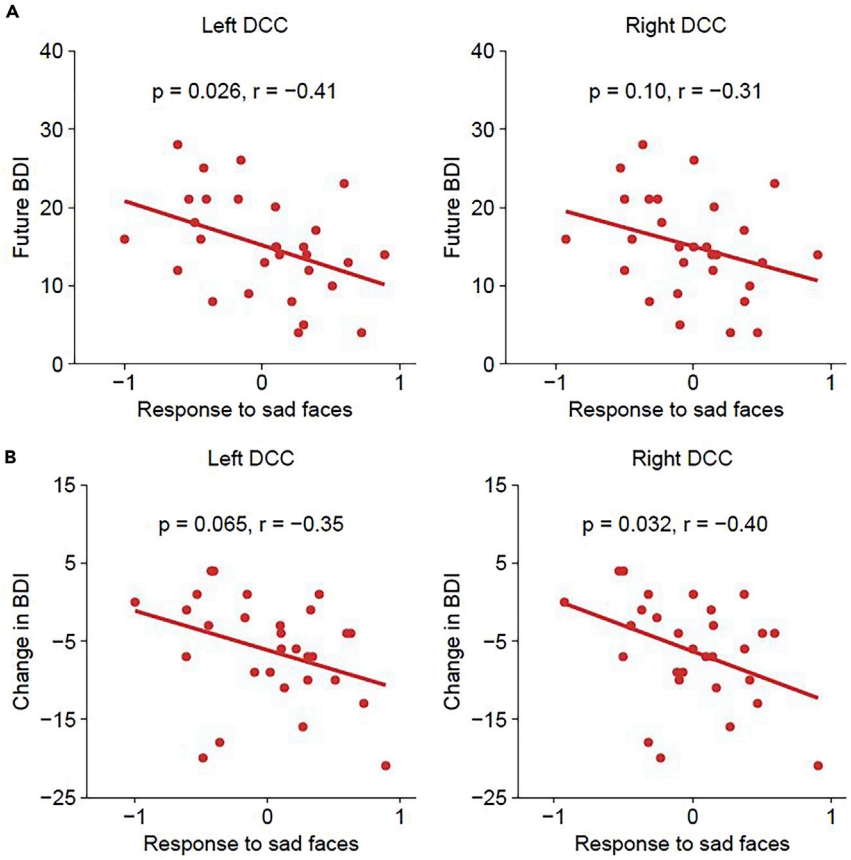

Figure 4. Correlations between the response to sad faces and future BDI or change in BDI in the DG

(A) Future BDI scores were plotted against the average beta values (activation of sad faces minus neutral faces) of each voxel in the left and right DCC in the DG. Responses to sad faces in the bilateral DCC were significantly (or nearly significantly) negatively correlated with future BDI scores.

(B) Change in future BDI scores were plotted against the average beta values (activation of sad faces minus neutral faces) of each voxel in the left and right DCC in the DG. Responses to sad faces in the bilateral DCC were significantly (or nearly significantly) negatively correlated with change in BDI scores.

Change in socializing during the COVID-19 pandemic and its effect on the relationship between negative memory biases and future BDI scores

To explore the reason underlying the fact that a more negative memory bias was associated with a greater decrease in future depressive degree in nonclinical depressed participants during the COVID-19 pandemic, we further investigated the change in socializing during the COVID-19 pandemic and its effect on the relationship between negative memory biases and future BDI scores. We found that social distance significantly increased in all three groups (for the HG, $t(32) = 2.55$, $p = 0.016$; for the BG, $t(27) = 2.59$, $p = 0.015$; for the DG, $t(29) = 3.47$, $p < 0.005$, Figure 6A). Social frequency (for the HG, $t(32) = -7.13$, $p < 0.001$; for the BG, $t(27) = -3.20$, $p < 0.005$; for the DG, $t(29) = -5.67$, $p < 0.001$, Figure 6A) and time spent on socializing (for the HG, $t(32) = -6.18$, $p < 0.001$; for the BG, $t(27) = -4.79$, $p < 0.001$; for the DG, $t(29) = -10.00$, $p < 0.001$, Figure 6A) significantly decreased. Moreover, we also found that degree of stress from socializing significantly or nearly significantly decreased during the COVID-19 pandemic in the BG ($t(27) = -1.77$, $p = 0.088$) and DG ($t(29) = -3.75$, $p < 0.001$, Figure 6A) but not in the HG ($t(32) = -1.22$, $p = 0.23$). A significant correlation was also found between the degree of change in social frequency and future BDI scores in the DG ($r = 0.94$, $p = 0.016$, Figure S2). However, the correlation between the degree of change in the stress from socializing and future BDI scores was not significant ($r = 0.04$, $p = 0.96$). The lack of significance might be due to the narrow range and unbalanced distribution of the degree of change in the stress from socializing (see Figure S2).

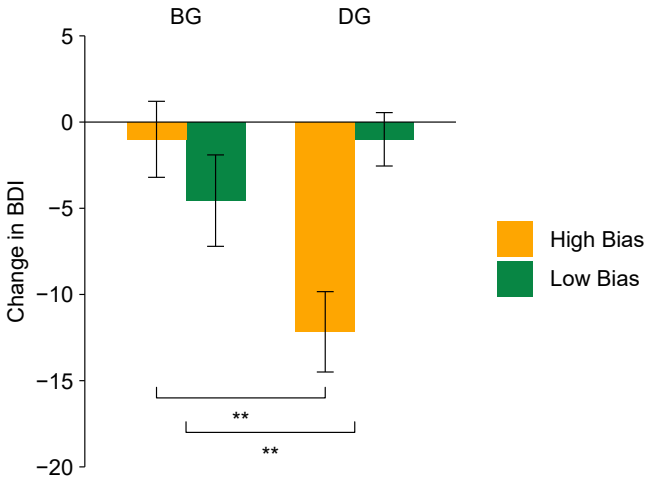

Figure 5. Comparisons of the changes in future BDI scores between the BG and DG in the higher and lower negative memory bias subgroups

Data are represented as mean +/− standard error. ** represents $p < 0.01$. two-way ANOVA was carried out.

We further divided the DG into subgroups according to their degree of change in socializing. The subgroup with a higher decrease of socializing always shows a more negative correlation between the negative memory biases and future BDI scores (Figure 6B).

DISCUSSION

In the present study, we found that a more negative memory bias was associated with a greater decrease in future depressive indices in nonclinical depressed participants during the COVID-19 pandemic but not before the pandemic. The result of the lack of a significant difference between the HG and BG in the correlation between current negative memory biases and future depressive indices provides further evidence that this finding is specific to the effect of the pandemic. We further showed that the responses to sad faces in the DCC, which were significantly correlated with negative memory biases, were also negatively correlated with future depressive indices during the COVID-19 pandemic. A comparison of the change in future depressive indices revealed that the change in future BDI in the high bias subgroup of the DG was significantly lower than that in the high bias subgroup of the BG. Investigation of socializing showed that social stress decreased significantly during the pandemic in the nonclinical depressive population and the subgroup of the DG with a higher decrease of socializing showed a more significant and more negative correlation between the negative memory biases and future BDI scores.

As we explained in the introduction section, the COVID-19 pandemic may have two possible effects on the relationship between current cognitive biases and future depressive indices in the nonclinical depressed population. One is an increased stress effect considering that the COVID-19 pandemic is a threat to life. The other one is a decreased stress effect considering that social distancing may reduce social stress during the COVID-19 pandemic. Our results support the latter effect. We have provided behavioral evidence that the COVID-19 pandemic promotes a negative correlation between negative memory biases and future depressive indices in the nonclinical depressive population, which means that a more negative memory bias was associated with a greater decrease in future depressive indices during the pandemic. This effect might be due to the low degree of social stress during the COVID-19 pandemic. The investigation of the socializing of participants also corroborated this explanation. Decreased social frequency, increased social distance and decreased social stress were all found in the nonclinical depressed population during the pandemic. Social stress has been reported to be a crucial risk factor of depression (Paykel, 2003; Slavich et al., 2009). Thus, reduced social stress during the COVID-19 pandemic may lead to decreased depressive indices. Our finding that the subgroup of the DG with a higher decrease of socializing showed a more significant and more negative correlation between the negative memory biases and future BDI scores provided further evidence for this explanation. However, it is worth noting that although future depressive indices were negatively correlated with negative memory biases in the DG, no significant difference was

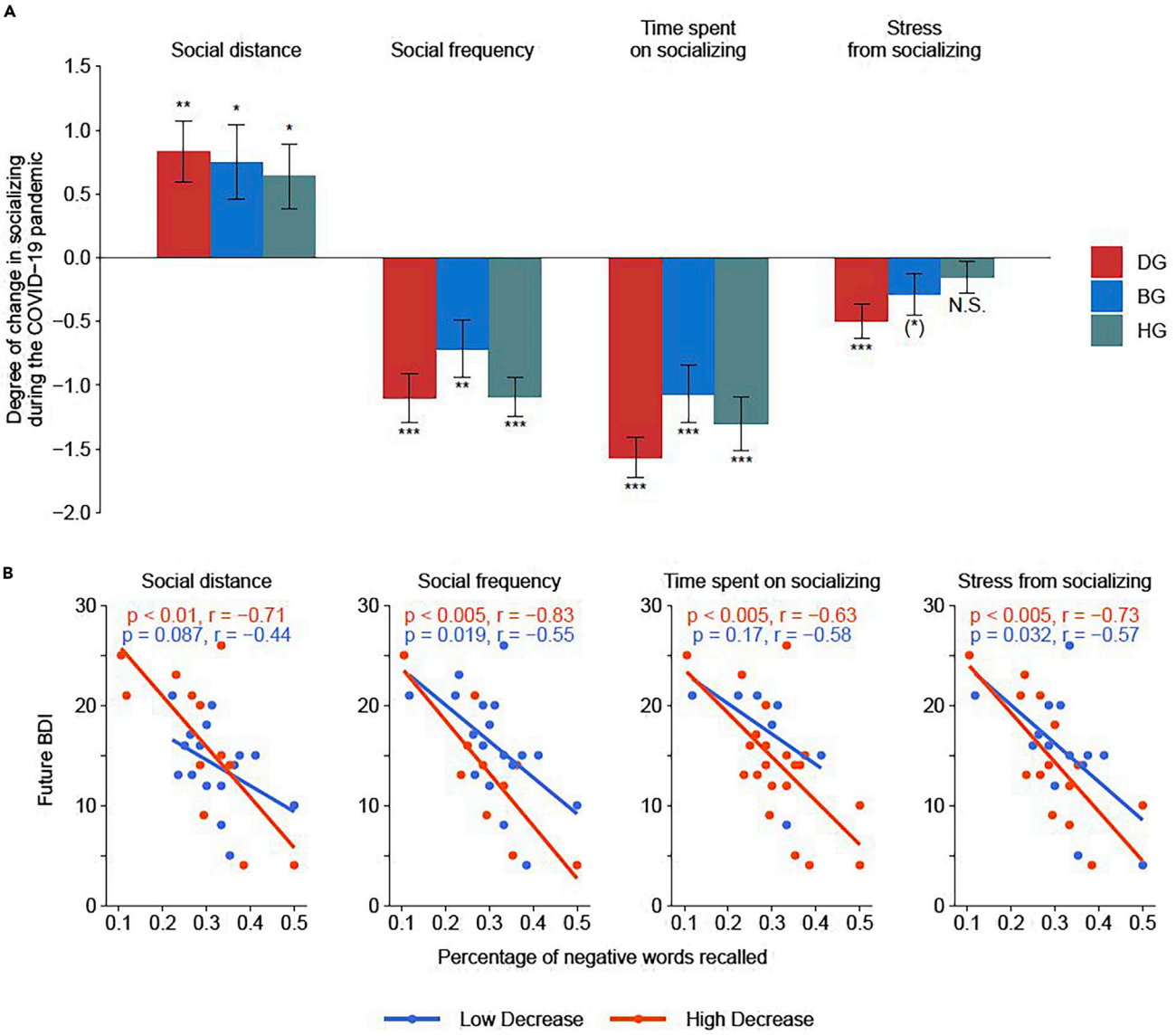

Figure 6. Change in socializing during the COVID-19 pandemic and its effect on the relationship between negative memory biases and future BDI scores

(A) Change in socializing during the COVID-19 pandemic. The degree of changes in the social distance, social frequency, time spent on socializing, and stress from socializing were shown. Data are represented as mean +/− standard error. * represents $p < 0.05$, ** represents $p < 0.01$, *** represents $p < 0.001$, (*) represents $p < 0.1$, N.S. represents no significance. One sample t-tests were carried out.

(B) Correlations between negative memory biases and future BDI in the higher and lower decrease of socializing subgroups of the DG. The median of change in socializing in the DG was used as the grouping criterion to ensure the balance of sample size in two subgroups. For the stress from socializing, social frequency, and time spent on socializing, subjects with a degree of change in socializing lower (or not higher, depends on the balance of sample size in the two subgroups) than the median was grouped into the high decrease subgroup. For social distance, subjects with a degree of change in social distance higher than the median was grouped into the high decrease subgroup. The subgroup with a higher decrease of socializing always shows a more negative correlation between the negative memory biases and future BDI scores.

found in the future depressive indices between the BG and DG. A possible explanation for this result is that reduced social stress only had a significant effect on individuals with a greater negative memory bias. For those with a less negative memory bias, the development of their depressive mood may be due to other events but not social stress. Thus, their depressive indices did not decrease with social stress during the pandemic. As a result, the depressive indices in the DG were not significantly lower than those in the BG. The results showing that the depressive indices in the high memory bias subgroup of the DG were

significantly lower than those in the BG also corroborated this explanation. Previous studies have found an association between social stress and negative memory biases (Fan et al., 2017, 2020; Romano et al., 2020; Zhang et al., 2019), which is also in line with our findings.

The other possible effect, that the COVID-19 pandemic may increase survival stress and thus promote a greater increase in future depressive indices in participants with a more negative cognitive bias, was not supported by our data (although a positive correlation was found between negative interpretation biases and future depressive indices in the DG, the correlation coefficient was not significant different from that in the BG). The reason for this finding may be that the most severely affected region in China was Wuhan during the COVID-19 pandemic, and the participants in this study mainly lived in other cities and might not have experienced much survival stress. However, the social distancing policy was carried out all over China, thus a reduced social stress effect was found in our data.

Brain imaging analysis further corroborated the findings of the behavioral data. We tested ten ROIs highlighted by a previous meta-analysis and found that the responses to sad faces in the bilateral DCC, which were found to be correlated with negative memory biases, were also negatively correlated with future depressive indices during the COVID-19 pandemic. The predefined DCC area was mainly in the ACC in this study. The ACC has been related to the function of cognitive control of emotion (Bush et al., 2000; Disner et al., 2011; Li et al., 2020; Ochsner and Gross, 2005). Individuals with a greater activation in the ACC when viewing sad faces may have a deficient inhibition ability and thus require greater cognitive effort to divert attention away from negative stimuli (Disner et al., 2011). A deficient ability to inhibit attention for negative stimuli may contribute to negative memory biases.

Although the response to sad faces in the right vlPFC was also correlated with negative memory biases in our results, their correlation with future depressive indices did not show the same pattern as in the behavioral data. A possible explanation for this finding is that the activity in this area might be related to many kinds of depressive symptoms, not only memory biases. Thus, their relationship with future depressive indices was not altered as in the relationship between memory bias and future depressive indices.

In the present study, only the relationship between current memory biases and future depression degree was affected by the COVID-19 pandemic in the nonclinical depressive population, which might be due to the mechanisms of the development of memory biases in depression. Previous studies have found that stress can suppress hippocampal neurogenesis (Gould and Tanapat, 1999), inhibit dopamine neurons (Tye et al., 2013), and sensitize the amygdala (Roozendaal et al., 2009), and these phenomena impair pattern separation and disrupt the encoding of positive experiences and bias retrieval toward negative events, respectively, thus leading to negative memory biases in depression (Dillon and Pizzagalli, 2018). Therefore, people with greater negative memory biases may experience more social stress during their daily lives, and thus, their depressive indices may have been decreased more when social stress was decreased during COVID-19 pandemic. The relationship between current attention or interpretation biases and future depressive indices was not altered by the COVID-19 pandemic, which might imply that there are some underlying particularities of the mechanism of memory biases compared with other cognitive biases, which requires further investigation.

Our results also support social distancing policies that carried out during the pandemic from a psychological perspective. Increasing social distance can not only prevent the spread of COVID-19 but may also reduce social stress and thereby decrease depressive indices in the nonclinical depressed population, especially in those with a more negative memory bias. Moreover, considering that social stress may re-emerge when social distancing goes back to normal, the resumption of work and school should be carried out gradually, not only to prevent the recurrence of the pandemic but also to provide time for people to adapt to re-emerging social stress in case they experience an increased degree of depression. Previous studies have linked too close interpersonal distances to increased feelings of threat and decreased pleasantness (Ahs et al., 2015; Kroczek et al., 2020), which is also in line with our findings.

In summary, this study revealed that a more negative memory bias was associated with a greater decrease in future depressive indices during the COVID-19 pandemic in the nonclinical depressive population, which

might be due to decreased social stress. The responses of the bilateral DCC to sad faces were found to be correlated with negative memory biases, and their negative correlation with future depressive indices converged with the results from the behavioral data. Our findings also support social distancing policies from a psychological perspective. Increasing social distance not only prevents the spread of COVID-19 but may also reduce social stress and thereby decrease depressive indices in the nonclinical depressed population, especially in those with a more negative memory biases.

Limitations of the study

Some limitations of this study must be acknowledged. For the VST, only sad and neutral faces were used. Thus, the reason why no significant correlation between attention biases and future depressive indices was found might be that the nonclinical depressive population may not pay more attention to negative stimuli but may instead pay less attention to positive stimuli. Moreover, all of the nondepressed participants' future BDI were assessed before the pandemic. Thus, our results might not generalize to nondepressed populations.

Resource availability

Lead contact

Further information and requests for resources should be directed to the lead contact, Xiaochu Zhang (zxcustc@ustc.edu.cn).

Materials availability

The sources of stimulus materials are provided in the Supplemental information file.

Data and code availability

The datasets supporting the current study have not been deposited in a public repository but are available from the lead contact on request. The statistics were performed on R version 3.6.1 (64-bit) platform. The code for statistical analysis is available from the Lead Contact on request.

METHODS

All methods can be found in the accompanying Transparent methods supplemental file.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2021.102081.

ACKNOWLEDGMENTS

We would like to thank the Information Science Center of University of Science and Technology of China for providing access to the GE scanner for the MRI acquisition. This work was supported by grants from The National Key Basic Research Program (2018YFC0831101), The National Natural Science Foundation of China (31771221, 71942003, 61773360, 31800927, 31900766 and 71874170), Major Project of Philosophy and Social Science Research, Ministry of Education of China (19JZD010), CAS-VPST Silk Road Science Fund 2021 (GLHZ202128), Collaborative Innovation Program of Hefei Science Center, CAS (2020HSC-CIP001). A portion of the numerical calculations in this study were performed with the supercomputing system at the Supercomputing Center of USTC.

AUTHOR CONTRIBUTIONS

PZ, ZW, XZ conceived and designed the study. PZ obtained findings. PZ, YP, and QB were responsible for acquisition of data. PZ and ZW analyzed and interpreted the data. YC, JR, and ZW provided administrative, technical, or material support. LZ, ZW, and XZ supervised the study. PZ drafted the paper. ZW and XZ contributed to critical revision for intellectual content.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: December 8, 2020
Revised: December 14, 2020
Accepted: January 14, 2021
Published: February 19, 2021

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iScience, Volume *24*

Supplemental Information

Outbreak of COVID-19 altered the relationship between memory bias and depressive degree in nonclinical depression

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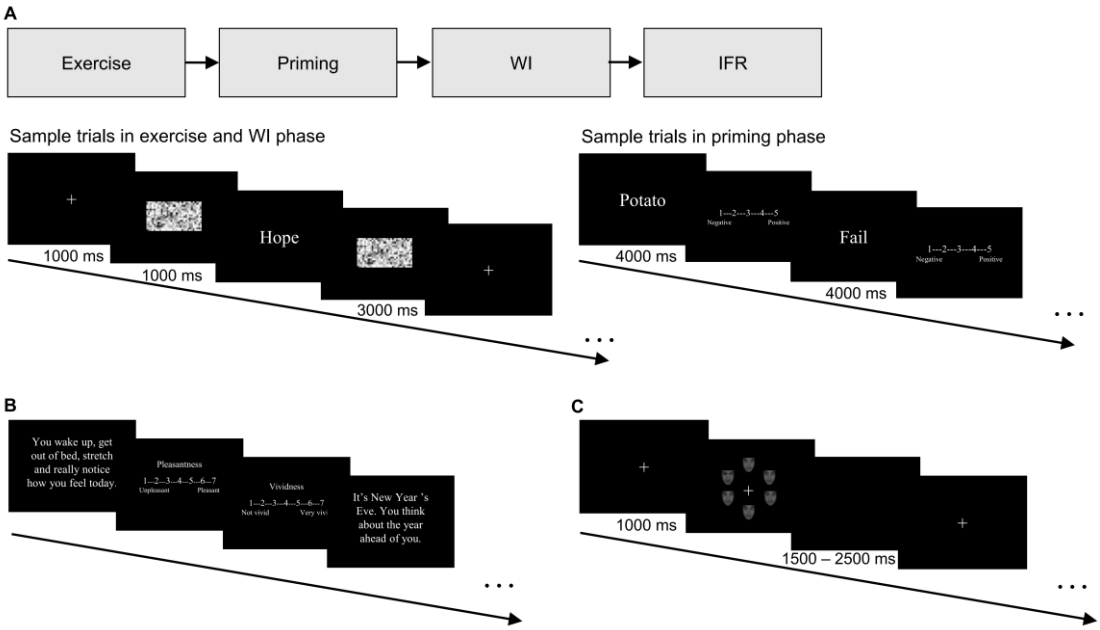

Figure S1. Tasks for the assessment of cognitive biases. Related to Figure 1. (A) The procedures of the tasks used to measure memory biases are shown as the flow chart. Sample trials in the exercise and WI phases and sample trials in the priming phase are also shown. (B) Sample trials in the AST-D task are shown. (C) Sample trials in the VST task are shown.

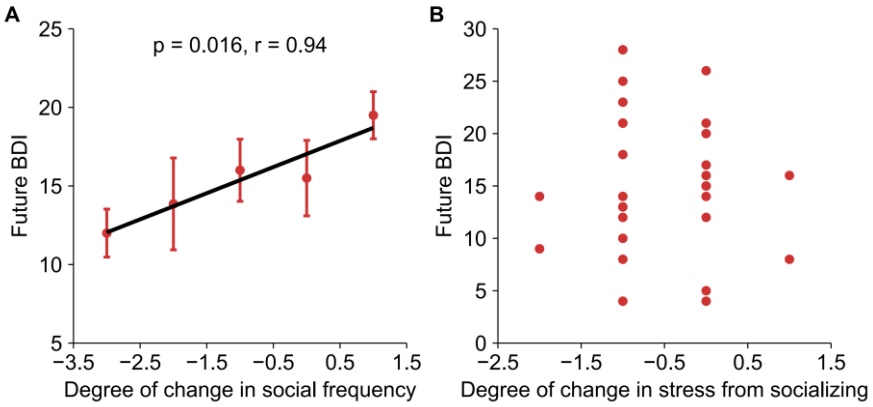

Figure S2. Relationship between degree of change in social frequency or change in stress from socializing and future BDI. Related to Figure 6. (A) Correlation between the degree of change in social frequency and future BDI scores in the DG. Samples were assigned into different bins based on their degree of change in social frequency. The average future BDI scores in each bin were calculated and were plotted against degree of change in social frequency. Data are represented as mean +/- standard error. (B) Distribution of the future BDI score against the degree of change in stress from socializing in the DG. The distribution of the degree of change in the stress from socializing was unbalanced and the range was narrow, which might lead to the lack of significance of the correlation between the degree of change in stress from socializing and future BDI scores in the DG.

Table S1. Comparison of correlations using ANOVA. Related to Figure 2.

Group	Correlation between negative memory biases and BDI scores				Comparison of correlations (ANOVA)					
	Present BDI		Future BDI		Pre V.S. Post		DG V.S. BG		DG V.S. HG	
	r	p	r	p	F	p	F	p	F	p
DG	-0.076	0.70	-0.63	< 0.001	8.54	0.007	5.13	0.028	6.07	0.017
BG	-0.039	0.84	0.057	0.77	0.18	0.68	-	-	-	-
HG	0.17	0.33	-0.052	0.77	1.46	0.24	-	-	-	-

Table S2. The results of regions in which the response to sad faces was significant or nearly significant correlated with negative memory biases but didn't survive the correction for multiple comparisons. Related to Figures 3-4.

Regions	Brain activation & Negative memory bias		Brain activation & Present BDI		Brain activation & Future BDI		Comparison of pre and post correlation coefficients	
	r	p	r	p	r	p	z	p
Left Insula	0.21	0.060	0.032	0.87	0.34	0.074	1.73	0.043
Left STG	0.19	0.092	0.14	0.48	0.38	0.044	1.16	0.13
Left Thalamus	0.23	0.042	0.16	0.41	0.33	0.085	2.27	0.012
Left vlPFC	0.25	0.021	0.25	0.18	0.12	0.53	0.31	0.73
Right Cuneus	0.20	0.069	0.15	0.43	0.36	0.057	2.39	0.008
Right dlPFC	0.20	0.067	0.31	0.10	0.023	0.91	1.35	0.91
Right Insula	0.19	0.087	0.12	0.53	0.23	0.23	1.62	0.053

The p values listed above were not adjusted for multiple comparisons. For the left insula, left thalamus, and right cuneus, although their correlation with negative memory biases didn't survive the correction for multiple comparisons, the correlations between their responses to sad faces and future BDI scores were also more negative during the pandemic than the correlations between their responses to sad faces and present BDI scores (all ps < 0.05, one side).

Transparent Methods

Participants

A total of 98 adults participated in our study. All of the participants were right handed and had normal or corrected-to-normal vision. They had no magnetic resonance imaging contraindications and no alcohol or drug abuse history. The participants were told to have no less than 7 hours of sleep the night before the experiment, and female participants needed to schedule their participation in the experiment for when they were not menstruating. The participants' present (measured no more than 1 week before the day of the experiment) and future (measured 3 month later) depressive indices were assessed using the Beck Depression Inventory-II (BDI-II) (Beck, 1996).

The participants were classified as the healthy group (HG, n = 34, BDI-II cut off range: 0–13) or the nonclinical depressed group (NDG, n = 64, BDI-II cut off range: 14–63) based on their present BDI score (Everaert et al., 2014). Three participants in the NDG were excluded because two quit the study after the behavior tests and the other slept during the experiment, resulting in 61 subjects left in the NDG (additional details of the exclusion criteria can be found in the Subjects Exclusion Criteria section). All of the HGs' future BDI-II questionnaires were collected before the COVID-19 pandemic, and the NDGs' questionnaires were collected before or during the COVID-19 questionnaires. Members of the NDG whose future BDI-II questionnaires were collected before the outbreak were further classified as the before the outbreak group (BG, n = 31), and those whose future BDI-II questionnaires were collected during the outbreak were further classified as during the outbreak group (DG, n = 30). The Human Research Ethics Committee of the University of Science and Technology of China approved this study. Written informed consent for the behavioral and fMRI experiments was obtained from all participants before the experiments started.

Procedure

The participants attended a present depressive indices assessment session, a cognitive biases assessment session, an fMRI scan session, a future depressive indices assessment session and a socializing information collection session (Figure S1). During the present depressive indices assessment session, the participants completed the BDI-II questionnaire. All of the participants' present depressive indices were assessed before the pandemic. The cognitive bias assessment session was attended within one week of the present depressive indices assessment session. The participants' memory biases, interpretation biases and attention biases were assessed using three behavior tasks during the cognitive bias assessment session. The fMRI scan session was attended on the same day as the cognitive bias assessment session. The participants were asked to complete a face viewing task during the fMRI scan. The future depressive indices were assessed three months later using internet-based questionnaires. The participants' BDI-II questionnaires were collected during this session. Internet-based questionnaires about socializing before and during the COVID-19 pandemic were collected in June 2020, which was the socializing information collection session.

Definition of the Start Time Point of the Pandemic

Although the first cases of COVID-19 were reported in December 2019 (Zhu et al., 2020), the public in China did not know about it or were not concerned until January 20, 2020, when Zhong Nan Shan, head of the high-level expert group of the National Health Commission of China,

made it clear to the public for the first time through China Central Television that COVID-19 has the ability to spread from person to person (http://tv.cctv.com/2020/01/20/VIDEbPjhFJ20Xt5n70T1OWhc200120.shtml). Therefore, we defined January 20, 2020, as the start point of the COVID-19 pandemic since we are interested in the impact that the pandemic has had on people's psychological states in this study.

Assessment of Cognitive Biases

Memory biases. A word identification task (WI) plus incidental free recall task (IFR) was used to assess memory biases (Tarsia et al., 2003). The task consisted of four phases: the exercise phase, priming phase, WI phase, and IFR phase (Figure S1A). During the first exercise phase, the participants were asked to read aloud a list of words presented one at a time in the center of the screen. This list of words was composed of 48 neutral words, which were presented in a fixed order in 16 blocks of three words. For each block, the three words were presented for a different duration. Each word was preceded by a mask displayed for 1000 ms and followed by a mask with variable duration. The total duration of a word and the mask following it was 3000 ms. Each trial was preceded by a fixation cross displayed in the center of the screen for 1000 ms. The subjects were invited to guess all of the words presented even if they were not sure or did not believe that they had actually seen a word since it did not matter whether their answers were right or wrong. As the participants read the words aloud, the experimenter checked the accuracy of their answers. The outcome of the exercise phase was used to set up the exposure duration of the word stimuli for the WI phase according to the subject's reading threshold (the corresponding duration of the word when the accuracy is approximately 50 percent). During the priming phase, the subjects were asked to pay attention to the words appearing one at a time for 4000 ms in the center of the screen and to rate them for their negativeness or positiveness on a five-point scale (1 = very negative, 5 = very positive) that appeared on the screen after each word. The rating scale remained on the screen until the subject pressed the selected key on the keyboard. Then, the next word appeared. Three types of words (negative, positive, neutral), with 16 words of each type, were used in this phase. During the WI phase, words were presented as in the first phase of the experiment, except for the exposure duration, which was constant and was adjusted according to each subject's reading threshold to avoid floor or ceiling effects. Three types of words (negative, positive, neutral), with 32 words of each type, were used in this phase. Half of the words were the same as those in the priming phase. Immediately after the end of the WIT phase, the IFR phase began. Although the aim of this phase was to investigate the participants' memory of the words in the priming phase, the subjects were asked to write down all the words they remembered to avoid false negatives (words not reported because they were falsely not attributed to the rating task) (Tarsia et al., 2003). The participants were asked to recall for at least 8 minutes. The WI and IFR phases measure implicit and explicit memory biases, respectively (Tarsia et al., 2003). Since we were only interested in explicit biases in this study, the data from the WI phase were not analyzed.

Interpretation biases. Interpretation biases were evaluated using the ambiguous scenarios test for depressed mood (AST-D, Figure S1B) (Berna et al., 2011). A total of 24 ambiguous scenarios were presented individually, followed by ratings. The participants were instructed to: ''Form a mental image of each of the scenarios. Imagine each scenario happening to you personally. Follow the first image that comes to mind and then rate how pleasant your image is, as well as how vivid it is.'' The pleasantness rating was scored on a 7-

point Likert scale ranging from extremely unpleasant to extremely pleasant. The vividness rating was scored on a 7-point Likert scale ranging from not vivid at all to extremely vivid.

Attention biases. A visual search task (VST) was used to investigate attentional biases to sad faces (Figure S1C) (Wieser et al., 2018). The stimuli were displayed as arrays of six faces arranged in a circle around the fixation cross. Faces from four males and four females (sad, neutral) were taken from the Chinese affective picture system (Bai et al., 2005) and converted to greyscale to minimize physical differences between categories. Each visual search array contained 6 faces with sad targets among neutral distractors, neutral targets among sad distractors, all neutral distractors and all sad distractors (4 conditions). For each condition, the targets occurred at the same times at each of the six positions in the matrix. The target positions were randomized over the trials. The participants were instructed to attentively watch the displays on the screen and to detect a discrepant face in the presented search arrays of six faces as quickly and accurately as possible. Participants had to press different keys (a “yes” or “no” button) depending on whether a discrepant target was present in the array. Before the task, all the participants practiced the visual search task in a series consisting of 7 trials with displays containing a target or not. A trial was started with a fixation-cross presented for 1000 ms before each onset of the search array. A trial was terminated by the participants' response. A variable intertrial interval of 1500, 2000, or 2500 ms was presented between trials. There was also a thirty-second break in the middle of the task.

Statistics of cognitive biases. The percentage of negative or positive words recalled in the IFR task was used to measure memory biases. Interpretation biases were measured by the pleasantness ratings of the AST-D. The accuracy and reaction time (RT) of the sad targets among the neutral distractors condition in the VST were used to measure attention biases. Analysis of variance and two sample t-test were used to compare differences of cognitive biases among groups. Pearson correlation analysis was used to measure the ability of cognitive biases to predict future depressive indices.

fMRI Methods

Experimental task. The fMRI experiment was a face viewing task composed of 2 runs, each with 6 blocks (Figure 1). The facial stimuli in each run consisted of grayscale normalized sad, happy, and neutral expressions of 30 men and 30 women taken from the Chinese affective picture system (Bai et al., 2005). In each block, 5 trials of male faces and 5 trials of female faces were shown. The expressions of the faces were the same in a single block and different between two adjacent blocks. In each trial, a face was shown in the center of the screen for 200 ms, followed by a black screen. Each trial lasted for 2 seconds. Then, the next face appeared. A fixation cross was presented for 20 seconds between two blocks and for 10 seconds before the first block and after the last block of each session. Prior to the experiment, the subjects were instructed to attentively watch the faces and recognize the corresponding expressions. The order of the expressions was balanced both within and between subjects.

Scan parameters. T2* functional data were acquired during the entire task, using a 3.0 T GE scanner, at the Information Science Center of University of Science and Technology of China, Hefei, Anhui province. Images were projected to the rear of the scanner. Volumes consisting of 36 slices were acquired (slice thickness = 3 mm; repetition time [TR] = 2 s; echo time [TE] = 30 ms; flip angle [FA] = 90°; matrix = 64 × 64). A high-resolution T1-weighted structural image was also obtained for each participant.

Preprocessing. The first 5 images of each run were discarded. The remaining images were corrected for temporal shifts between slices, realigned, spatially normalized to the MNI space and spatially smoothed (Gaussian kernel, 8 mm full-width at half maximum [FWHM]) using a toolbox for Data Processing & Analysis of Brain Imaging (DPABI) (Yan et al., 2016) based on Statistical Parametric Mapping (SPM12; Welcome Department of Cognitive Neurology, London, United Kingdom, http:// www.fil.ion.ucl.ac.uk/spm).

Model construction. To elucidate neural responses that correlated with emotional and neutral faces, a general linear model (GLM) was used. The regressors of interest were sad face blocks, happy face blocks and neutral face blocks. The regressors of no interest were the fixation blocks. These regressors were convolved with a hemodynamic response function (HRF) and simultaneously regressed against the blood oxygenation level-dependent (BOLD) signal in each voxel. Six regressors for head motion were also included.

Regions of interest. Regions of interest (ROI) were defined according to the Talairach Daemon database atlases (Lancaster et al., 2000) using the WFU pick atlas tool (Maldjian et al., 2003). The caudate, thalamus, PHG, cuneus, insula, and STC were defined as the gyrus level partitions in the Talairach Daemon database atlases. The combination of Brodmann areas (BA) in the cell type level partitions in the Talairach Daemon database atlases were used to define the DCC (BA 32), sgACC (BA 25), vlPFC (BA 44, BA 45, BA 47), and dlPFC (BA9, BA 46) since there are no corresponding gyrus level partitions for these areas. The location of the ROIs were shown in Figure 3A. The average activation of sad faces minus neutral faces was extracted from each ROI as the response to sad faces (For each type of emotional stimuli (sad, happy or neutral), the percent change relative to baseline (the fixation) was calculated. Then the contrast between sad and neutral stimuli was performed to obtain the activation of sad faces relative to neutral faces for each voxel. The mean of the activation of sad faces relative to neutral faces from all of the voxels in each ROI was calculated and was defined as the ROI's response to sad faces.). False discovery rate (FDR) method has been performed for the correlations between brain activity and negative memory biases.

Statistical Method for the Correlation Analysis

Pearson correlation coefficients were calculated for the correlation analysis. For the comparison between two correlations from independent groups, Fisher's z procedure was performed (Fisher, 1925). For the comparison between two correlations from the same group with one variable in common, a backtransformed average Fisher's z procedure was used (Hittner et al., 2003). Both of the two statistical procedures were performed by using the cocor 1.1.3 package in R (Diedenhofen and Musch, 2015).

Subjects Exclusion Criteria

Two subjects in each of the BG and DG were excluded from the analysis of IFR task because the number of words they recalled was too small (more than double the standard deviations below the average numbers). One subject in the HG, one subject in the BG and one subject in the DG did not receive the fMRI scan and were excluded from the analysis of fMRI data. Another 3 subjects in the HG and 3 subjects in the BG were also excluded from the analysis of fMRI data because of bad normalization or high head motion (translation > 2.5 mm or rotation > 2.5°). Three subjects in the BG and 1 subject in the HG did not participate in the socializing information collection session and were excluded from the analysis of socializing information.

Questions used in the socializing information collection session

On January 20, 2020, Zhong Nanshan made it clear to the public for the first time through China Central Television that COVID-19 had the ability to spread from person to person. Assuming that January 20, 2020, is defined as the start point of the pandemic, please recall the status of your social interactions before or during the pandemic and choose the option that best matches your situation.

1. What was your social frequency before the pandemic?
    a. Almost never participated in social interactions.
    b. Occasionally participated in social interactions.
    c. Sometimes participated in social interactions.
    d. Often participated in social interactions.
    e. Almost always participated in social interactions.
2. What was your social stress before the pandemic?
    a. No stress.
    b. Mild.
    c. Moderate.
    d. Severe.
    e. Very severe.
3. What was your social frequency during the pandemic?
    a. Almost never participated in social interactions.
    b. Occasionally participated in social interactions.
    c. Sometimes participated in social interactions.
    d. Often participated in social interactions.
    e. Almost always participated in social interactions.
4. What was your social stress during the pandemic?
    a. No stress.
    b. Mild.
    c. Moderate.
    d. Severe.
    e. Very severe.
5. What was the change in the time you spent on socializing per week during the pandemic compared with the days before the pandemic?
    a. The time spent on socializing during the pandemic is much less than that before the pandemic.
    b. The time spent on socializing during the pandemic is slightly less than that before the pandemic.
    c. The time spent on socializing during the pandemic is the same as that before the pandemic.
    d. The time spent on socializing during the pandemic is slightly more than that before the pandemic.
    e. The time spent on socializing during the pandemic is much more than that before the pandemic.
6. What was the change of your social distance during the pandemic compared with the days before the pandemic?
    a. The social distance during the pandemic is much shorter than that before the pandemic.

b. The social distance during the pandemic is slightly shorter than that before the pandemic.
c. The social distance during the pandemic is the same as that before the pandemic.
d. The social distance during the pandemic is slightly longer than that before the pandemic.
e. The social distance during the pandemic is much longer than that before the pandemic.

Statistics of the questions about socializing

For the questions about social frequency and stress from socializing, the score of the options ranged from 1 to 5. The score of the options for social frequency or stress from socializing during the pandemic were subtracted by the corresponded score before the pandemic and were used as the degree of changes in social frequency or stress from socializing. For the questions about changes in social distance and time spent on socializing during the pandemic, the score of the options ranged from -2 to 2 and were used as the degree of changes in social distance and time spent on socializing. One sample t-tests were used to compare the degree of changes. Pearson correlation analysis was used to evaluate the relationship between cognitive biases and changes in social stress.

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