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Low cognitive competence as a vulnerability factor for behavioral despair in rats

Nilay Atesyakar, Resit Canbeyli, Gunes Unal*

Behavioral Neuroscience Laboratory, Department of Psychology, Boğaziçi University, 34342, Istanbul, Turkey

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ABSTRACT

Elucidating the multi-faceted relationship between cognitive competence and affective states is a major pursuit in behavioral sciences. Mood disorders constitute a good research model for this question, as cognitive impairment may accompany clinical depression and persist after full remission. This suggests cognitive dysfunction as an etiological factor of depression, rather than an epiphenomenon. Complementing clinical studies, animal models utilizing well-controlled, systematic paradigms are essential to elucidate the complex relationship between cognitive competence and affective states. In current set of experiments, we investigated the extent to which cognitive competence determines the stress response in Wistar rats by utilizing two well-established spatial memory paradigms with different degrees of complexity together with the forced swim test. We revealed that rats with low cognitive competence as assessed by learning performance in the Y-Maze, but not in the radial arm maze, were significantly more vulnerable to behavioral despair. In contrast, rats with high cognitive competence were resilient to the negative effects of the forced swim test, irrespective of the spatial memory task used. These results point to a nonlinear relationship between spatial memory performance and behavioral despair, suggesting that different types of cognitive functioning may have differential effects on affective processes.

1. Introduction

The complex relationship between cognition and affect is one the most studied themes in behavioral sciences. The power of this relationship is well-observed in stress-inducing conditions, which often lead to a decline in different forms of cognitive functioning. Mood disorders, such as clinical depression, have been the center of attention in studying the multifaceted relationship between cognitive functioning and affective states. Both human (Austin et al., 2001; Schwabe et al., 2012) and animal (Bangasser and Shors, 2010; McEwen and Sapolsky, 1995) studies have documented depressive states as a leading cause of deterioration in various forms of cognitive processes. Persistent impairment in attention, executive function, and declarative memory have all been documented in individuals remitted from depression (Rock et al., 2014), suggesting a major role of cognitive processes in the etiology of the affective disorder, as opposed to merely being an epiphenomenon (Knight et al., 2018; Rock et al., 2014). Studying the relationship between different types of cognitive functioning and stress response is key to understand whether low cognitive competence may be considered as a vulnerability factor for affective disorders. More importantly, not only the stress response, but virtually all other forms of animal behavior, whether species-specific or acquired, are the co-product of cognitive and affective processes.

Previous attempts to delineate the nature of the association between cognitive competence and affective states have found its roots in cognitive reserve hypothesis (Barnett et al., 2006; Stern, 2002) and the concept of overexcitability (Dabrowski, 1967; Dabrowski and Piechowski, 1977a,b; Piechowski, 1997). Longitudinal studies (Batty et al., 2005; Hung et al., 2016; Koenen et al., 2009; Schaefer et al., 2017) as well as cross-sectional designs (Mackenzie et al., 2018) have been initiated to understand the nature of this association. Having considered intelligence scores, education and occupational attainment as proxy measures of the so called cognitive reserve, studies have revealed low intelligence as a predictor of several mental disorders including depression (Hung et al., 2016; Koenen et al., 2009; Zammit et al., 2004). Further clinical research has documented that first-degree relatives of individuals with major depressive disorder (MDD) perform poorer on cognitive tests compared to individuals without such

Abbreviations: CUS, chronic unpredictable stress; FST, forced swim test; IQ, intelligence quotient; RAM, radial arm maze; RME, reference memory errors; WME, working memory errors

* Corresponding author.
E-mail address: gunes.unal@boun.edu.tr (G. Unal).

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relatives, suggesting a familial risk factor for depression associated with lower cognitive functioning (see Mackenzie et al., 2018). In contrast, several other studies have associated high intelligence scores with an enhanced risk for clinical depression (Jackson and Peterson, 2003; Karpinski et al., 2018; Wraw et al., 2016), leading to numerous but equivocal findings that require adoption of animal models employing systematic and well-controlled research paradigms.

Rodent models of stress have been instrumental in gaining insights into the association between affective states and cognitive functioning (Bangasser and Shors, 2010; Joëls et al., 2006; McEwen and Sapolsky, 1995; Sandi and Pinelo-Nava, 2007). Behavioral research has well established the effect of different forms of stress on performance in several cognitive domains, including attentional set-shifting (Liston et al., 2006; Nikiforuk and Popik, 2011), and spatial learning and memory (Conrad, 2010; Conrad et al., 1996; Naudon and Jay, 2005; Song et al., 2006). Exposure to chronic restrained stress (Luine et al., 1994), long-term disturbing noise (Manikandan et al., 2006), chronic psychosocial stress (Park et al., 2001), and prenatal stress (Lemaire et al., 2000) were all found to deteriorate spatial memory performance, accompanied by various physiological and molecular abnormalities in the hippocampal complex. Against these efforts linking stress models and behavioral despair to various forms of cognitive functioning, to our knowledge, there is a paucity of research on how task difficulty relates to affective states in animal models.

A relatively recent study revealed that cognitive impairment induced by permanent occlusion of common carotid arteries predisposed rats to behavioral despair when exposed to chronic unpredictable stress (CUS) for 21 days, while rats with cognitive impairment but no CUS exposure did not display depression-like behavior (Khojasteh et al., 2015). These finding, however, do not reveal the directionality of the relationship between cognitive competence and the stress response. It is crucial to understand whether low cognitive competence paves the way for behavioral despair or high cognitive competence constitutes a protective factor against it. Another critical question is whether different types of cognitive ability that entail different degrees of complexity have distinct relationships with affective states.

In an attempt to answer these questions, we implemented two separate memory tasks with different degrees of complexity to evaluate the extent to which cognitive competence modulates vulnerability to behavioral despair—a well-established acute stress paradigm, in which enhanced immobility in the test session of the forced swim test (FST) compared to the acclimatization session is considered an indicator of depressed behavior (Porsolt et al., 1977; Slattery and Cryan, 2012; Unal and Canbeyli, 2019). The FST, being the most common screening tool for antidepressant efficacy (Petit-Demouliere et al., 2005; Slattery and Cryan, 2012; Unal and Canbeyli, 2019), was chosen to assess behavioral despair over more specific rodent models of clinic depression, such as the anhedonia-based sucrose preference test. We used a 3-day Y-Maze test to create a low difficulty memory task, assessing spatial working memory and requiring relatively low cognitive competence to master (Conrad et al., 1996; Dellu et al., 1992; Sharma et al., 2010). We then switched to a complex design with an increased number of arms and test sessions, and utilized the radial arm maze (RAM) over 12 days. The RAM is widely used to assess reference, that is long-term, memory in addition to spatial working memory (Olton and Samuelson, 1976; Vorhees and Williams, 2014). Both memory tasks were followed by FST sessions.

2. Material and methods

2.1. Subjects

A total of 40 experimentally naïve, adult male Wistar rats (initial weight: 245 − 320 g) were used. Each animal was group-housed in a temperature (22 ± 2 °C) and humidity (40–60 %) controlled vivarium with three other littermates and maintained on a 12-h light:dark cycle (lights on at 07:00) with *ad libitum* water. Food-restriction was applied to all animals prior to spatial learning tasks until they reached 80 % of their original free-feeding weight.

Twenty rats were randomly assigned to be tested in the Y-Maze and twenty others in the RAM experiments. One rat was removed from the RAM group due to excessive weight loss during food restriction prior to testing, which was conducted with nineteen animals. All experimental procedures were approved by the Boğaziçi University Institutional Ethics Committee for the Local Use of Animals in Experiments (BÜHADYEK).

2.2. Materials and procedure

2.2.1. Y-Maze

A wooden Y-Maze consisting of three arms symmetrically located at 120° angles from each other (45 cm long x15 cm wide x45 cm high) was adopted to assess cognitive competence in a relatively easy task (n = 20). The procedure started with an acclimatization day which allowed the rats to freely explore the maze for 5 min. This was followed by three consecutive days of 5-min behavioral testing. Coco Pops (Kellogg's, Turkey) were placed as baits at the end of each arm during acclimation and test days. The total time spent finding and consuming all three baits (latency) was recorded. The animal was placed back to its home cage at the end of each trial and the maze was thoroughly cleaned with ethanol (70 %) in order to eliminate the odor cues for the next rat.

2.2.2. Radial arm maze (RAM)

Spatial memory performance of the animals in a complex task was examined by means of a typical Radial Arm Maze (RAM) consisting of eight arms (45 cm long x10 cm wide), extending radially from a small central area. Each animal started with a 10-min acclimation session during which all eight arms of the maze were baited. Subsequently, 12 days of behavioral testing were carried out for which four arms were supplied with Coco Pops pseudo-randomly such that no more than two adjacent arms were baited. The same combination of baited arms was used for each animal over the 12-day task. Each trial was terminated either when the rat retrieved all baits in all arms or at the end of 10 min. Latency to finish a trial by consuming all the baits as well as entries to non-baited arms and re-entries to baited arms that were previously visited (errors) were recorded. As in the Y-Maze, RAM was cleaned with ethanol (70 %) at the end of each trial to minimize the odor cues.

2.2.3. The forced swim test (FST)

Following the standard method to evaluate behavioral despair (Porsolt et al., 1977; Slattery and Cryan, 2012), each rat underwent two FST sessions on two consecutive days separated by 24 h. Sessions were conducted in a Plexiglas cylindrical container with 45 cm height and 30 cm diameter. The container was filled with 25 °C water reaching 30 cm. On the first -acclimation- day of FST (FST-1), each rat was tested for 15 min. On the following -test- day (FST-2), the duration was reduced to 5 min (Porsolt et al., 1977). Upon completion of the trial, each rat was taken into a single cage for 30 min for drying. All testing was recorded by a video camera for off-line analyses of immobility and related passive behaviors. Researchers who analyzed the behavioral data were blind to the maze condition and did not know whether the rat was a poor or good learner.

Behavioral despair was assessed based on total duration of immobility, operationally-defined as a complete lack of movement other than those required to keep the nostrils above water. Increased immobility in FST-2 as compared to the first 5 min of FST-1 was considered an indicator of behavioral despair. This comparison is utilized when the effects of genetic factors, or long-term manipulations or treatments are assessed in the FST (see Arndt et al., 2015; Bielajew et al., 2003; Brenes et al., 2009; Drossopoulou et al., 2004; Ecevitoglu et al., 2019; Slattery and Cryan, 2012; Unal and Canbeyli, 2019). A behavioral despair index was calculated for each rat by taking the ratio

of total duration of immobility in the test day to that in the acclimation day (FST-2/FST-1). It should be noted that in order to minimize potential maze-specific stress, each rat was subjected to the FSTs one week after the end of Y-Maze or RAM testing.

2.2.4. Statistical analyses

In Y-Maze and RAM analyses, animals were grouped as poor and good learners based on their memory performance as indicated by their latency scores. The median split was applied for initial grouping and regression analyses were run to check for a potential linear relationship between memory performance and behavioral despair (index). Simple linear regression and the method of weighted least squares were used for homoscedastic and heteroscedastic data, respectively.

For group-level comparisons, each dataset was tested for normality by the Shapiro-Wilk test. Parametric statistics (i.e. the paired samples *t*-test or independent samples *t*-test) were used for normally distributed data, while non-parametric (i.e. the Wilcoxon signed-rank test or Mann-Whitney U test) models were applied to non-normal data. Statistical analyses were performed in MATLAB (MathWorks) and SPSS (IBM). Figures were initially drafted in these software and refined with Adobe Illustrator CS5.

3. Results

3.1. Assessment in the Y-Maze task and subsequent FST performance

Animals that underwent the Y-Maze task were ranked and categorized as good learners and poor learners based on their last day performance (latency to finish the trial). One rat (ID: Rat 5) failed to learn the task over 3 days, never consuming all the baits. This animal and another outlier with a z-score of -3.14 on the difference between immobility scores over two days of the FST (ID: Rat 13) were excluded from the analyses. Remaining animals with Y-Maze latency scores above and below the median value (115.5 s) were respectively classified as good (n = 9) and poor learners (n = 9; Fig. 1). The latency to finish the trial on the last day had a non-normal distribution (Shapiro-Wilk test, $p = 0.00$), necessitating a Mann-Whitney U Test to compare memory performance. Good learner rats finished the trial significantly sooner (Mdn = 105.00) than the poor learners (Mdn = 149.00; $U = .00$, $n_{good} = n_{poor} = 9$, $p = .00$, $r = 0.84$).

Comparing these two groups for potential differences in resilience to behavioral despair revealed that poor learners remained immobile for a

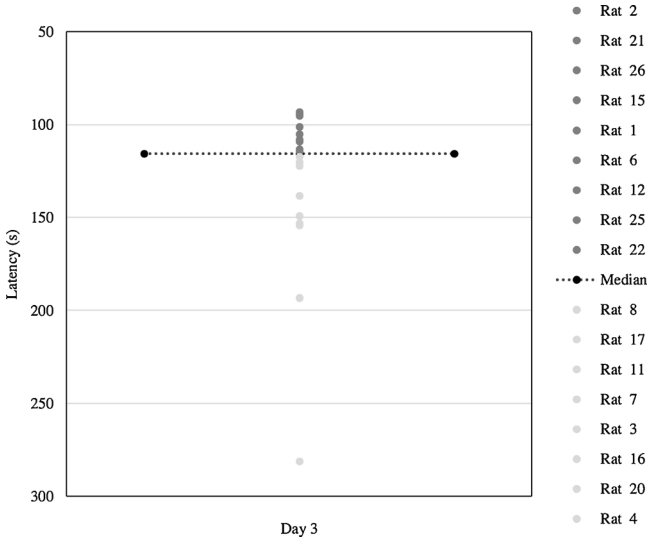

Fig. 1. Latency to finish the trial when learning was achieved on the last day of Y-Maze task differentiates good (dark grey) and poor (light grey) learners by median value. Rat IDs follow the descending order in the plot.

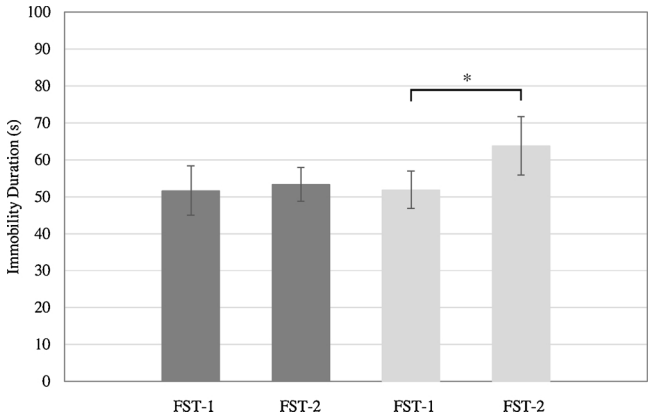

Fig. 2. Durations of immobility (mean ± SEM) in the initial five minutes of the acclimation (FST-1) and test day (FST-2) of forced swimming for good (dark grey) and poor learners (light grey) of the Y-Maze task. Asterisk indicates statistical significance at $p < 0.05$.

significantly longer duration in FST-2 (M = 63.78, SD = 23.75; paired samples *t*-test) compared to FST-1 (M = 51.89, SD = 15.04; $t(8) = -2.667$, $p = 0.028$, $d = -0.889$; Fig. 2). In contrast, good learners' immobility scores of FST-2 (M = 53.33, SD = 13.88) did not differ from their FST-1 scores (M = 51.67, SD = 20.16; $t(8) = -0.230$, $p = 0.824$, $d = -0.077$, paired samples *t*-test; Fig. 2). It should be noted that the difference between immobility durations in FST-1 and FST-2 were normally distributed for both groups (Shapiro-Wilk test, $ps > 0.05$).

In order to determine the strength of the relationship between Y-Maze performance and behavioral despair, we ran a weighted least squares regression analysis, for which the last day latency score was set as a predictor for behavioral despair index. The regression equation was not significant ($F(1,16) = .007$, $p = 0.933$) with an $R^2 < .000$, indicating that no general linear relationship can be drawn between Y-Maze memory performance and behavioral despair based on this limited sample.

3.2. Assessment in the RAM task and subsequent FST performances

We investigated the association between cognitive competence and behavioral despair in a complex task by utilizing RAM with a new group of naïve animals. The latency to finish the trial on each test day revealed a non-normal distribution (Shapiro-Wilk tests, all $ps < 0.05$). A Friedman test was carried out to compare the latencies for twelve days, revealing a significant difference between the days, $\chi^2(11) = 89.50$, $p = .000$, Kendall's $W = .416$. Dunn-Bonferroni post hoc analyses revealed learning by the eleventh day of the 12-day RAM task, by comparing the latency scores in Day 1 and Day 11 ($p = 0.014$), as well as Day 1 and Day 12 ($p = 0.002$).

We therefore ranked the animals with regard to their average latency to finish the task by collecting all the baits over the last two days of the RAM. After removing an outlier with a z-score of 3.02 on the difference between FST immobility scores (ID: Rat 13), the animals were grouped as good (n = 9) and poor learners (n = 9) with respect to the median latency value (279 s; Fig. 3), as done for the Y-Maze task. The average latency to finish the trial over the last two days had a non-normal distribution (Shapiro-Wilk tests, $p = 0.00$). Good learner rats (Mdn = 118.00) had a significantly better performance than the poor learners, many of which failed to complete the task (Mdn = 600.00; $U = .00$, $n_{good} = n_{poor} = 9$, $p = .00$, $r = -0.85$, Mann-Whitney U Test).

Our assessment of cognitive competence in the substantially more difficult RAM task did not reveal poor performance as a vulnerability factor for behavioral despair as observed in the Y-Maze. Poor learners of the RAM displayed similar levels of immobility in FST-2 (M = 70.33, SD = 21.59) and FST-1 (M = 63.78, SD = 8.31; $t(8) = -1.042$, $p =$

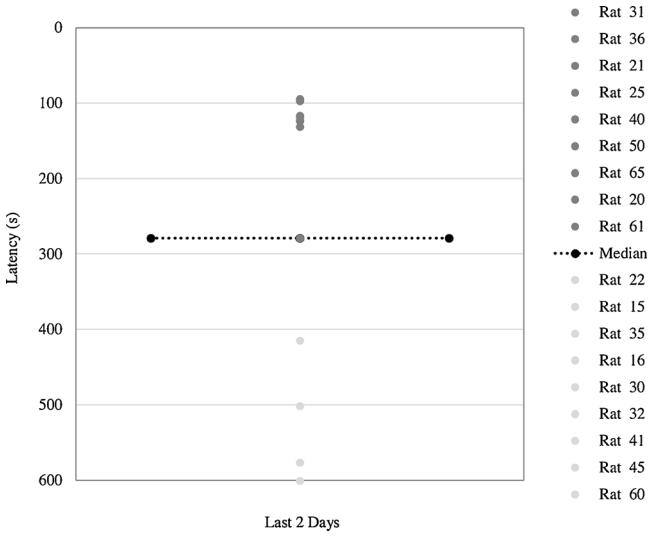

Fig. 3. Average latency to finish the trial when learning was achieved on the last two days of RAM task differentiates good (dark grey) and poor (light grey) learners by median value. Note that the data points of last six poor learner animals (Rats 60, 45, 41, 32, 30 and 16) overlap at 600 s. Rat IDs follow the descending order in the plot.

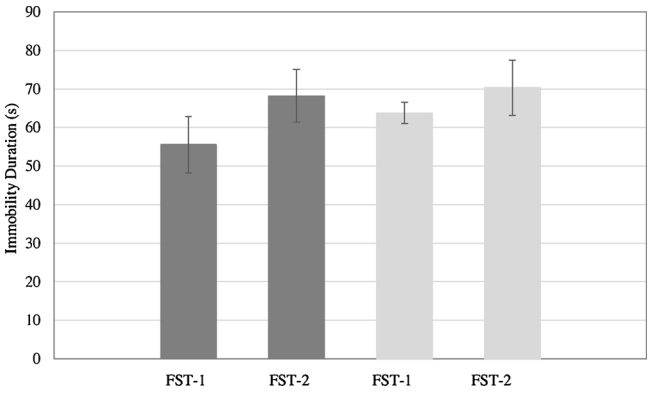

Fig. 4. Durations of immobility (mean ± SEM) in the initial five minutes of the acclimation (FST-1) and test day (FST-2) of forced swimming for good (dark grey) and poor learners (light grey) as assessed by their average latency scores in the RAM task.

0.328, d = -0.347, paired samples t-test; Fig. 4). Likewise, good learners did not show a significant change in immobility (FST-1: M = 55.55, SD = 21.88 and FST-2: M = 68.22, SD = 20.58; $t(8)$ = -1.475, p = 0.178, d = -0.491, paired samples t-test; Fig. 4). The immobility difference between the two swim tests was normally distributed in all groups (Shapiro-Wilk test, all $ps > 0.05$).

Finally, we sought to predict behavioral despair levels based on latency scores of the last two days of RAM by a simple linear regression. As for the Y-Maze performance, current sample size revealed a non-significant regression equation ($F(1,17) = .267$, p = 0.612) with an R^2 of .015.

3.3. FST performance according to memory errors in the RAM task

In order to cross-check these behavioral despair findings, we repeated the categorization of animals as good and poor learners by using memory errors instead of average latency scores of the last two days. Entries to non-baited arms correspond to reference memory errors (RME) whereas re-entries to baited arms that have already been visited constitute working memory errors (WME; Jarrard, 1983). The immobility difference between the two swim tests was normally distributed for rats with good (Shapiro-Wilk test, p = .831), but not for poor reference memory (Shapiro-Wilk test, p = .017). Based on this categorization, good learner rats with few/no RME (M = 1.06, SD = 0.86) did not display increased immobility in FST-2 (M = 72.50, SD = 17.80) compared to FST-1 (M = 63.87, SD = 8.13; $t(7)$ = -1.813, p = 0.113, d = -0.641, paired samples t-test). Poor learner rats with many RME (M = 3.75, SD = 1.23) followed the same trend (FST-1: Mdn = 46.50 vs. FST-2: Mdn = 73.00; Z = -1.02, n = 10, p = 0.308, r = -0.322, Wilcoxon signed-rank test). Accordingly, we did not find a meaningful correlation between the number of RME and the behavioral despair index, r = .099, n = 18, p = .696, r^2 = 0.009; normally distributed as indicated by Shapiro-Wilk test, all $ps > .05$.

Working memory-based categorization of the animals led to similar results. There was no significant alteration in immobility across FST sessions either for good learners with no WME (M = .00, SD = .00; FST-1: M = 60.91, SD = 19.17 vs. FST-2: M = 68.33, SD = 18.70; $t(11)$ = -1.319, p = 0.214, d = -0.38, paired samples t-test), or for poor learners with many WME (M = 1.25, SD = 0.93; FST-1: M = 57.16, SD = 10.83 vs. FST-2: M = 71.16, SD = 25.52; $t(5)$ = -1.215, p = 0.279, d = -0.49, paired samples t-test). The immobility difference between the two swim tests was normally distributed for both groups (Shapiro-Wilk test, all $ps > .05$). Correlation analysis did not find a major trend between the number of WME and the behavioral despair index, r_s = .161, n = 18, p = .523, $r_s{}^2$ =. 025, Spearman's rank-order correlation; non-normally distributed, Shapiro-Wilk test for average working memory errors was significant (p = .000).

Furthermore, in order to control for potential stress associated task performance following spatial memory assessment and check whether maze-led stress differentially modulates baseline behavior in the FST, we compared the FST-1 immobility scores of rats in the Y-Maze group (M = 51.77, SD = 17.25) and the RAM group (M = 59.66, SD = 16.60), and found no significant difference ($t(34)$ = -1.40, p = 0.171, d = 0.473; independent samples t-test, normally distributed as indicated by Shapiro-Wilk test, all $ps > .05$).

4. Discussion

Utilizing two spatial memory paradigms with substantially different levels of complexity, we sought to test whether a linear increase in task difficulty has differential effects on affective behavior. Furthermore, this design would reveal whether low cognitive competence constitutes a vulnerability factor for behavioral despair. When we evaluated memory performance by means of a relatively simple Y-Maze task, the results showed that poor learners were prone to behavioral despair, while good learners were protected from the negative effects of forced swimming. On the other hand, this differential effect was not observed when we utilized a more complex spatial memory task by increasing the total number of arms (i.e. from three in Y-Maze to eight in RAM) and decreasing the proportion of baited arms (i.e. from 3/3 in Y-Maze to 4/8 in RAM). Thus, the complexity of the RAM task does not only rely on a linear increase in the number of arms/routes that can be chosen, but also a decrease in the ratio of baited/rewarded arms from 100 % to 50 %. As a result, neither poor nor good learners were found to be susceptible to behavioral despair in the RAM, indicating that the acquired level of complexity in this paradigm can no longer differentiate animals in their stress response to forced swimming.

An alternative explanation for the absence of a difference between good and poor learners of the RAM in behavioral despair relies on the relatively high number of test days. By exposing them to mild stress over thirteen days, the RAM task could have provided the animals with immunity against the subsequent induction of stress by forced swim tests. Comparison of FST-1 immobility durations of the Y-Maze and RAM animals ruled out this possibility. A significant difference here would indicate presence of maze-specific stress associated with task performance; yet both groups displayed similar levels of baseline immobility in the acclimation day of FST. It is possible that the extended

test schedule of RAM results in cognitive alterations that level good and poor learners in their stress response. A thirteen day-long complex maze training may have enabled even the poor learner animals to expect to be ultimately taken out of the water-filled cylinder in FST-2 based on their earlier experience 24 h ago (FST-1). This explanation, however, questions the validity of FST as a despair model, considering it as a behavioral adaption or learning model (see Unal and Canbeyli, 2019).

The results of the Y-Maze task provide support for previous research indicating low capacity cognitive functioning as a risk factor for psychological disorders (Batty et al., 2005; Hung et al., 2016; Koenen et al., 2009). An earlier study successfully linked cognitive impairment to behavioral despair in Sprague-Dawley rats, by observing a significant increase in both reference and working memory errors following occlusion of common carotid arteries (Khojasteh et al., 2015). However, the nature of this invasive procedure did not allow for a precise assessment of the relationship between cognitive impairment and the stress response. In particular, occlusion of common carotid arteries could have led to damage in several neuronal circuitry that collectively underlie both the affective and the cognitive and processes (Griffin, 2015; Jarrard et al., 2012; Negrón-Oyarzo et al., 2018; Olton and Paras, 1979; Xia et al., 2019). Avoiding such invasive manipulations, our design naturally identified animals with low cognitive competence by behavioral testing in the Y-Maze, a cognitive task with minimal affective component (i.e. it does not induce stress other than that of handling).

There is an important implication of our Y-Maze findings regarding another very popular rodent paradigm, the FST (Unal and Canbeyli, 2019). A major criticism of the FST, the most common rodent test to evaluate antidepressant treatment, has purported to link increased immobility displayed in the test phase of the test (i.e. FST-2) to phenomena other than despair (see Commons et al., 2017; De Kloet and Molendijk, 2016; Molendijk and de Kloet, 2015). According to this hypothesis, increased immobility observed in FST-2 is a mere behavioral adaptation rather than an indicator of autonomic stress response or behavioral despair. From the perspective of this argument, one would expect to find rats with higher cognitive competence as assessed by means of maze learning (i.e. good learners) to display increased immobility in FST-2, as they may “have already acquired / know” that they will eventually be taken out of the FST pool. As such, the FST would measure behavioral adaptation of these animals rather than behavioral despair. However, our results revealed an opposite pattern in the Y-Maze: rats with low cognitive competence (i.e. poor learners) displayed significantly more behavioral despair, providing further support for the FST as a rodent model of clinical depression.

In contrast to the differentiating effect of the Y-Maze, the categorization of animals in the RAM, whether based on latency scores or reference or working memory-errors, did not alter the animals’ stress response to forced swimming. This may indicate that the association between cognitive competence and depression primarily depends on comorbid disorders (Nissen et al., 2019; Schaefer et al., 2017) and the symptoms of the disease, but not the depression by itself (Scult et al., 2017). Alternatively, the discrepancy between results of the relatively simple Y-Maze and the complex RAM tasks demonstrates the non-linear relationship between cognitive competence and affective states, including resilience to depression.

The multifaceted nature of the association between cognitive ability and mood has been documented in a handful of human studies that sometimes report contradictory findings. For instance, an early study found a positive relationship between lower childhood IQ and enhanced risk for later depression as well as anxiety and schizophrenia (Koenen et al., 2009). In contrast, another study found a significant positive correlation between higher intelligence scores in youth and lifetime diagnosis of depression (Wraw et al., 2016). Furthermore, previous research in humans has often group intelligence scores within one standard deviation. Karpinski and colleagues (2018) note that this is method is problematic as the relationship between intelligence and affective states follows a non-linear pattern. The evidence comes from a study showing that students with the poorest grades as well as those with top grades were more susceptible to bipolar disorder in adulthood, compared to mainstream students with average scores (MacCabe et al., 2010). Similarly, it was revealed that not only men with the lowest intelligence scores, but also those with the highest had an increased risk of developing bipolar disorder, again pointing to a U-shaped relationship (Gale et al., 2013).

It should be noted that human studies have reported substantial gender differences in learning style (Severiens and Ten Dam, 1994), memory performance (Lowe et al., 2003) and clinical depression (Nolen-hoeksema, 2001). Like most animal research, this limits the generalizability of our findings to the male population.

The differential results we have observed with the Y-Maze and RAM tasks extend the aforementioned clinical observations to animals, showing that the non-linear relationship between cognitive competence and affective states can be elucidated under controlled conditions. However, the aforementioned work in humans fail to explain why low cognitive competence as measured in the Y-Maze constitutes a vulnerability factor for behavioral despair, while no such differentiation could be achieved in a substantially more complex task, the RAM. Our results suggest that different types of cognitive functioning may have differential effects on affective processes. As such, the predictive value of cognitive competence in affective disorders would depend on the specific requirements of the cognitive paradigm, such as the intelligence test, used. Furthermore stimulating conditions prior to cognitive testing, such as environmental enrichment or aerobic training (Pietrelli et al., 2012), may differentially affect the predictive value of cognitive competence. Following our experimental design, a wider range of cognitive competence tasks that likely depend on different neuronal circuits and behavioral mechanisms, such as those that rely on numerical vs. temporal strategies (see Davis, 1996; Hodges, 1996) should be utilized to reveal the full etiology of the relationship between cognitive and affective processes.

CRediT authorship contribution statement

Nilay Atesyakar: Investigation, Writing - original draft. **Resit Canbeyli:** Conceptualization, Methodology, Writing - review & editing. **Gunes Unal:** Conceptualization, Methodology, Funding acquisition, Investigation, Validation, Supervision, Writing - review & editing.

Declaration of Competing Interest

None.

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