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Chronic paradoxical sleep deprivation-induced depressionlike behavior, energy metabolism and microbial changes in rats

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ABSTRACT

Aims: Given the lasting impact of chronic paradoxical sleep deprivation (PSD) on behavior and organism metabolic alternations, along with the role of the microbiome in neurobehavioral development and metabolism, we sought to examine the relationship between the microbiota and chronic PSD-induced behavioral and metabolic changes.

Materials and methods: Psychological status of 7-day PSD (7d-PSD) male rats was tested by behavioral method, serum inflammatory cytokines and hypothalamic-pituitary-adrenal (HPA) axis-related hormones. In addition, GC–MS based urine metabolomics and 16S rRNA gene sequencing approaches were applied to estimate the influences of chronic PSD on host metabolism and gut-microbiota. Furtherly, microbial functional prediction and Spearman's correlation analysis were implemented to manifest the relations between the differential urinary metabolites and gut microbiota.

Key findings: 7d-PSD rats displayed depression-like behavior, metabolic and microbial changes. By integrating differential gut bacteria with indicators of depression and differential metabolites, we found that the alterations of *Akkermansia*, *Oscillospira*, *Ruminococcus*, *Parabacteroides*, *Aggregatibacter* and *Phascolarctobacterium* were closely related to abnormalities of depression symptoms and inflammatory cytokines. These bacteria also had close connections with host energy metabolism concerning arginine and proline metabolism, glycine, serine and threonine metabolism, and glyoxylate and dicarboxylate metabolism, pyruvate metabolism, which overlapped with the results of 16S rRNA gene function annotation.

Significance: These data suggest that a specific situation of circadian disturbance, chronic PSD-induced alterations in gut microbiota and related host changes in metabolism may be the pathogenesis of depression.

Abbreviations: ACTH, adrenocorticotropic hormone; CORT, corticosterone; CRH, corticotropin-releasing hormone; CRP, C-reactive protein; FST, forced swimming test; IBD, irritable bowel syndrome; IL-6, interleukin-6; MDD, major depressive disorder; OPLS-DA, orthogonal projections to latent structures discriminant analysis; OFT, open field test; OTUs, operational taxonomic units; PCA, principal component analysis; PICRUSt, Phylogenetic Investigation of Communities by Reconstruction of Unobserved States; PSD, paradoxical sleep deprivation; SD, sleep deprivation; SPT, sucrose preference test; TCA, tricarboxylic acid; TNF-α, tumor necrosis factor alfa; TST, tail suspension test; VIP, variable importance on projection

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1. Introduction

Sleep disorder is a highly encountered phenomenon affecting millions of depressed patients worldwide, and has been adapted into the diagnostic criteria for major depressive disorder (MDD) [1,2]. Despite short-term or acute paradoxical sleep deprivation (PSD) has been reported as a therapeutic option for depressive disorder [3–5], PSD can influence mood [6] and cognitive state [7,8], and initiate depressive behavior [9–11]. Notably, researches have shown that long-term consecutive or intermittent PSD could alter monoamine neurotransmitters (norepinephrine, serotonin), serotonin metabolite (5-hydroxyindoleacetic acid) and related degrading enzyme (monoamine oxidase A) content, as well as increase neuro-inflammatory cytokines (IL-1β and TNF-α), microglial activation and neuronal apoptosis in the brain [10–12]. Nevertheless, lacking systematic assessments is a critical gap to cognize the holistic impact of chronic PSD on depression.

Metabolomics, a versatile systematical biology approach, is widely used in the discovery of molecular biomarkers, the diagnosis or prognosis of clinical diseases [13,14]. Previous metabolomics studies of human urine and serum [15,16] suggested that 24-h SD could lead to widespread disturbance of metabolic profiling. Our previous work also demonstrated that chronic PSD could induce metabolites abnormities in brain tissue, serum and urine, which were involved in neurotransmitters and branched chain amino acids metabolism, adenosine metabolism, energy expenditure and oxidative stress metabolism, nicotinate and nicotinamide metabolism, glyoxylate and dicarboxylate metabolism, glycine, serine, and threonine metabolism, and arginine and proline metabolism [17,18]. Most of them were also reported in other literatures on MDD [19–23] or chronic sleep disorder [24–26]. These results highlighted the link between chronic PSD and mood disorders in form of metabolites.

Gut microbiota, a vital hub of the brain-gut axis, has emerged as a versatile player in emotional processing, behavior regulation [27], as well as metabolic processing, energy production and immune cell development [28–30]. In fact, bacterial supplements (*Bifidobacterium* and *Lactobacillus* strains) have been reported to alleviate depressive symptoms and improve poor sleep quality inflicted by psychological stress [31–33]. In the meanwhile, gut microbiota is readily vulnerable to various environmental factors, including life stress and pathophysiological states [34,35]. Gut microbiota composition was altered in both short term [36] and chronic PSD [37]. It's noteworthy that some strains, such as *Coriobacteriaceae*, *Erysipelotrichaceae*, *Tenericutes*, etc., have same changing trends as the fecal bacteria in MDD patients [38,39]. As gut microbiota dysbiosis has also been verified to influence behavior and mood through the “brain-gut-microbiota” axis [40,41], we sought to determine whether chronic PSD causes behavior and microbiota changes and interrogate how they communicate.

Here, we investigated the alterations in gut microbiota while chronic PSD affected depression-like behavior, pro-inflammatory cytokines and hypothalamic-pituitary-adrenal (HPA) axis, in parallel with associated changes in urinary metabolites. Moreover, in order to elucidate the role of gut microbiota on the brain-gut bidirectional communication, we carried out gut microbiota functional prediction and correlation analysis between altered gut microbiota genera, urinary metabolites and depression indicators in chronic PSD rats.

2. Materials and methods

2.1. Animals

Twenty inbred strain male Wistar rats (240 ± 10 g) were purchased from the Sippr-BK Laboratory Animal Co. Ltd. (Shanghai, China). After 1 week adaption, rats were randomly divided into 2 groups (10 in each group), control group (CON) and seven days paradoxical sleep deprivation group (7d-PSD). Animal welfare and experimental protocols were strictly in accordance with the Guide for the Care and Use of Laboratory Animals as well as the ethics and regulations of Shanghai University of Traditional Chinese Medicine (IACUC Issue No: PZSHUTCM190329001)

2.2. Paradoxical sleep deprivation procedure

PSD procedure for 7 days was carried out as literature reported [42] applying multiple platform method within a few changes. Rats were individually placed into a water tank (170 × 44 × 44 cm), containing a round platforms (6.5-cm-diameter was performed for the PSD group, and 16-cm-diameter was performed for the CON group, both 10-cm-height) rising 1 cm above the water level. A 6.5-cm-diameter platform is small enough to eliminate paradoxical sleep completely. A loss of muscle tonus wakes animals up by falling themselves into water. Water and food were given with free access hanging over the tank in a climate-controlled room (24 ± 1 °C, 55 ± 15%) on a 12 h light/dark schedule (light on at 07:00–19:00). Sleep deprivation box was cleaned and sterilized with 75% alcohol every day. After the last sleep deprivation procedure, rats were subjected to metabolic cages separately for urine and fecal pellets collection with fasting overnight.

2.3. Behavioral testing

Behavioral study took place between 17:00 and 20:00 PM. Exploring behavior was evaluated applying the open field test (OFT); anti-depressant behavior was evaluated using the forced swimming test (FST) and tail suspension test (TST); and anhedonia was assessed using the sucrose preference test (SPT) as previously established [43,44] (details can be seen in Supplement). None of other behavioral tests took fasting behavior except that all rats were deprived of food and water 24 h before SPT test.

After the last time of behavioral testing, rats were fasted 6 h before euthanasia. The experimental design and time schedule were shown in Supplemental Fig. 1.

2.4. Biochemical detection in serum

Frozen aliquots of serum samples were thawed firstly on ice. Subsequently, commercial ELISA kits were used to detect the levels of interleukin-6 (IL-6), tumor necrosis factor alfa (TNF-α), C-reactive protein (CRP), adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH), and corticosterone (CORT) in serum, following the instructions provided by the manufacturer (Cusabio Biotech Co. Ltd., Wuhan, China).

2.5. Urine metabolic profiling

2.5.1. Sample preparation, derivatization and spectral acquisition

Urine sample preparation was conducted following our previous research [45]. Samples were thaw on ice, and 200 μL aliquot was added into a 1.5 mL tube and centrifuged at 13, 000 rpm for 10 min at 4 °C. Afterwards, 50 μL supernatant was transferred into a new tube followed by adding 70 μL urease (100 U/mg), and incubated at 37 °C for 15 min. The metabolite extraction procedure was carried out after adding two internal standard solutions (10 μL tetradecanoic acid and 10 μL heptadecanoic acid in methanol, both 1 mg/mL) and 800 μL methanol. After vortexing for 1 min, the mixture was centrifuged at 13,000 rpm for 5 min. 200 μL supernatant was transferred to a glass tube and dried in a nitrogen atmosphere using blowing nitrogen analyzer at 30 °C. The dried extract aforementioned was derivatized into its methoxime derivatives using a two-step procedure same as our published method before [46].

Each 1 μL aliquot of analyte was injected into a DB-5MS capillary column coated with 5% diphenyl cross-linked 95% dimethylpolysiloxane (30 m × 250 μm, film thickness 0.25 μm, Agilent J&W Scientific, Folsom, CA) in GC–MS analysis system (Agilent 7890B/5977A, GC/

MSD system), and the solvent delay time was set to 5 min. The temperatures of the injector, the EI iron source, and interface were set to 280 °C, 230 °C, and 260 °C, respectively. The flow rate of helium carrier gas was controlled at a steady rate of 1 mL/min. The column temperature was initially kept at 70 °C for 2 min and increased to 160 °C at a rate of 2.5 °C min^{-1}, then raised to 240 °C at a rate of 10 °C min^{-1} and maintained at that temperature for 16 min. Electron impact ionization (70 eV) at full scan mode (m/z 30–550) was acquired [47].

2.5.2. Urine GC–MS data processing and multivariate analysis

GC–MS raw files were converted into easily identified Net-CDF format using Agilent MSD workstation, and subsequently pretreated according to our previous published work [48]. The resulting three-dimensional matrix involving peak index (RT-m/z pair), sample numbers (observations), and normalized peak area percent were subject to SIMCA-P 11.0 software package (Umetrics, Umeå, Sweden) for multivariate statistical analysis. Principal component analysis (PCA) was utilized to display natural separation among two groups. Orthogonal projections to latent structures discriminant analysis (OPLS-DA) was employed to strengthen classification between groups as well as extract discriminating metabolic ions. OPLS-DA pattern brought about two key parameters: R^2Y (cumulative model variation in Y) and Q^2 (the cumulative predicted variation of the pattern). As these parameters approached 1.0, a robust model with predictive reliability was suggested. The result was presented in the form of the score plot, where each point represented an individual sample. The significant variables selected from the OPLS-DA pattern with variable importance on projection (VIP) value > 1.0, were validated with the nonparametric Mann-Whitney U test. Fold-change was calculated as the normalized relative average mass response value ratio between two groups.

2.5.3. Discriminating metabolites identification and pathway analysis

Discriminating compound identification was performed as our identification method before [45]. In addition, the Human Metabolome Database (HMDB; http://www.hmdb.ca/) was applied to confirm whether identified compounds were endogenous metabolites. Finally, MetaboAnalyst 3.0 (http://www.metaboanalyst.ca/) was utilized [49,50] to excavate the pathways behind identified significant endogenous metabolites.

2.6. 16S rRNA microbial community analysis

2.6.1. Bacterial DNA extraction and 16S rRNA amplicon pyrosequencing

The 16S rRNA analysis of fecal samples was performed at Personalbio (Shanghai, China). Total fecal DNA was extracted using the DNA Fast Stool extraction kit (Qiagen, Hilden, Germany) (see Supplement).

2.6.2. Sequence analysis, bacterial community characterization and function annotation

The raw sequenced reads were further disposed by firstly quality screening to obtain valid sequence for each sample, and secondly elimination of interrogative sequences utilizing Flash and Qiime software. The quality filtered sequences were clustered into operational taxonomic units (OTUs) by UCLUST method [51] with a threshold of 97% sequence similarity and the representative sequence with the highest abundance was assigned taxonomically by BLAST method [52] by Green genes Database [53]. Alpha diversity indexes (Chao1, ACE, Simpson and Shannon) were calculated to evaluate species richness and evenness. Beta diversity analyses were used by employing PCA based on the Bray-Curtis distance to inspect the similarity of gut microbial community structure among samples. The microbial community structure in phylum and genus of different samples were also described via Qiime software. For gut microbial function annotation, the current 16S rRNA gene sequencing data were compared with known functional spectrum database-KEGG Pathway Database (http://www.genome.jp/kegg/pathway.html), by means of Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt) approach [54], so as to predict the metabolic function of microbiota.

2.7. Data statistical analysis

Statistical analyses were performed using the Statistical Package for Social Science program (SPSS 21.0, Chicago, USA). Data from behavioral test and biochemical index were analyzed by two tailed Student's t-test. For other nonparametric data, the nonparametric Mann−Whitney U test was used. Pearson correlation analysis was performed using correlation coefficients ($|r| > 0.4$). Statistical significance was set at $P < 0.05$. GraphPad 6.0 and OriginPro 9.0 software were used to draw pictures.

3. Results

3.1. Chronic PSD induced a depression-like behavioral phenotype and led to elevated levels of inflammatory cytokines and hyper-activated HPA axis in rats

3.1.1. Depression-related behavior

Chronic PSD remarkably decreased total behavioral score in OFT and increased total immobility time in FST and TST ($P < 0.001$). Simultaneously, reduced consumption for sucrose in SPT ($P < 0.05$) was also observed (Supplemental Fig. 2).

3.1.2. Pro-inflammatory response

Chronic PSD for 7 days resulted in higher levels of serum pro-inflammatory cytokines including IL-6, TNF-α, and CRP with P values < 0.001, 0.01 and 0.001, respectively (Table 1).

3.1.3. Endocrine response

Serum levels of CRH, ACTH and CORT were strongly up-regulated ($P < 0.05$, 0.05 and 0.01, respectively) after PSD (Table 1), as a signal for hyper-activated HPA axis.

3.2. Chronic PSD altered global urinary metabolic profiling in rats

Obvious separation was observed between CON and 7d-PSD rats in PCA and OPLS-DA score plots (Supplemental Fig. 3a, b), suggesting discrepant metabolic profiling between two groups. Based on OPLS-DA plot, differential icons were obtained and highlighted in red square (Fig. 1a). After identification, 18 metabolites were differentially expressed between two groups as shown in heatmap (Fig. 1b). The detailed messages of differential metabolites were listed in Table 2. Pathway analysis obtained five pathways with impact value > 0.1. They were: (a) glyoxylate and dicarboxylate metabolism, (b) glycine, serine and threonine metabolism, (c) nicotinate and nicotinamide metabolism, (d) beta-Alanine metabolism, (e) pyruvate metabolism and (f) arginine and proline metabolism (Fig. 1c).

Table 1
Effects of seven days consecutive PSD on depression related serum indicators.

	Parameter	CON (n = 10)	7d-PSD (n = 10)
Serum cytokines	IL-6 (pg/mL)	9.30 ± 0.74	15.76 ± 1.30***
	TNF-α (pg/mL)	6.35 ± 0.31	11.61 ± 1.33**
	CRP (ng/mL)	19.70 ± 3·80	72.37 ± 8.01***
Serum hormones	CRH (ng/L)	56.05 ± 8.08	63.77 ± 7.68*
	ACTH (ng/L)	39.08 ± 3.63	44.32 ± 2.94*
	CORT (ng/L)	125.60 ± 11.93	219.42 ± 17.50**

All data in the table are described as mean ± SD.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

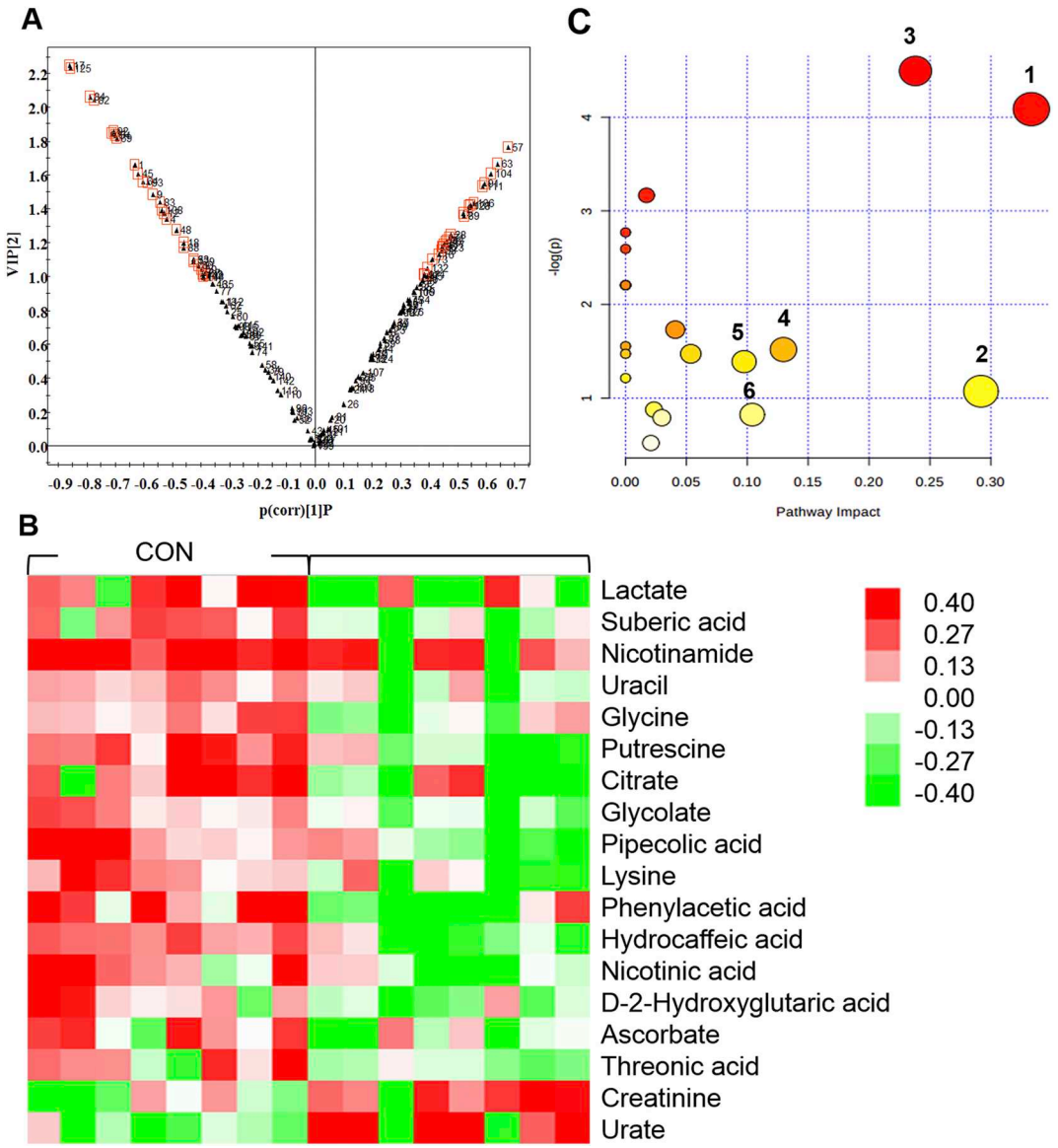

Fig. 1. Urine metabolic analysis results in response to 7d-PSD treatment. **a** V-plots between pairwise groups based on OPLS-DA pattern analysis. **b** A heat map describing significant differences of urinary metabolites between CON and 7d-PSD group. **c** Pathway analysis of differential metabolites with MetaboAnalyst 3.0, (1) glyoxylate and dicarboxylate metabolism; (2) glycine, serine and threonine metabolism; (3) nicotinate and nicotinamide metabolism; (4) beta-Alanine metabolism; (5) Pyruvate metabolism; (6) arginine and proline metabolism.

3.3. Chronic PSD modulated gut microbial community profiling in rats

3.3.1. Sequencing depth and α-diversity analysis

Sequencing depth was examined firstly. The Chao1 rarefaction curve in two groups reached plateaus (Supplemental Fig. 4a), suggesting sufficient sequencing depth for diversity of the bacteria. The analysis of α-diversity indicated a higher microbial diversity in CON than in 7d-PSD (Table 3). Furthermore, clearly segregated bacterial composition between two groups by the PCA confirmed this inference (Supplemental Fig. 4b and Supplement).

3.3.2. Bacterial distribution and abundance

Chronic PSD significantly altered bacterial composition in phylum and genus levels (Supplemental Fig. 5) relative to CON. The differential bacteria were displayed in a box plot (Fig. 2). *Firmicutes*, *Verrucomicrobia*, *Proteobacteria* and *Bacteroidetes* were the four most predominant bacterial phyla, totally accounting for > 80% of the bacterial sequences in two groups (see Supplement). Referring to the bacterial genera, *Akkermansia* ($P < 0.01$) was distinctly decreased. Nevertheless, *Oscillospira Parabacteroides*, *Ruminococcus*, *Phascolarctobacterium* and *Aggregatibacter* were markedly enriched in 7d-PSD group ($P < 0.05$).

3.3.3. Function prediction of the bacterial community

Bio-functions of the bacterial community were predicted from bacterial sequences data applying PICRUSt software. All the functional genes were divided into 6 categories, including metabolism, genetic information processing, environmental information processing, cellular processes, organismal systems, and human diseases. At level II, 41 classified KEGG ortholog groups were represented in the data set (Supplemental Table 1). Among these genes, diseases-related genes were compared between two groups. In 7d-PSD group, the genes relevant to neurodegenerative diseases ($P < 0.001$), immune system

Table 2
List of differential metabolites for discrimination between CON and 7d-PSD group.

No.	Retention time (min)	Metabolites	VIP score[a]	*P* value[a]	Fold change[b]	Pathway
U1	5.39	Lactate	1.59	0.021	0.51	Pyruvate metabolism
U2	5.62	Glycolate	1.77	0.001	0.37	Glyoxylate and dicarboxylate metabolism
U3	8.87	Nicotinic acid	1.24	0.012	0.48	Nicotinate and nicotinamide metabolism
U4	8.93	Phenylacetic acid	1.66	0.005	0.43	Phenylalanine metabolism
U5	9.01	Glycine	1.54	0.012	0.48	Glycine, serine and threonine metabolism
U6	9.98	Pipecolinic acid	1.48	0.012	0.48	Lysine degradation
U7	12.14	Nicotinamide	1.75	0.012	1.08	Nicotinate and nicotinamide metabolism
U8	12.25	Alanine	1.58	0.009	0.46	beta-Alanine metabolism
U9	13.66	Creatinine	1.60	0.012	2.09	–
U10	13.79	Threonic acid	1.48	0.027	0.53	–
U11	14.15	D-2-Hydroxyglutaric acid	1.16	0.016	0.49	–
U12	14.32	Suberic acid	1.72	0.012	0.48	–
U13	17.81	Putrescine	1.91	0.002	0.39	Arginine and proline metabolism
U14	19.91	Citrate	1.48	0.021	0.51	Glyoxylate and dicarboxylate metabolism
U15	22.24	Lysine	1.32	0.016	0.49	Biotin metabolism
U16	22.73	Hydrocaffeic acid	1.48	0.036	0.36	Aminoacyl-tRNA biosynthesis
U17	26.30	Urate	2.10	0.001	1.83	Purine metabolism
U18	33.58	Ascorbate	1.40	0.027	0.53	Purine metabolism

Note: VIP score was from the PLS-DA model and the P value came from Mann–Whitney U analysis.
[a] Only metabolites with VIP value > 1.0 and *P*-values < 0.05 were considered statistically significant.
[b] Fold change was calculated as the average peak area between the two classes (i.e., Fold change = SD / CON). Thus, fold change values of > 1.0 indicate significantly higher levels in SD relative to CON rats, and fold change values of < 1.0 indicate significantly lower levels in SD relative to CON mice.

Table 3
The microbial OTU information, and diversity estimation of the 16S rRNA gene libraries at 97% similarity from the pyrosequencing analysis between 7d-PSD and CON group.

Group	OTU numbers	ACE	Chao 1	Chao1/ACE	Shannon	Simpson
CON	464.75	577.66	465.92	0.81	5.34	0.86
7d-PSD	472.50	544.75	472.50	0.87	4.63**	0.94**

All data in the table are described as mean ± SD, ** $P < 0.01$.

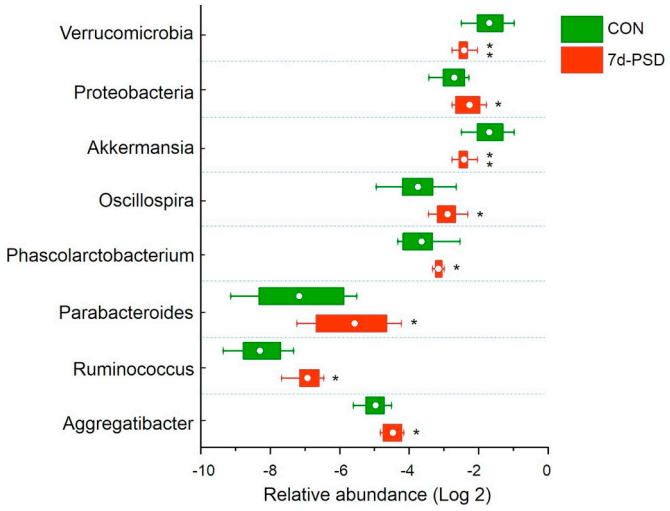

Fig. 2. The relative abundances of differential bacteria were expressed by box plot. Boxes represent the 25th–75th percentile of the distribution; the median is shown as a thick line in the middle of the box; the mean is shown as a circle in the middle of the box; whiskers extend to values with 1.5 times the difference between the 25th and 75th percentiles. Comparing with CON, *$P < 0.05$, **$P < 0.01$.

disease ($P < 0.01$) and metabolic diseases ($P < 0.05$) were more abundant (Fig. 3a). In fact, researches have proven that sleep disorders are closely related to these three diseases [55–57]. With further investigation at level III, 141 metabolic pathways were acquired, which were highly expressed in each sample (Supplemental Table 2). Based on Mann-Whitney *U* test, 64 metabolic pathways were significantly disturbed after PSD paradigm. Among them, 4 pathways displaying higher relative abundance were overlapped with primary metabolic pathway analysis in urine samples. They were pyruvate metabolism, arginine and proline metabolism, glyoxylate and dicarboxylate metabolism, glycine, serine and threonine metabolism (Fig. 3b). Results above suggested that gut microbiota might involve in systemic metabolic pathway changes induced by chronic PSD.

3.4. Gut microbiota correlates with urinary metabolites and depression indicators

Alternations in gut microbiota are correlated with observed depressive behavior, pro-inflammatory cytokines, and differential urinary metabolites ($|r| > 0.4$, $P < 0.05$). The correlating results were displayed in Fig. 4 and detailed in Supplement.

4. Discussion

Mental illness such as depression and bipolar disorder have been demonstrated to be closely related to disruptions in circadian rhythms [58–60]. In particular, subjective or objective sleep–wake cycle alterations are by far the most widely reported circadian disturbances related to depression [61]. Multiple evidence bolsters the view that the sleep disorders give rise to the development of depression [9,62,63]. Chronic PSD has been demonstrated to result in mood related monoaminergic network fluctuation in striatum and hippocampus, as well as cognitive impairment and depressive behavior [11,12]. In this study, we observed that 7 day-PSD markedly triggered depression-related behavior, systemic inflammatory levels and brain HPA axis in rats. Similarly, mice suffering from disturbed day–night cycles also displayed depressed behaviors (decreased latency to immobility and increased immobility time in FST) and imbalanced immune system, such as elevated IL-6 [64]. Elevated systemic pro-inflammatory cytokines and hyper-activated HPA axis were also consistent with previous PSD studies [65]. Chronic low-grade inflammation or elevated HPA axis related hormones were regarded as the causes of depression [66–68]. Accordingly, we propose that a particular case of circadian disruption, chronic

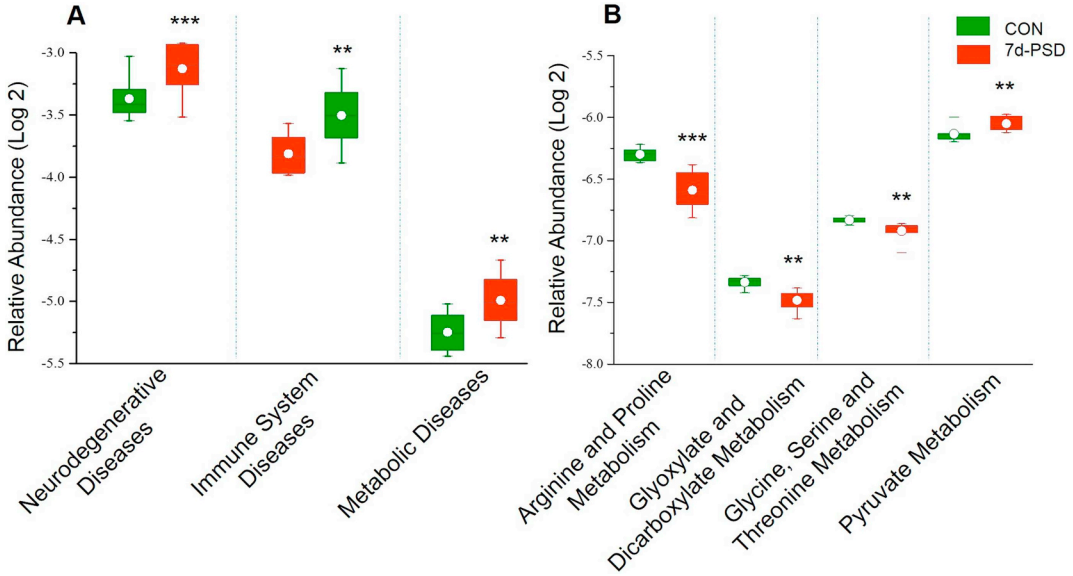

Fig. 3. PICRUSt predicted functions of the gut microbiota relevant to **a** human diseases, and **b** metabolism between CON and 7d-PSD group were expressed by box plot. Boxes represent the 25th–75th percentile of the distribution; the median is shown as a thick line in the middle of the box; the mean is shown as a circle in the middle of the box; whiskers extend to values with 1.5 times the difference between the 25th and 75th percentiles. Comparing with CON, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

PSD can lead to depressive symptoms.

The metabonomic results demonstrated that chronic PSD disturbed energy metabolism (Fig. 5), which was in line with our previous research [17]. Glyoxylate and dicarboxylate metabolism and pyruvate metabolism belong to energy and carbohydrate metabolism, both of which are critical for the tricarboxylic acid cycle (TCA cycle), a central metabolic pathway in aerobic organisms. Glyoxylate and dicarboxylate metabolism regulates TCA cycle by glycolate and citrate. Low urinary concentration of glycolate has been reported to be one of the sex-specific biomarkers for MDD patients [21]. Glycolate can be transformed into serine and glycine, via glyoxylate intermediate. Subsequently, glycine can be turned into pyruvate, which is then converted into acetyl-coenzyme A (acetyl-CoA), and enters the TCA cycle. In addition, glycine, as a co-agonist of *N*-methyl-D-aspartate receptor (NMDAR), which is crucial for controlling synaptic plasticity and memory function, glycine was deceased in periphery, and may serve as a clinical trait-marker for depression [69,70]. Glycine is currently a favored therapeutic target for rapid antidepressant action [71–73]. Under anoxic conditions, pyruvate is reduced to lactate through lactate dehydrogenase (LDH) to generate energy. In addition, lactate participates in synaptic plasticity, and has been viewed as a good biomarker for brain status [74]. Reduced citrate and lactate have been studied to discriminate moderate and severe MDD patients [49].

Arginine and proline metabolism, a primary pathway for the biosynthesis of the amino acids arginine and proline, was also reported significantly disturbed in the prefrontal cortex of learned helplessness rat model in metabolomics study [23]. Studies have shown that polyamines enhanced phosphorylation processes, and phosphorylation of functional proteins in neurons might be involved in the therapeutic mechanisms of antidepressants [75]. For instance, hippocampal putrescine in rats was reduced in depressive stress model [76]. However, intraperitoneally injection of putrescine promoted depressant-like phenotype [77]. Thus, we proposed that the reduction of putrescine in urine can be used as a biomarker for the diagnosis of depression.

In a previous study of sleep restricted rats [78], only one bacterium, TM7-3a was found to be increased in sleep restricted rats induced by forced locomotion. This might be due to the fact that rats in this study still had 4 h-sleep per day, as well as the setting of controversial control group. In another study [37], gut microbiota was found to be altered in the level of phyla, order and family as the results of sleep fragmentation paradigm. It is known that forced locomotion, sleep fragmentation and PSD are three main techniques for depriving sleep of laboratory rodents [79]. In this study, we also discovered the microbial composition of PSD rats varied in phylum and genus levels.

A decrease in *Akkermansia* sp. was also found in some stress-related disorders [80]. This species of microbiota is widely studied in obesity and diabetes as a disease-preventing gut bacterium [81,82], and was reported to have a negative connection with autism [83]. *Oscillospira*, belonging to the *Clostridial cluster IV*, is an enigmatic bacterial genus possessing potential importance for human health such as negative association with inflammatory diseases and body mass index [84]. Though remarkably reduced *Oscillospira* was also found in depression related studies [85], higher abundance of this bacteria was found in the gut of obstructive sleep apnea treated mice [86]. This observation implies the necessity of deeply exploring the role of *Oscillospira* in sleep. *Phascolarctobacterium* is regarded as a number of functional core groups in intestinal flora, since this genus has ability to produce propionate. Propionic acid, a common short chain fatty acid, could trigger autism-like behavior in animals or humans [87,88]. Therefore, the increased *Phascolarctobacterium* in this study implied that propionic acid was increased and contributed to depression-like behavior. Studies showed that chronic periodontal disease could increase the incidence of depression [89]. In 7d-PSD group, *Aggregatibacter*, the main pathogenic bacteria of periodontal disease [90], was significantly increased, which may be a cause of depression-like phenotype. Increased *Parabacteroides* in 7d-PSD group was also found in the stool of patients with depression [91]. It was also proved that *Parabacteroides* is the most representative microbial feature of Crohn's diseases, a kind of irritable bowel syndrome (IBD) [92]. Since depression or anxiety disorders are closely related to IBD in clinic [93], and the experimental phenomena of loose

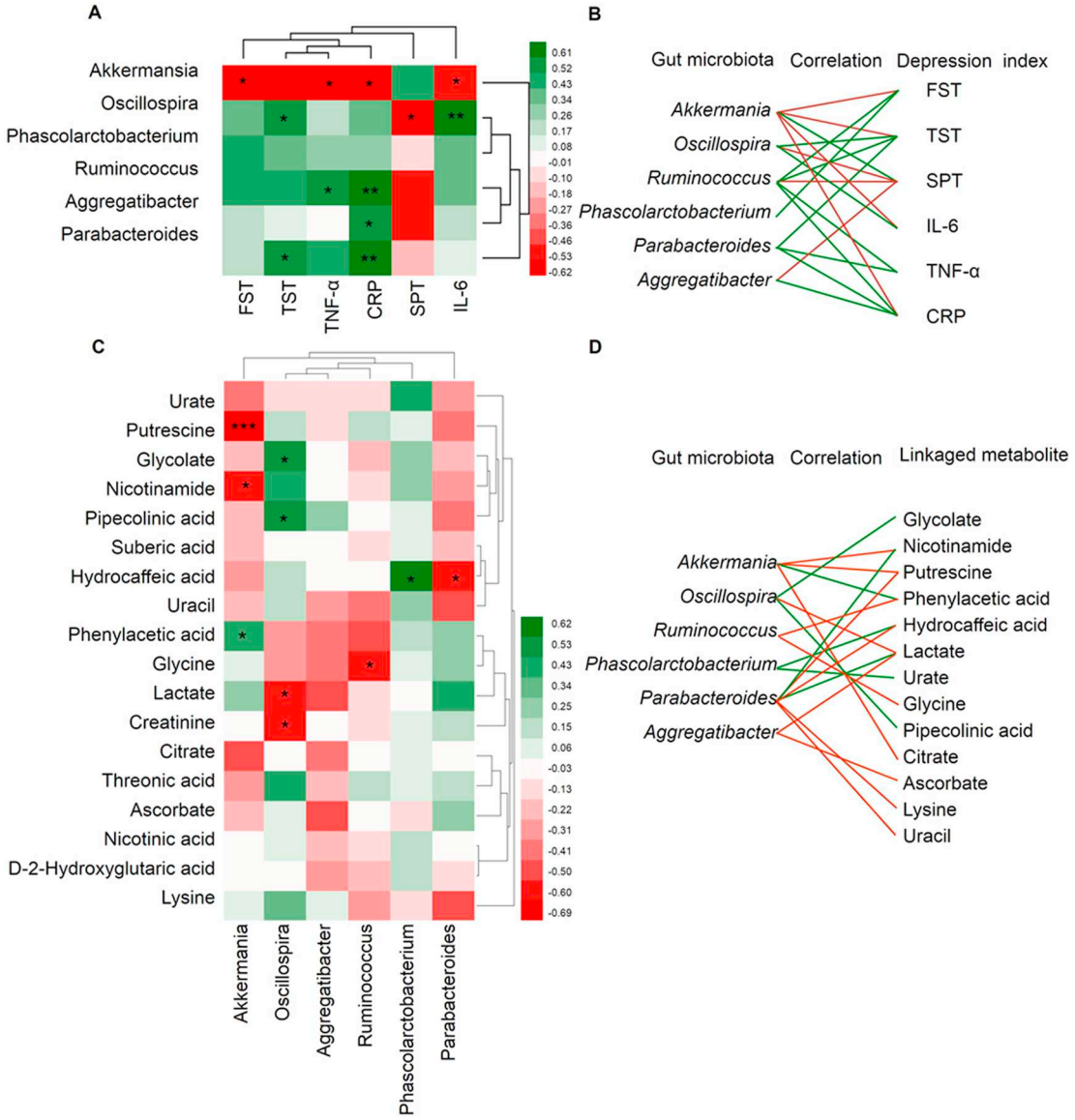

Fig. 4. Correlations between altered gut microbiota genera, depression indicators and urinary metabolites. **a**, **c** Heat maps exhibit notable statistical correlation values (r). Green squares imply significant positive correlations ($r > 0.4$, $P < 0.05$), white squares imply no correlations ($P > 0.05$), and red squares indicates significant negative correlations ($r < -0.4$, $P < 0.05$). The deeper color means the greater correlation ($^{*}P < 0.05$, $^{***}P < 0.001$). **b**, **d** Direction of correlation indicated by green (positive) or red (negative) lines based on $|r| > 0.4$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

stool and reduced food intake were also observed in 7d-PSD rats. *Parabacteroides* may also be used as a microbiological basis for depression phenotype in 7d-PSD rats. *Ruminococcus gnavus* and *Ruminococcus albus* are two species of genus *Ruminococcus*. The former was found enriched in IBD patients, while the later displayed neuroprotective effects on oxidatively stressed cells or animals [94,95]. Therefore, it is worthwhile to further study the classification of *Ruminococcus* at the species level in PSD paradigm.

The above microbiological analysis indicated that the modification of gut microbiota at the genus level in 7d-PSD rats may increase intestinal permeability, which is consistent with the literature report [96]. Changes in intestinal permeability increased the entry of lipopolysaccharides through intestinal barrier into the systemic circulation, triggering the production of pro-inflammatory factors, which is the basis of chronic low-grade inflammation, and is commonly observed in psychiatric disorders [97]. Genes related to 'peptidoglycan biosynthesis', which participates in LPS synthesis, was found more abundant in the microbial functional annotation of 7d-PSD group than that in CON, which may interpret the observed higher serum concentrations of TNF-α, IL-6 and CRP in 7d-PSD group (Supplemental Table 2).

Taken together, the observed behavioral, pro-inflammatory and metabolic alterations induced by PSD might be partly mediated by gut microbiota. The correlation data (Fig. 4) intensely supported this viewpoint. In fact, certain bacterial supplements (*Bifidobacterium* and *Lactobacillus* strains) have been confirmed to alleviate depressive symptoms [31,32]. Microbial functional analysis further strengthened the relationships between metabolites and bacteria obtained from Pearson analysis. Future studies are expected to confirm whether supplementing the differential gut microbiota could alleviate depression-like phenotype and metabolic disorder in chronic PSD model.

5. Conclusion

The present study augmented the view that a specific situation of circadian disturbance, chronic PSD brought about depression-like performance, as well as altered host metabolism and gut microbiota

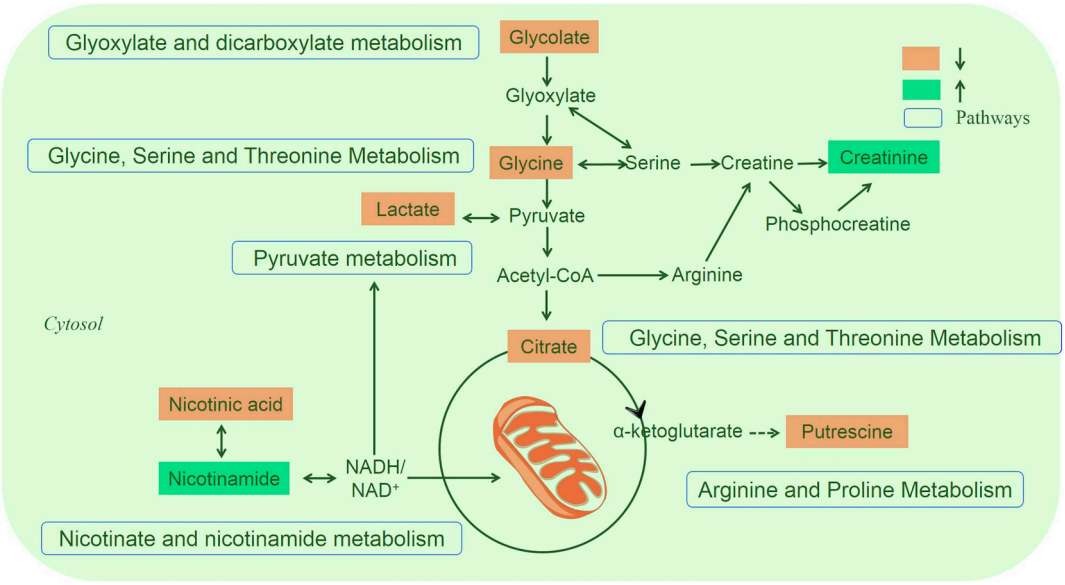

Fig. 5. The disturbed energy metabolism in 7d-PSD rats.

composition. Correlation analysis suggested that *Akkermansia*, *Oscillospira*, *Phascolarctobacterium*, *Aggregatibacter*, *Parabacteroides* and *Ruminococcus* participated in host metabolic regulation. These gut microbiota can provide a basis for deep disclosing mechanism underlying chronic PSD and depression.

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Conflict of interest

All authors report no biomedical financial interests or potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lfs.2019.04.006.

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