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ORIGINAL RESEARCH

Differences of physical vs. psychological stress: evidences from glucocorticoid receptor expression, hippocampal subfields injury, and behavioral abnormalities

Yuefeng Li[1,2] · Jiasheng Qin[1] · Jinchuan Yan[1] · Ningning Zhang[1] · Yuhao Xu[1] · Yan Zhu[1] · Liangju Sheng[3] · Xiaolan Zhu[4] · Shenghong Ju[2]

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Abstract

The glucocorticoid receptor (GR) is the main effector of the activation of the hypothalamus-pituitary-adrenal (HPA) axis, which is caused by different types of stress that can be divided into two major categories: physical stress and psychological stress. Given the marked presence of GR in the hippocampus, GR-mediated hippocampal injury might be the core event under stress. The aim of this study was to investigate GR expression, hippocampal injury, and behaviors in rats to explore the differences between these types of stressors. Adult male rats were stressed using a classical model (electrical foot shock and a yoked psychologically stressful situation) to induce physical or psychological stress. The GR expression, injury of hippocampal subfields and behavioral abnormalities were dynamic, as demonstrated using immunofluorescence, 3D magnetic resonance imaging (MRI) and open field exploration (OFE), respectively. In addition, housing in a normal environment for 6 weeks was used to verify the recovery ability of rats. First, GR-mediated hippocampal atrophy and behavioral abnormalities were found in the second week under physical stress, but those changes did not appear until the fourth week under psychological stress. Second, the effects of stress were more pronounced after physical stressors than after psychological stressors in the fourth week, but this trend had reversed by the sixth week, especially in the DG (Dentate Gyrus) subfield. Except for the rats that had experienced 6 weeks of psychological stress, all rats showed significant recovery after 6 weeks of housing in a normal environment. The effects of physical stress appeared early but were relatively moderate, whereas the effects of psychological stress appeared late but were more severe. In addition, GR-mediated serious injury in the DG might be the cause of the DG volume loss and behaviors that could not be reversed.

Keywords Stress · Glucocorticoid receptor · Hippocampal atrophy · Magnetic resonance imaging · Immunofluorescence

Introduction

Establishing stress models in rats, such as chronic unpredictable mild stress (CUMS) (Li et al. 2018), chronic restraint stress (CRS) (Taslimi et al. 2018), social defeat stress (SDS) (Sathyanesan et al. 2018), learned helplessness (LH) (Liu et al. 2018), maternal deprivation (MD) (Cabbia et al. 2018), and injecting inducer (Majcher-Maslanka et al. 2018), is a common method for studying mental illness in humans. In fact, these stress patterns can be divided into two major categories: physical stress and psychological stress (Liu et al. 2018). Many studies have proved that both stress patterns can induce behavioral abnormalities, cerebral atrophy and cognitive dysfunction, abnormal neurotransmitters and cytokines, disordered hormone levels, and increased inflammatory factors in rats (Xu et al. 2017; Li et al. 2017a; Gu et al. 2018). However, recent reports have indicated that there might be essential

Yuefeng Li and Jiasheng Qin contributed equally to this work.

✉ Xiaolan Zhu
zxl2517@163.com

✉ Shenghong Ju
jshtougao@126.com

[1] Department of Radiology, Affiliated Hospital of Jiangsu University, Zhenjiang, China

[2] Department of Radiology, Zhongda Affiliated Hospital of Southeast University, No.87, Dingjiaqiao Road, Nanjing 210009, Jiangsu Province, China

[3] Medical College, Affiliated Hospital of Jiangsu University, Zhenjiang, China

[4] Department of Central Laboratory, The Fourth Affiliated Hospital of Jiangsu University, No.20, Zhengdong Road, Zhenjiang 212001, Jiangsu Province, China

differences between physical and psychological stress. Differences in Fos expression, metabolic differences, motor and cognitive functions of the offspring, neurochemical changes, and diazepam-binding inhibitor (DBI) in two stress patterns have been found (Briski and Gillen 2001; Uehara et al. 2005; Nazeri et al. 2015; Katsura et al. 2002). However, the most important indicator of the stress model, i.e., the differences in behaviors after physical and psychological stress has not yet been reported, although some investigators have suggested the strong possibility that physical stress-induced behavioral anomalies in adult rats usually disappear after 6 weeks of housing in a normal environment, whereas this phenomenon was not found in rat models of psychological stress (Bai et al. 2012).

An individual's capacity to address stress is largely controlled by the hypothalamus-pituitary-adrenal (HPA) axis. A dysregulated stress response system, as evidenced by the hyperactivity of the HPA axis, is a vulnerability factor for psychiatric disorders and is one of the most consistent findings in mental patients (Hu et al. 2016). The hyperactivity of the HPA axis and increased levels of glucocorticoid (GC) hormones in mental patients have, for the most part, been ascribed to the impaired feedback regulation of the HPA axis, which is likely caused by the altered function of the receptor for glucocorticoid hormones, the glucocorticoid receptor (GR) and mineralocorticoid receptor that contributes to the secession of the stress response by acting on the HPA negative feedback loop and mediates the beneficial effects of stress on memory consolidation (Sasaki and Yoshizaki 2015). Considerable experimental data have suggested that GR is the main effector of the activation of the HPA axis, which is caused by different types of stress (Tyler et al. 2014). Given the marked presence of GR in the hippocampus (Reul and de Kloet 1985), which is associated with cognitive functions, behaviors, spatial orientation, memory, and attention, the injury of this brain region was considered the most direct evidence of GC elevation, hyperactivity of the HPA axis, and stress (Spencer et al. 1991). That is, GR-mediated hippocampal injury might be the fundamental cause of behavioral abnormalities under stress.

To date, volume loss has been known as the best-replicated finding of hippocampal injury. Magnetic resonance imaging (MRI) systems with magnetic fields lower than 3.0 T provide only a global volume of measure; in fact, the changes might be diverse in different hippocampal subfields composed of different cellular and molecular characteristics. In our previous studies, we successfully established the division and measurement of rat hippocampal subfields on 7 T MRI for the first time. Therefore, in the present study, we established rat models of two stress types to investigate the behavioral differences and explore GR expression and hippocampal injury at the subfields level using immunofluorescence and 3D neuroimaging from ultra-high field (UHF) 7.0 T MRI.

Materials and methods

Animals

Sixty male Wistar rats (170–200 g) were purchased from the SLAC Animal Center (Shanghai, China). Thirty rats were randomly selected and prepared for the physical stress group, another thirty were also randomly selected and prepared for the psychological stress group. These rats were observed at four time-points (0 weeks (0 W), 2 weeks (2 W), 4 weeks (4 W), 6 weeks(6 W)). Animals were housed independently in standard Plexiglas cages under a normal 12 h /12 h light/dark schedule. The animals were allowed to acclimate to the housing conditions for 1 week before the experiments. Ambient temperature and relative humidity were maintained at 22 ± 2 °C and 55 ± 5%, respectively. The animals were granted free access to standard chow and water for the duration of the study. All animal procedures were in accordance with the National Institute of Health Guide for the care and use of laboratory animals, and the experimental protocol was approved by the Animal Care Committee at Jiangsu University.

Stress exposures

Physical and psychological stress was induced in rats placed in a communication box (Sutoo and Akiyama 2002). The floor of the communication box was composed of 0.5-cm-diameter stainless steel rods set 1.0 cm apart. The box was divided into 48 small compartments (10/10/45 cm) using transparent plastic sheets. An electric shock generator (ASTEC, Fukuoka, Japan) with a timer (H3CA, Omron, Kyoto, Japan) produced electric foot shocks (2 mA) for 5 s at 55-s intervals. The physically stressed group was transported to the communication box and was given electric foot shocks for one h (8:00–9:00 am) every day; this group was defined as the physically stressed group in this study. The rats in the psychological stress group were placed in a compartment adjacent to the electric foot-shocked animals in the same communication box, but they were not given electric foot shocks. They were instead exposed to emotional stimuli, such as visual, auditory and olfactory sensations from the electric foot-shocked rats of the physically stressed group; this group was defined as the psychologically stressed group in this study. Rat behaviors, hippocampal volume, and GR expression were examined at week 2 and (or) 4, respectively.

Behavior tests-Open field exploration (OFE)

The OFE was performed to explore the locomotors activity and anxiety behavior in rats. Evaluations was carried out in an arena (diameter 45 cm). Each rat was placed at the center of the arena and was allowed to explore it for either 5 or 10 min. The time spent in the central of the arena was quantified, as

well as the time that the rat spent in freezing behavior. Freezing behavior was defined as the absence of any movement of the rat with the exception of those needed for breathing. The movement of the rats was tracked during the habituation phase in the object displacement task, which resembled an open field exploration task, using Mouse Lab Tracker software. The time spent and the path travelled in the center region, defined as a circular region with the center being the center of the arena and radius being one-third the radius of the arena (15 cm), was calculated for further analysis.

MRI acquisition

The rats were anesthetized using urethane (1.25 g/kg) at week 0, 2 and 4 after stress. All MRI data were acquired using a 7 T Bruker PharmaScan system (Bruker Biospin, Ettlingen, Germany) with a 38-mm-diameter bird-cage coil. The rats were restrained in an animal holder with ear pins and a bite bar. For eliminate the motion artifact of body to the greatest extent, the rat's respiratory rate was reduced by intaking appropriate amount of soflurane. Respiration was monitored via a pressure sensor and maintained at 40–50 breaths per minute. Structural T2-weighted images (T2WIs) were obtained using a 2D-rapid acquisition with relaxation enhancement (RARE) sequence with the following parameters: repetition time = 4600 ms, echo time = 30 ms, RARE factor = 4, sampling band width = 100 kHz, flip angle = 90°, FOV = 32 × 32 mm2, matrix size = 256 × 256, pixel size = 125 × 125 μm2, number of slices = 34, slice thickness = 0.3 mm, slice gap = 0 mm, and number of repetitions = 10. Total imaging time was approximately 45 min.

Detection of hippocampal subregion atrophy

Detailed image segmentation schemes have been described in our previouly published methods (Li et al. 2017b). The segmentation of hippocampal subfields were implemented using Mimics 15.0 and 3-matic 7.0 (http://www.materialise.com). In the MIMICS software, each subfield was delineated into different colors of the mask according to different signal thresholds. Based on the reconstruction of these masks, the volume and 3D images of the hippocampus and its subfields were obtained. Accounting for variations in brain sizes, hippocampal volume was normalized to the intra-cranial volume (ICV), which was extracted based on the Pulse Coupled Neural Network (PCNN) method Fig. 1.

Immunofluorescence

The rats were anaesthetized using calipsol (75 mg/kg), and they were perfused transcardially using 4% formaldehyde in 0.1 M phosphate buffer. After perfusion, the brains were isolated and were postfixed overnight in the same fixative at 4 °C. On the next day, they were cut into serial 50-μm-thick coronal slices using a vibratome. Free-floating brain slices containing the hippocampus were washed with 0.1 M phosphate buffer, were additionally fixed using 50% ethanol for 20 min and were immersed in blocking solution containing 1% normal goat serum and 0.3% TritonX-100. The frozen sections were mounted on Silane-coated slide glass and coverslipped with Gelvatol (20% polyvinyl alcohol and glycerol mixture). They were viewed using a confocal laser microscope (20 × 0.40 NA objective, FV1000-BX61WI, Olympus, Japan). For immunofluorescent staining, the mounted sections were incubated with the antibody against rat GR diluted 1:1000 (24050–1-AP, Proteintech, USA) at 4 °C after blocking with bovine serum albumin in a humidified chamber. After rinsing the first antibody from the sections, they were incubated with IgG labelled with Alexa Fluor 488 (Molecular Probes, USA) diluted 1:1000 for 2 h at room temperature and subsequently were coverslipped with Gelvatol. Controls sections were incubated with equal amounts of normal IgG (Santa Cruz Biotechnology, USA), which were used as substitute for the primary antibody. Additionally, secondary fluorescent labels were swapped to check cross-reactivity and sections were incubated without any primary antibodies to check for any aspecific binding of the secondary antibodies.

Statistical analyses

A repeated variance analysis was used in the experimental design. All data were presented as the mean ± standard deviation (SD). Data were analyzed using one or two-way analysis of variance (ANOVA) and Tukey's post-hoc honest significant difference (HSD) test. For correction of multiple

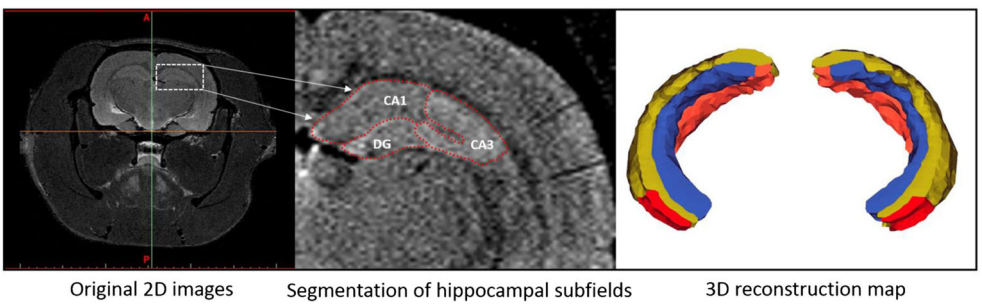

Fig. 1 Segmentation and reconstruction of the subfields of hippocampus

comparisons, the Bonferroni corrections were applied to the comparisons of subfield volume in each hippocampus of the rats to correct for multiple comparisons ($p < 0.05$). Graphpad Prism 5 (GraphPad Software, Inc., La Jolla, CA) was utilized to create statistical graphs. The results were considered significant at $P < 0.05$.

Results

Differences between the physical and psychological stress response at 2 weeks

At this stage, only a decrease in GR expression in CA1 and the volume atrophy of CA1 were found in the physical stress group ($F = 5.003$, $p = 0.009$). In addition, behavioral abnormalities were found in rats in the physical stress group, which spent less time in the centre of the arena ($F = 2.916$, $P = 0.041$), as shown in Fig. 2.

Differences between the physical and psychological stress response at four weeks

At this stage, GR expression in both the CA3 and DG groups and their volume were decreased significantly in the physical stress group ($F = 5.716$, $P = 0.008$; $F = 6.104$, $P = 0.006$), and significant behavioral abnormalities were found ($F = 2.887$, $P = 0.038$). In addition, GR expression in all hippocampal subfields (CA1, CA3, DG) and their volumes were decreased significantly in the psychological stress group ($F = 7.251$, $P = 0.003$; $F = 3.157$, $P = 0.033$; $F = 2.818$, $P = 0.030$), and significant behavioral abnormalities were found ($F = 3.099$, $P = 0.034$), as shown in Fig. 3.

Differences between physical and psychological stress response at six weeks

At this stage, only further decrease of GR expression in the CA3 and volume atrophy of the CA3 were found in the physical stress group ($F = 3.024$, $P = 0.031$), and more significant behavioral abnormalities were found ($F = 2.997$, $P = 0.036$). In addition, GR expression in both the CA3 and DG and their volumes were further decreased by psychological stress ($F = 7.755$, $P = 0.003$; $F = 6.286$, $P = 0.004$), and more significant behavioral abnormalities were found ($F = 5.517$, $P = 0.008$), as shown in Fig. 4.

Differences in comprehensive comparison

First, the results of this analysis showed that hippocampal atrophy and behavioral abnormalities were found at two weeks under physical stress but did not appear until the fourth week under psychological stress. Second, the effects of stress were more pronouncedin the physical group than in the psychological group at the fourth week, but it had reversed by the sixth week. That is, the effects of physical stress appeared earlier but were mild, whereas the effects of psychological stress appeared later but increased sharply. Furthermore, the most notable difference between the groups was that the DG volume was still decreasing at six weeks under psychological stress, and the final volume was significantly smaller than that of the physical stress group, as shown in Fig. 5.

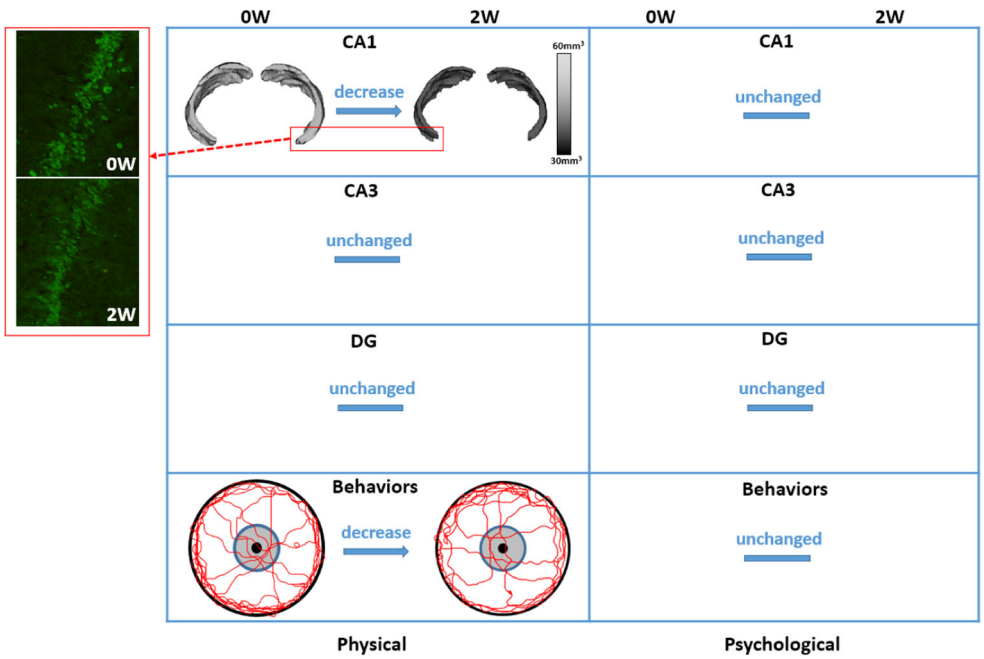

Fig. 2 Changes in two stressors at 2 weeks. Only decreases in the GR expression in CA1, the volume atrophy of CA1, and behavioral abnormalities were found in the physical stress. Immunofluorescence staining for GR in CA3. Immunofluorescence staining for GR were taken using a confocal FV1000-BX61WI microscope (Olympus, Japan), 20 × 0.40 NA objective (Olympus, Japan)

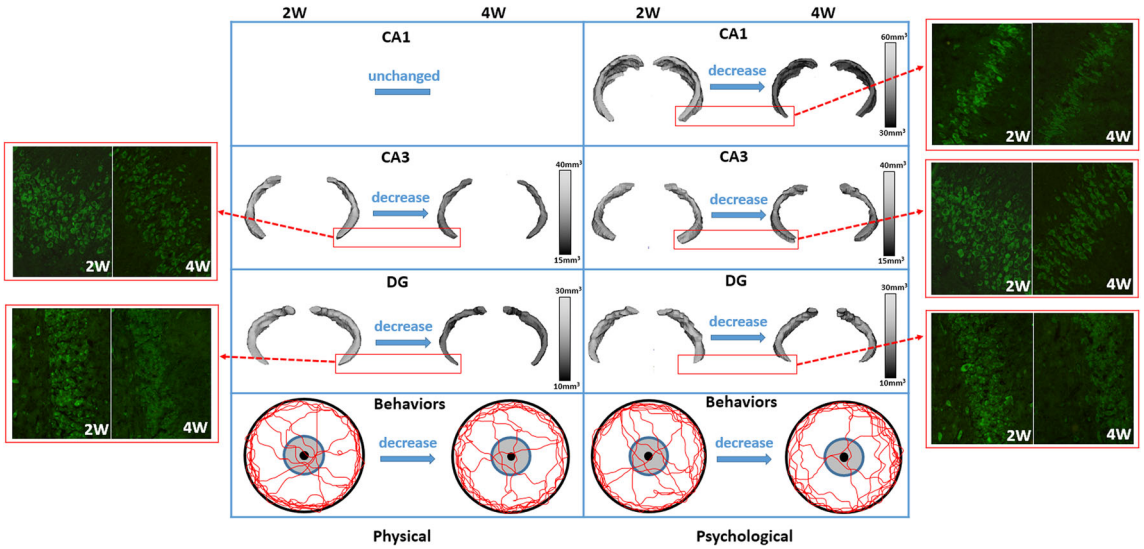

Fig. 3 Changes in two stressors at four weeks. The decrease in GR expression in the CA3 and DG, the volume atrophy of the CA3 and DG, and further behavioral abnormalities were found in the physical stress group, while GR expression in all hippocampal subfields (CA1, CA3, DG), the volume atrophy of all subfields, and the significant behavioral abnormalities were also found in the physical stress. Immunofluorescence staining for GR were taken using a confocal FV1000-BX61WI microscope (Olympus, Japan), 20 × 0.40 NA objective (Olympus, Japan)

Follow-up after 6 weeks of housing in normal environment

Twelve rats were randomly selected at four weeks (physical stress group 6 rats, psychological stress 6 rats), and another 12 rats were randomly selected from the rats with stress for 6 weeks (physical stress group 6 rats, psychological stress 6 rats). After 6 weeks of housing in a normal environment, the behaviors of these rats and volume of hippocampal subfield were evaluated. No change was found in rats that had experienced 6 weeks of psychological stress, whereas rats that experienced both 4 and 6 weeks of physical stress showed a recovery of DG volume and behaviors. Interestingly, this recovery could also be found in rats experiencing 4 weeks of psychological stress Fig. 6.

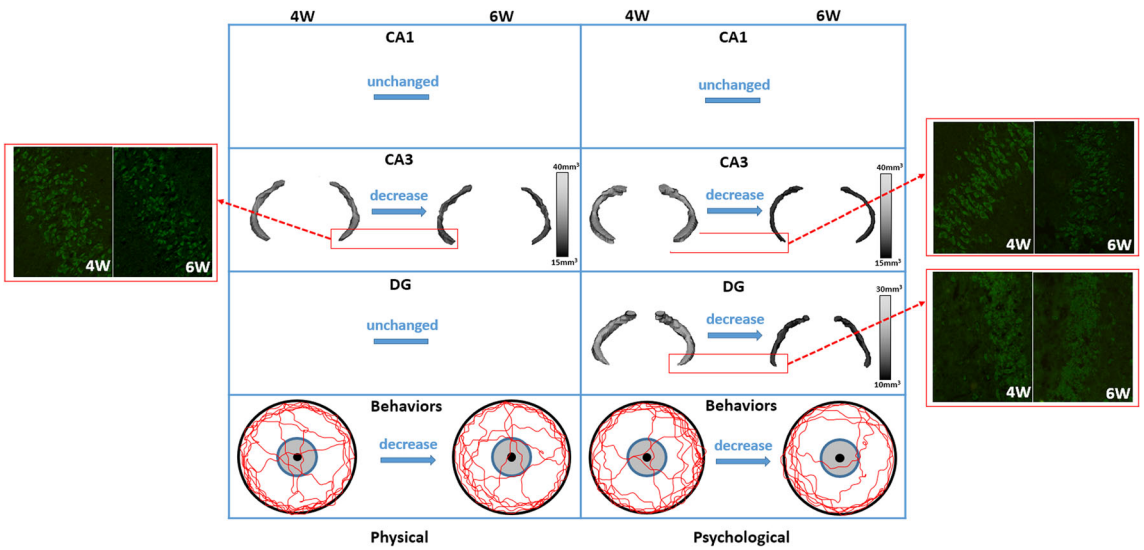

Fig. 4 Changes in two stressors at six weeks. The decrease of GR expression in the CA3, the volume atrophy of the CA3, and further behavioral abnormalities were still found in the physical stress group, while GR expression in the CA3 and DG, the volume atrophy of the CA3 and DG, and more significant behavioral abnormalities were found in the physical stress. Immunofluorescence staining for GR were taken using a confocal FV1000-BX61WI microscope (Olympus, Japan), 20 × 0.40 NA objective (Olympus, Japan)

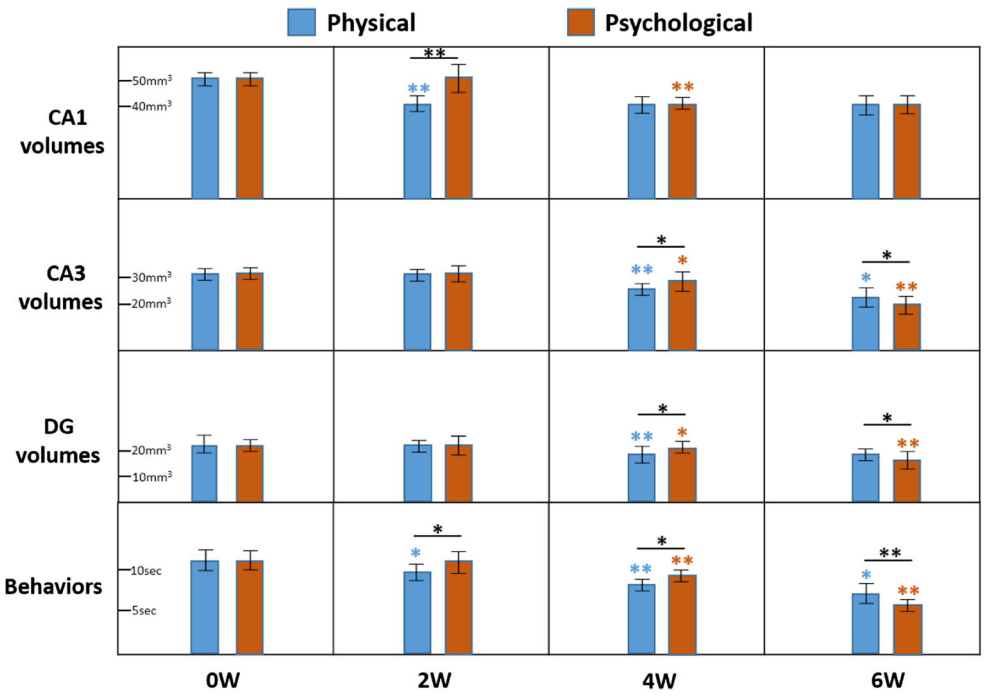

Fig. 5 Comprehensive comparison. The intra-group differences were compared longitudinally, and the inter-group differences were compared by cross section. Statistical significance was determined using ANOVA followed by Tukey's post hoc HSD test. *denoted $P < 0.05$; **denoted $P < 0.01$

Discussion

In this present study, differences in rat behaviors, GR expression and structural atrophy in male rat hippocampal subfields were first shown under physical vs. psychological stress using OPE, immunofluorescence, and 3D neuroimaging. This study showed that the effects of physical stress appeared early but were relatively moderate, whereas the effects of psychological

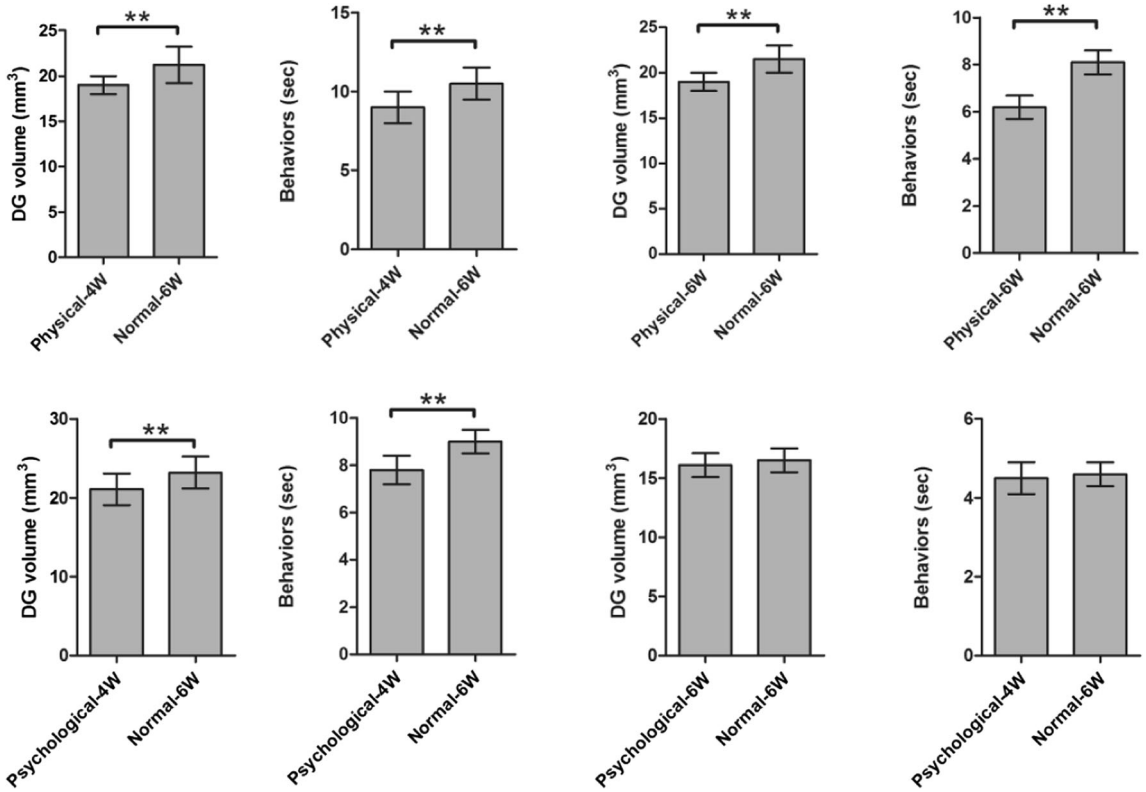

Fig. 6 Changes in two stressors at sixth weeks after housing in normal environment. Rats experienced 4 or 6 weeks of physical stress. Those that experienced 4 weeks of physical stress showed significant recovery, whereas the rats that experienced 6 weeks of psychological stress did not. *denoted $P < 0.05$; **denoted $P < 0.01$

stress appeared later but were more severe. In addition, compared with the physical stress group and the psychological stress group at four weeks, GR-mediated DG injury was still be found in the psychological stress group at six weeks, which might be the cause of further reduction inDG volume; andbehaviors could not be recovered after 6 weeks of housing in a normal environment.

The hippocampus is an anatomically complex structure that is composed of multiple subfields (Wisse et al. 2012). As different hippocampal subfields have different cellular and molecular characteristics (Keuker et al. 2004), they are considered differentially vulnerable to processes associated with stress (Datson et al. 2013). Studying the morphometry of hippocampal subfields is crucial in neuroscience research because changes in these structures may be helpful in discovering the pathological causes of memory deficits. As a noninvasive examination method, structural MRI is one of the most important tools for monitoring hippocampal atrophy in clinical and animal studies (Lee et al. 2009). Attributed to the use of UHF MRI, more detailed studies of hippocampal subfields atrophy have been performed in recent years. Certain studies on human hippocampal subfield atrophy have found important information related to the clinical symptoms of mental illnesses; e.g., unmediated major depressive disorder participants had a smaller DG volume (Travis et al. 2015), higher levels of perceived stress were associated with smaller CA2/CA3 volume in older adults (Zimmerman et al. 2016), and DG volume was decreased and associated with depressive episodes (Cao et al. 2017). Unfortunately, previous studies on volume changes in rat hippocampal subfields of under stress models are scarce. Although we had recently reported atrophy in the hippocampal subfields of rats under CUMS (Li et al. 2017b), one important deficiency in that paper was that our research used only one stress model, physical stress, and ignored psychological stress, a stress-mimic model that is more similar to mental disorders. In fact, it is becoming more important to analyse mental disorders under both types of stress condition.

The characterization of stress-specific increases in circulating adrenocorticotropic hormone (ACTH) and corticosterone (CORT) levels by several laboratories supports the discriminative capacity of the HPA axis to respond to different stressors, particularly physical vs. psychological stress (Burton et al. 2007). Because the stress-induced activation of the HPA is mediated by central neural mechanisms, it is likely that the variation in the magnitude of CORT responses to stress reflects differential activation effects of experimental stressors on the neural circuitry mediating this and other alterations in peripheral endocrine function (Sutoo and Akiyama 2002). In our study, we found that rats showed different behaviors, GR expression levels and magnitudes of hippocampal subfields atrophy under physical vs. psychological stress and that the effects of physical stress appeared early but were relatively moderate, whereas the effects of psychological stress appeared later but were more severe. Several studies had reported that the effects of psychological stress were more significant than those of physical stress; for example, the ethanol-induced sleeping time in physically stressed mice was significantly more than that of psychological stressed mice, and physical stress-induced behavioral anomalies in adult rats usually disappeared after 6 weeks of housing in a normal environment, but this phenomenon was not found in rat models of psychological stress (Bai et al. 2012). Our results were consistent with the outcomes reported in the literature. It should be noted that not all psychological stress-induced behavioral abnormalities could not be reversed after housing in a normal environment. Our results showed that recovery could be found in rats that experienced 4 weeks of psychological stress; and yet an absence of recovery was only found in rats that experienced 6 weeks of psychological stress. In fact, it might be the more serious injury in DG subfield (the famous nerve regeneration area) of rats experienced 6 weeks of psychological stress that caused of the failure to recover.

Damage to the hippocampus, which is a key grey-matter nucleus of the limbic system, is closely associated with behavioral abnormalities in mental disorders (Anacker et al. 2018). In the present study, the atrophy of the hippocampal subfields showed unique characteristics under stress. In our results, atrophy was first found in CA1 subfield, which indicated that CA1 showed the highest sensitivity to stress. Although both CA3 and DG showed significant atrophy in subsequent observations, no permanent atrophy of the DG was found under weaker physical stress, but it continued to shrink under strong psychological stress, which indicates that a medium sensitivity to stress was found in the CA3 and the lowest sensitivity was found in the DG. These results in this part were consistent with those of other neurobiological studies on the hippocampal subfields (Datson et al. 2013; Buresh et al. 1999), which proved that the damage tolerance of the CA1 was the lowest and that of the DG was the highest. In the brain of adult rodents, there are two neural stem cell groups (that can be differentiated into neurons and glial cells), which are located in the subventricular zone (SVZ) and the subgranular zone (SGZ) of the DG (Taupin 2005). The regenerative ability in the SGZ maybe perfectly explained the strong stress resistance of the DG, and suggested the excessive DG injury induced by six weeks of psychological stress might damage this nerve regenerative ability and neural plasticity.

Our study has several limitations that should be considered in future studies. i) Both type I and II errors might have been caused by the small sample size in our experiments. ii) Additionally, GR expression and atrophy of the hippocampal subfields under physical psychological stress were assessed every 2 weeks; however, the dynamics of these changes may be more accurately determined if they are measured over a 1-week cycle or even shorter period. iii) Because the method of

immunofluorescence that we used could not determine GR expression in the subiculum, this subfield was not included in this experiment.

In conclusion, we dynamically elaborated the differences of physical vs. psychological stress. Our findings may provide an important reference for related studies.

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Compliance with ethical standards

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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