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Prolonged chronic social defeat stress promotes less resilience and higher uniformity in depression-like behaviors in adult male mice

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ABSTRACT

Chronic social defeat stress (CSDS) is widely applied to study of depression in rodents. 10-day CSDS was a most commonly employed paradigm but with high resilience ratio (~30%), producing potential variation in depression-like behavioral symptoms. Whether prolonged period (21 days) of CSDS would promote less resilience and reduce behavioral variability remains unknown. We applied 10-day and 21-day CSDS paradigms to induce mouse model of depression and compared their resilience ratio and behavioral phenotypes. Mice under 21-day CSDS had significantly lower resilience ratio and greater changes in behavioral indicators relative to mice under 10-day CSDS. Behavioral indicators from 21-day CSDS paradigm had higher correlations and better prediction for susceptibility which indicating higher uniformity in behavioral phenotypes. Furthermore, a subset of behavioral indicators in 21-day CSDS had high prediction efficacy and should be first applied to screen susceptibility of CSDS. Thus, our study demonstrates that 21-day CSDS is a more robust paradigm inducing reliable depression-like behaviors relative to 10-day CSDS, and should be preferentially used in rodent studies of depression.

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1. Introduction

Major depressive disorder (MDD) has become a leading cause of disability worldwide. To date, over 264 million people globally suffer from depression with some typical symptoms: long-lasting sadness, despair, anhedonia, social avoidance and anxiety [1]. The etiology and pathogenesis of depression have not been well known and more effective therapies or drugs are needed. Several animal models of depression, such as chronic social defeat stress (CSDS) [2–6], chronic restraint stress (CRS) [7,8], chronic unpredictable mild stress (CUMS) [9] have been developed to uncover the mechanism of depression and to understand mechanisms of antidepressants and brain stimulation therapies.

CSDS has been wildly used in study of depression as it can not only well mimic the physical and psychological stress which humans suffer from in daily life [10] but also predict responses of chronically administrated antidepressants [11,12]. CSDS has several paradigms in which social defeat stress has distinct periods of 10 days or 21 days [13–15]. However, the difference in behavioral symptoms between these paradigms remains elusive. It is reported that animals under 10-day CSDS generally have high ratio of resilience (as indicated by social index > 1, the ratio is 30–45%)

Abbreviations: MDD, major depressive disorder; CSDS, chronic social defeat stress; CRS, chronic restraint stress; CUMS, chronic unpredictable mild stress; SIT, social interaction test; EPM, elevated-plus maze test; OFT, open field test; SPT, sucrose preference test; FST, forced swimming test.

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[4,6,13,16–19]. High resilience ratio may implicate variable behavioral symptoms or even different levels of pathogenesis of depression. Indeed, the behavioral phenotypes under 10-day paradigm are heterogeneous, which is indicated by the large variability of between-group difference in behavioral indicators [3,5,20,21]. Whether extended social defeat stress such as 21-day CSDS can reduce the resilience ratio and produce more uniform behavioral phenotypes of depression remains unclear.

In this study, we applied both 10-day and 21-day CSDS paradigms to induce depression-like behaviors in adult male mice, and then compared the resilience ratio and behavioral phenotypes of susceptible mice from two paradigms. To further compare the uniformity of these behavioral indicators from two paradigms, correlation analysis among behavioral indicators and a susceptibility prediction model based on different sets of these behavioral indicators was employed. Our study gives a systematic comparison of 10-day and 21-day CSDS paradigms and suggests that prolonged (21 days) CSDS is an effective approach to stress animals to generate depression-like behaviors with high uniformity.

2. Materials and methods

2.1. Animals

In total, 435 male C57BL/6JNju mice (aged 8–10 weeks) and 250 male CD-1 mice (aged 12–16 weeks) were purchased from Charles River Laboratories (Beijing, China) and maintained in a steady-state condition (12:12 light: dark cycle; environment temperature: ~23 °C; humidity, ~55%) with water and food *ad libitum*. All experiments were approved by the Institutional Animal Care and Use Committee at Tsinghua University and all animal treatment procedures strictly followed the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978).

2.2. Chronic social defeat stress (CSDS)

CD-1 mice were used for screening aggressors. C57BL/6JNju mice were randomly divided into control and CSDS groups and underwent CSDS paradigm according to a standard protocol [13]. Each mouse in CSDS group was defeated by a strange aggressor for 5 min in one side of the cage, and then transferred to the other side to experience sensory stress for 24 h. 10-day and 21-day CSDS paradigms last for 10 days and 21 days respectively.

2.3. Behavioral tests and analysis

After the last session of CSDS, all control and CSDS mice were singly housed with an interval about 24 h. Behavioral tests including social interaction test (SIT), elevated-plus maze test (EPM), open field test (OFT), sucrose preference test (SPT) and forced swimming test (FST), were performed in accordance with procedures described previously [3,4] with minor modifications. Analyses were performed in a manner with blinded treatment assignments in all behavioral experiments. Duration (in SIT, EPM and OFT) and entries (in EPM and OFT) to designated area and immobile time (in FST) of all mice were quantified using EthoVision XT 11.5 (Noldus, Netherlands).

2.4. Behavioral results z-score calculation

To compare the depression-like behaviors of susceptible groups from 10-day and 21-day CSDS paradigms, z-score for each susceptible mouse was applied as it can indicate how much standard deviation (σ) that an observation (X) is above or below the mean (μ) of the related control group [22].

$$z = \frac{X - \mu}{\sigma}$$

2.5. Multi-behavioral indicators-based prediction model

This prediction model is to evaluate the classification efficacy of susceptibility from a mixed group which contains control and susceptible mice. Theory and methodology of this model are shown in supplementary materials.

2.6. Statistical analysis

Normalized behavioral results (z-score) and F1 scores from two paradigms were analyzed using two-way ANOVA followed by Fishers' least significant difference (LSD) post hoc test. Correlations among behavioral indicators in each paradigm were determined by Pearson correlation analysis. All statistical tests were two-tailed, and the significance was assigned at $P < 0.05$.

3. Results

3.1. Prolonged social defeat stress significantly reduces the resilience ratio

In this study, 10-day and 21-day CSDS paradigms were separately applied. After CSDS, SIT and other behavioral tests were conducted to estimate the depression-like phenotypes of all mice (Fig. 1A). To determine whether 21-day CSDS can effectively reduce resilience, we compared the resilience ratio from multiple batches of 21-day and 10-day CSDS mice (Fig. 1B) and found that the average resilience ratio of 21-day CSDS was significantly lower than that of 10-day CSDS (9.1% vs 30.4%, $P = 0.006$, Fig. 1C).

3.2. Susceptible mice in 21-day CSDS had greater changes in depression-like behaviors

To compare the behavioral phenotypes of susceptible groups across two CSDS paradigms, the behavioral results from both paradigms were standardized by computing their z scores based on the mean and standard deviation of their own control group according to previous studies [22].

For all behavioral indicators of control groups in two CSDS paradigms, there were no significant differences in their z scores ($P > 0.05$, Fig. 2). The susceptible group from 10-day CSDS only showed significant changes in social index (SI), time in interaction zone in SIT ($P = 0.00017$ and 9.02E-06, respectively, Fig. 2A and B), time and entries in central area of OFT ($P = 0.0079$ and 0.0019, respectively, Fig. 2F and G) but not in time in corner zone (Fig. 2C), time and entries in open-arm of EPM (Fig. 2D and E), sucrose preference score (Fig. 2H) and immobile time in FST (Fig. 2I). However, z scores of all behavioral indicators of susceptible mice in 21-day CSDS paradigm were significantly different from control mice ($P < 0.0001$ for social index, time in interaction zone, time in corner zone, time and entries in open arms, time and entries in central area; $P = 0.002$ for sucrose preference and $P = 0.00097$ for immobile time in FST, Fig. 2). Furthermore, the susceptible mice in 21-day CSDS paradigm had greater changes in social index ($P = 0.0044$, Fig. 2A), time in interaction zone ($P = 0.0265$, Fig. 2B), time in corner zone ($P = 3.94E-06$, Fig. 2C), time and entries in open arms of EPM ($P = 0.00078$ and 3.8E-06, respectively, Fig. 2D and E) and sucrose preference ($P = 4.3E-05$, Fig. 2H) relative to the

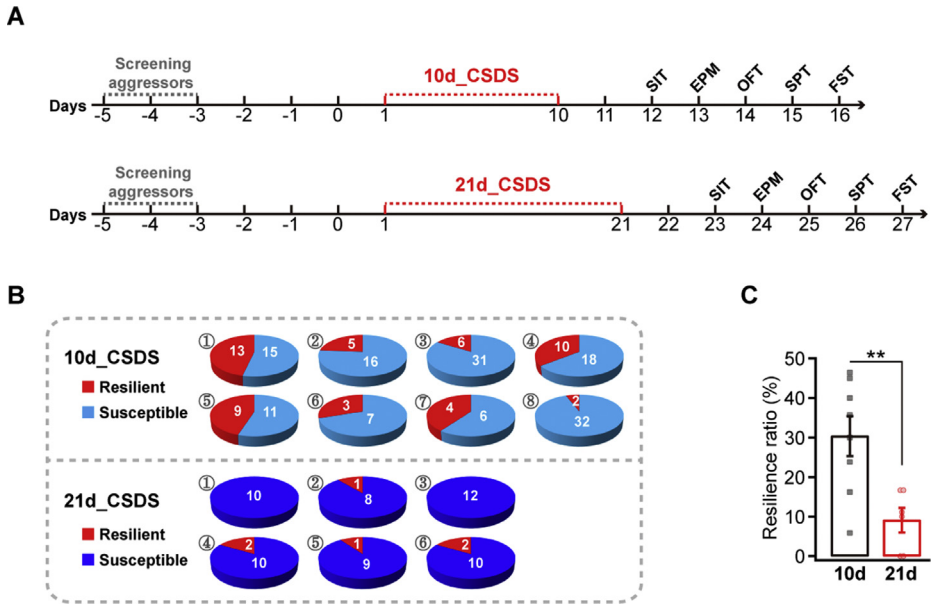

Fig. 1. Less resilience in 21-day paradigm than that in 10-day paradigm. (**A**) Timeline of 10-day or 21-day chronic social defeat stress and behavioral tests. SIT, social interaction test; EPM, elevated-plus maze test; OFT, open field test; SPT, sucrose preference test; FST, forced swimming test. (**B**) Resilience ratio of different batches of mice from 10-day or 21-day CSDS paradigm. Each pie chart indicates one batch. (**C**) Comparison of resilience ratio between 10-day and 21-day CSDS paradigms. Data are showed as mean ± s.e.m. n = 8 and 6 batches for 10-day and 21-day CSDS paradigms respectively, student t-test, $^{**}P < 0.01$.

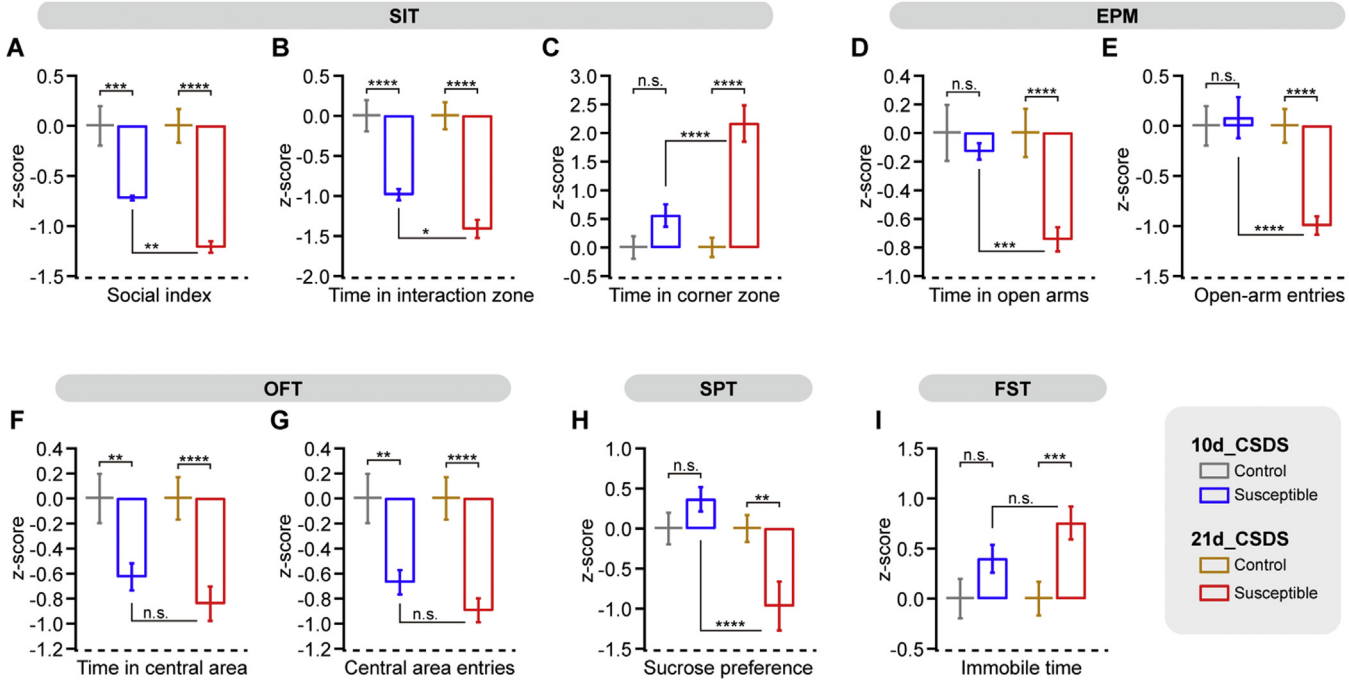

Fig. 2. Normalized behavioral results from 10-day and 21-day CSDS paradigms. (**A**) Normalized (z-score) social index of control and susceptible mice of 10-day and 21-day paradigms. (**B**) Normalized time in interaction zone. (**C**) Normalized time in corner zone. (**D**–**E**) Normalized duration and entries in open arms of EPM. (**F**–**G**) Normalized duration and entries in central area of OFT. (**H**) Normalized sucrose preference of mice from two CSDS paradigms. (**I**) Normalized immobile time in FST. All data are shown as mean ± s.e.m. n = 26 control and 32 susceptible mice in 10-day CSDS; n = 35 control and 40 susceptible mice in 21-day CSDS. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$, n.s., not significant.

susceptible mice in 10-day paradigm.

3.3. More behavioral indicators in 21-day CSDS paradigm have higher correlations among each other

We further analyzed the correlations among these behavioral indicators from 10-day or 21-day CSDS paradigm. As the results showed, behavioral indicators for anxiety (only OFT but not EPM) had significant correlations with some indicators in social interaction and despair in 10-day CSDS paradigm (Fig. 3A, Supplementary table 1). However, there were more behavioral indicators, for anxiety (including time and entries both in open arms of EPM and in central area of OFT), social interaction and despair, that had significant correlations with each other in 21-day

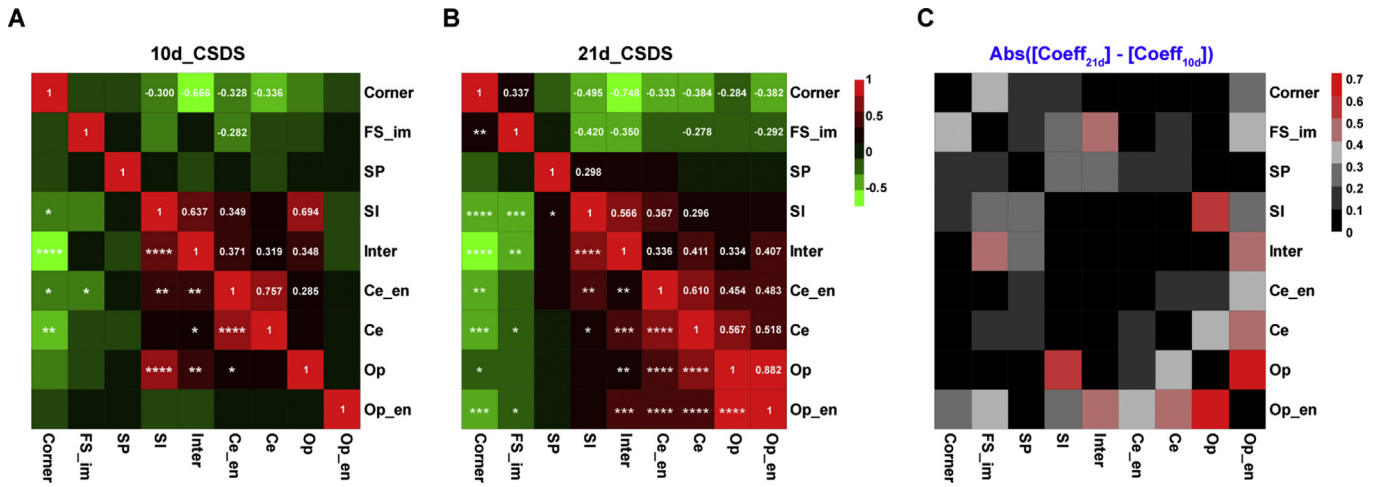

Fig. 3. Correlation coefficients of the nine behavioral indicators in 10-day or 21-day CSDS paradigm. (**A**) Correlation coefficients of behavioral indicators from 10-day CSDS. Colors indicate correlation coefficients and some of them are shown in upper right with significant correlation (shown as asterisks in lower left). Other pairs of behavioral indicators do not show correlation coefficient and asterisk indicating with not significant correlation ($P > 0.05$). (**B**) Same as **A** but from 21-day CSDS. (**C**) Absolute change of correlation coefficients in the same pair of behavioral indicators between 21-day and 10-day CSDS. Labels' meaning: Corner, time in corner zone in social interaction test; FS_im, immobile time in forced-swimming test; SP, sucrose preference; SI, social index; Inter, time in interaction zone; Ce_en, entries in central area of OFT; Ce, time in central area of OFT; Op, time in open arms of EPM; Op_en, entries in open arms of EPM. n = 58 mice (including 26 control and 32 susceptible mice) from 10-day CSDS and 75 mice (including 35 control and 40 susceptible mice) from 21-day CSDS respectively. Pearson correlation analysis, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

paradigm (Fig. 3B, Supplementary table 2). Moreover, when compared with 10-day CSDS paradigm, most pairs of behavioral indicators had greater correlation coefficients in 21-day CSDS than those in 10-day CSDS (Fig. 3C, Supplementary table 3).

3.4. Behavioral indicators from 21-day paradigm had higher efficacy for predicting susceptibility

Next, we built a model based on hierarchical clustering (of different sets of behavioral indicators) and binary classification to determine the susceptibility prediction property of behavioral indicators from two paradigms. Precision, recall, and F1 score were introduced to quantify the prediction efficacy (see Supplementary materials and Supplementary Fig.1). The set of nine indicators in 21-day CSDS was with a higher accuracy than those in 10-day CSDS (F1 score, 0.892 and 0.566 respectively, Supplementary Fig. 2A and B). We then systematically compared the prediction efficacy of a varying number of indicators from two to nine in two CSDS paradigms. The recall and precision of prediction results among different sets of indicators were quite different and these differences also existed between two paradigms (Fig. 4A). The F1 score of different sets of indicators in 21-day CSDS were significantly higher than those in 10-day CSDS (Fig. 4B). Furthermore, the average F1 score increased significantly with more indicators in 21-day CSDS ($F_{(6,\ 494)} = 2.94$, $P = 0.0079$) (Fig. 4C) but not in 10-day CSDS ($F_{(6,494)} = 0.228$, $P = 0.967$).

Although SI was generally used to define susceptible mice, the highest prediction accuracy using more than two indicators was higher than SI in 21-day CSDS paradigm (Fig. 4B), indicating that some of other indicators contribute to the prediction. Thus, we selected all sets of behavioral indicators with F1 score higher than SI (Fig. 4D) and counted the occurrence frequency of all behavioral indicators. Six of these behavioral indicators (SI, social index; Op_en, open-arm entries; Inter, time in interaction zone; SP, sucrose preference; Op, time in open arms) were highlighted (marked with red serial number) as key indicators based on the occurrence frequency (Fig. 4E). Using different combinations of these indicators can typically predict susceptible mice with high F1 score (Fig. 4F).

4. Discussion

As one of the most commonly used models of depression, CSDS has different paradigms with various periods of social defeat stress, such as 10 days [13,23–25], 14 days [26,27] and 21 days [14,15,28–32]. Both male and female animals under 10-day CSDS were with high resilience ratio (30–45%) [6,16,17,33]. As the behavioral phenotypes of depression were induced by accumulation of physical and psychological stresses from CSDS and resilience ratio gradually increased after ceasing CSDS [34], we speculated that the high resilience ratio under 10-day CSDS may largely due to insufficient stress. Thus, we extended the period of CSDS to 21 days and quantified various behavioral phenotypes and the resilience ratio and compared with those of 10-day CSDS. We found that the resilience ratio of 21-day paradigm was significantly lower than that in 10-day paradigm, which is in line with other studies [14,35]. However, several studies which applied 21-day CSDS to adult mice or 30-day CSDS to young mice (3-week-old age) reported high resilience ratio of 28% (7 resilient mice in 25 defeated mice) [32] and 40% (12 resilient mice in 30 defeated mice) [36], respectively. The discrepancy may be due to the shorter physical stress (generally > 2 min) used for adult mice and neurogenesis in the developing young brain that is beneficial for reversing depression.

Susceptible mice under 10-day CSDS exhibited variability in behavioral indicators of depression as indicated by evident change only in some of these indicators relative to control mice [3,4,18,20,21]. Consistent with this, we found that susceptible mice under 10-day CSDS only had 4 out of 9 indicators with significant change. However, all 9 behavioral indicators of susceptible mice under 21-day CSDS had significantly changed and 6 out of these indicators showed significant greater change than the indicators from 10-day CSDS, which is supported by other studies [37]. Furthermore, the behavioral indicators from 21-day CSDS had higher correlation among each other than those from 10-day paradigm. These results demonstrate that prolonged (21-day) CSDS not only reduce the number of resilient mice, but also

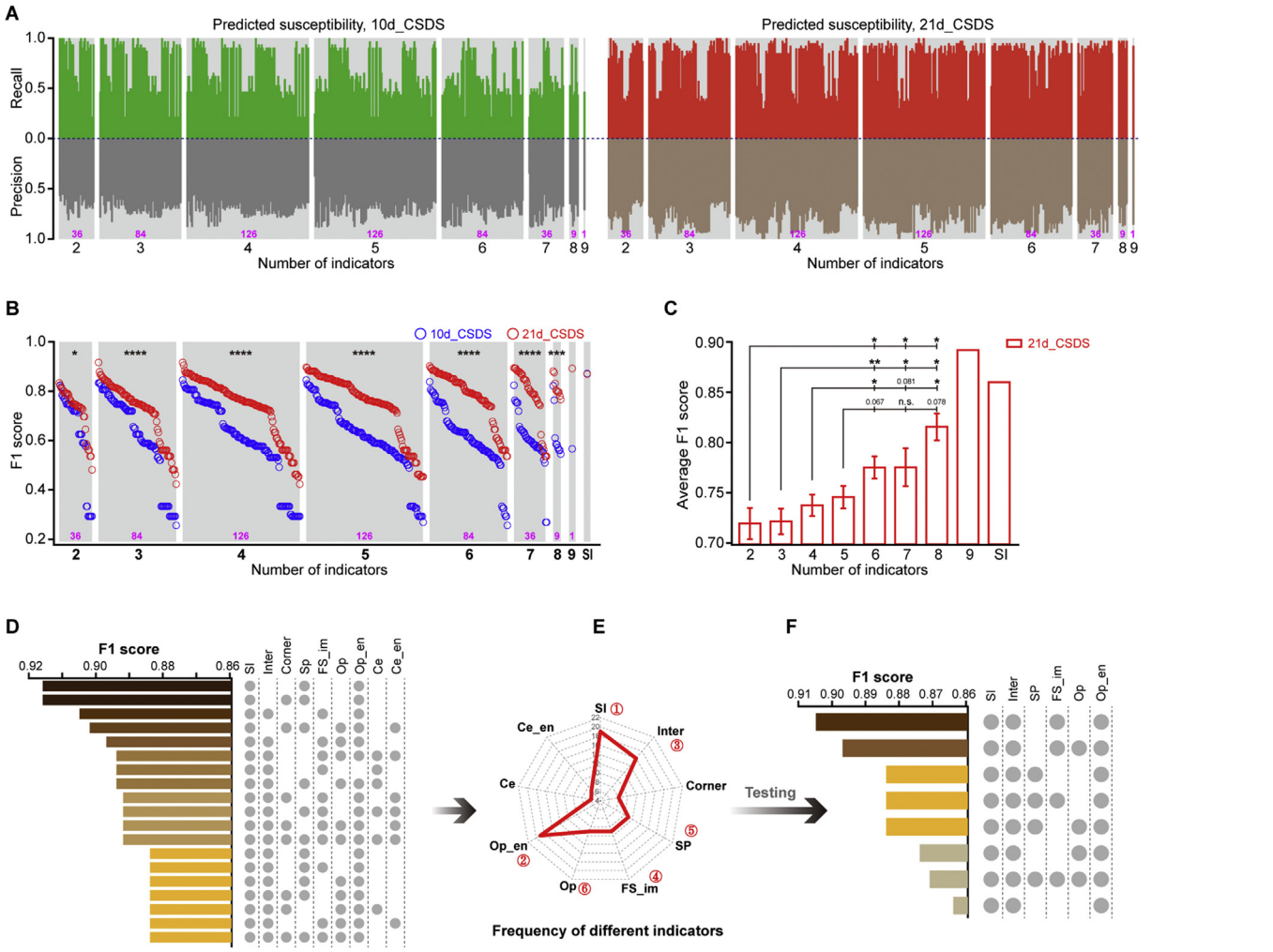

Fig. 4. Prediction efficacy of the behavioral indicators in 21-day paradigm is higher than those in 10-day paradigm. (**A**) Recall and precision of predicted susceptible mice based on different number of behavioral indicators (from 2 to 9), the number of combinations for 2–9 indicators is 36, 84, 126, 126, 84, 36, 9, and 1, respectively (shown as purple number). (**B**) F1 score of prediction based on different sets of behavioral indicators. (**C**) Mean F1 score under different sets of behavioral indicators of 21-day CSDS. Data are shown as mean ± s.e.m. Statistics, one-way ANOVA with LSD analysis among different indicators, $F_{(6,494)} = 2.94$, $P = 0.0079$. n = 36, 84, 126, 126, 84, 36, 9, 1 for 2–9 indicators respectively. F1 score based on social index is 0.860. (**D**) Top 19 combinations of different sets of indicators with higher F1 scores (0.88–0.92) than that of SI (0.860) from 21-day CSDS paradigm. (**E**) Frequency of nine indicators from the 19 combinations and the top six frequent key indicators marked with red serial numbers (SI, social index; Op_en, entries in open arms of EPM; Inter, time in interaction zone; FS_im, immobile time in forced-swimming test; SP, sucrose preference; Op, time in open arms of EPM). (**F**) High F1 score (0.87–0.91, which is larger than the F1 score based on SI) based on combinations of the top six key indicators. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$, n.s., not significant. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

promote susceptibility with reliable behavioral symptoms of depression.

We also applied a susceptibility prediction model based on hierarchical clustering and binary classification to evaluating the classification efficacy of these behavioral indicators from two CSDS paradigms. Generally, the susceptible and resilient mice were divided only based on the social index (SI < 1 is susceptible, SI > 1 is resilient) from social interaction test [13]. Consistently, prediction of susceptibility from a mixed group consisted of control and susceptible mice using only social index achieved similar accuracy in 21-day and 10-day CSDS paradigms (0.860 vs 0.865). Some studies suggested that more brain-body indicators such as light-dark test and interleukin-6 (IL-6) score increased accuracy of prediction for susceptibility and resilience [38]. We found that behavioral indicators in 21-day CSDS had better prediction for susceptible animal than those in 10-day CSDS. The prediction efficacy increased when involving more behavioral indicators, which occurred in 21-day CSDS but not 10-day CSDS. Consistently, there was significant lower resilience ratio and reliable behavioral symptoms under 21-day CSDS compared with 10-day CSDS. These results further demonstrate that 21-day CSDS is a more effective paradigm to produce animal model of depression. Furthermore, we found that a subset of indicators in 21-day CSDS can differentiate control and susceptible CSDS mice with high accuracy, even better than SI that was used to define susceptible mice. These indicators can be primary used in testing behavioral phenotypes of depression, and thus efficiently reduce the number of behavioral tests required to identify mice of depression. Whether the differences in susceptible mice between 21-day and 10-day CSDS paradigms exist at molecular, circuits and behavioral level requires further study.

Our study provides the first evidence to our knowledge that extending the period of social defeat stress to 21 days can effectively decrease the resilience to psychological and physical stress. The behavioral phenotypes in 21-day CSDS had higher uniformity and can better predict the susceptibility. Some key behavioral indicators and related combinations can be preferentially applied as

they can well indicate the susceptible animals. In conclusion, the 21-day CSDS is a robust paradigm to induce depression-like phenotypes with high uniformity in mice and may be adopted in various animal models of depression.

Author contributions

Conceived and designed the study: J.L., Z.V.G., P.X.

Performed the experiments: J.L., X.G., Y.G., Y.H., W.Z., H.Y.W., W.W., S.J.B., H.G.

Analyzed the data: J.L., X.G., X.Y., Y.G., H.J.Y., R.N.J.

Prepared the manuscript: J.L., Z.V.G., P.X.

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Declaration of competing interest

The authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrc.2021.03.058.

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