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Research Article

Female Sprague Dawley Rats Show Impaired Spatial Memory in the 8-Arm Radial Maze under Dim Blue and Red Light

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Light intensity and wavelength strongly influence mood and cognition in humans and rodent animal models. The aim of the present study was to explore if dim white (7.6–17.7 lux) , blue (1.3–2.3 lux), and red light (0.8–1.4 lux) affect spatial memory of male and female Sprague Dawley rats in the 8-arm radial maze. Our data show that spatial memory significantly improved within 5 daily learning sessions (each 5 trials) under dim white light, which was not different between male and female rats. However, dim blue and red light significantly reduced spatial learning of female rats in the 8-arm radial maze in the last training session (session 5). In conclusion, we suggest that female Sprague Dawley rats show reduced learning under blue and red light.

1. Introduction

Light strongly influences human behavior, and it has positive effects on mood and cognition. These nonvisual effects of light rely on the wavelength, intensity, and duration of light exposure [1]. However, recent studies indicate that the nonvisual effects of light are acute (within 50 seconds) [2] and even occur at dim light exposure [1]. Interestingly, it has been found in humans that blue light increased alertness and speed of information processing and improved cognitive performance [3]. Furthermore, working memory was affected in a wavelength-dependent manner in humans [4]. In addition, a wavelength-dependent effect of light therapy was observed in patients with seasonal affective disorders [5]. The observed effects of light on human behavior are based on the activation of the nonvisual photoreceptor system and related structures, like the suprachiasmatic nucleus, and the release of hormones and neurotransmitters [6–8]. This nonvisual photoreceptor system was extensively studied in rodents. However, only little is known about the influence of different wavelengths on cognition in rats.

The 8-arm radial maze is a prominent tool to study spatial learning and memory of rats under controlled conditions. Numerous recent studies revealed significant differences between male and female rats in spatial memory tasks [9–11], which may rely on anatomical and hormonal dimorphisms. Interestingly a growing body of evidence reveals sexual differences in diverse brain areas [12–14]. The nonvisual photoreceptor system together with the circadian system is closely connected to brain structures associated with learning and memory [15, 16]. Therefore, it is likely that wavelength differentially affects spatial learning in male and female rats.

Thus, in the present study we were interested to investigate the effects of dim white, blue, and red light on spatial learning and to compare male and female Sprague Dawley rats. To differentiate between working and reference memory, we tested rats in a partially baited 8-arm radial maze. To reduce stressful influences, we exclusively used dim lightsources (<18 lux).

2. Methods

2.1. Animals. Adult male and female Sprague Dawley rats aged between 12 and 13 weeks were used for the memory testings. Male and female rats were kept at the animal department in separate cages (4/cage) with free access to food and water with a 12/12 h light-dark circle. All experiments were confirmed by the Austrian Ministry of Science. Per treatment-group (white, blue, red) 7-8 rats were tested.

2.2. The Eight-Arm Radial Maze. The maze (Figure 1(a)) was purchased from PanLab (Spain, http://www.panlab.com) and consists of eight identical open dark plexiglas arms (70×10 cm) with side panels and sunk-in-food cups at the end radiating from a circular platform (27 cm diameter). The maze is elevated 100 cm above the floor. The maze is equipped with motor-driven doors at each entrance of an arm and pressure and movement sensors for an automated acquisition of animal locomotion data. The maze is automatically regulated by a computer with Mazesoft Software (Version 8.1.9). A single 15W (6–15 Lux) white (Osram), blue, or red (both Phillips) lamp was located 60 cm above the center of the platform. The room was a separate room without windows, and no animals or other equipment or chemicals were stored in that room. The person doing the experiments was sitting in front of the computer in the corner of the room. All experiments were performed by the same person. To facilitate spatial navigation small high-contrast visual cues (a triangle, vertical bars, an X, and a square) were placed above the doors of arms 1, 3, 5, and 7 (marked arms) and in a higher magnification on the corresponding walls (Figure 1(a)). For the memory testing Kellog's Choco Pops pellets (113 ± 25 mg, $n = 60$) were used. To exclude any olfactory effects additional baits were also placed under the food cups of all arms, and the maze was cleaned with 70% ethanol after every trial.

2.3. Spatial Memory Testing in the Maze. A scheme of the study design is shown in Figure 1(e). *Day 1 (food deprivation):* food deprivation was performed by restriction of 2 g food pellets per animal per day at the animal department. The animals reached approximately 85%–80% of their weight until food deprivation ended on day 10. *Day 3 (handling and shaping):* animals were brought to the laboratory where they were familiarized with the maze room and the person doing the experiments. The shaping session consisted of 4 trials. In the first shaping trial the doors were left open and all arms were baited. In the second shaping trial all arms were baited and the doors were opened and closed every 5 min. In the third shaping trial the arms 1-4-5-7 were baited but only the baited arms were open. In the fourth shaping trial the arms 1-4-5-7 were baited and all arms were open. All 4 trials of the shaping session ended after 20 min or if all baits were found. *Days 6–10 (training sessions):* each training session consisted of 5 identical trials, where only arms 1-4-5-7 were baited. Rats were placed in the center of the maze with all arms closed. After 10 sec all doors opened and the rat was allowed to explore the maze. When the rat entered an arm all other arms closed. The rat was allowed to explore the entered arm and to eat the pellet and when the rat returned to the center all arms were closed. After 10 sec all arms opened again and the rat was allowed to explore the maze again. The trial ended after 10 min or if all baits have been found. The intertrial time interval for each rat decreased from 72 ± 2 min (session 1) to 38 ± 1 min (session 5). The intertrial interval decreased, because 4 individual animals were tested each 5 trials per day in a rotational manner (e.g., 1st trial—animal 1—white light; 1st trial—animal 2 blue light; 1st trial—animal 3—red light; 2nd trial—animal 1—white light; 2nd trial—animal 2 blue light; 2nd trial—animal 3—red light...). As the animals finished the trials became faster as the training progressed, the intertrial-interval decreased with time. All behavioral tests were performed between 8:00 and 16:00, and the housing light cycle was 6:00–18:00 lights on, 18:00–6:00 lights off.

2.4. Light Exposure. All tests were performed between 8 AM and 3 PM. Only one animal was tested in the maze-room at a time. Animals were only exposed to dim white or blue or red light during a trial (max 10 min in training trials and max 20 min in shaping trials). The wavelength of each light source is given in Figure 1(b). The brightness of each light source was measured with a Gossen Panlux Electronic 2 luxmeter and the light intensities of each light source at the center of the maze and the proximal and distal arm compartments are given in Figure 1(d). After every trial, animals were brought back to the homecage in the laboratory with a constant 12 h/12 h light-dark cycle (bright white light) until the next trial started being in phase with natural light. However, the respective test lighting conditions did not change for individual animals. When housed in the animal department, animals were also kept under a constant 12 h/12 h light-dark cycle (bright white light).

2.5. Error Definition. Memory errors were quantified according to Jarrard's definition of orthogonal working and reference memory errors [17]. Briefly the first visit of a baited arm (arms 1, 4, 5, or 7) was counted as a correct choice whereas a first visit of an unbaited arm (arms 2, 3, 6, or 8) was defined as a reference memory error (RME). Furthermore, repeated visits of baited arms were defined as working memory errors (WMEs; working memory correct error according to Jarrard) whereas repeated visits of unbaited arms were considered as reference-working memory errors (RWMEs; working memory incorrect error according to Jarrard) (Figure 1(c)). In all cases (correct choice, RME, WME, or RWME) a visit was only counted after an animal reached the distal part of an arm where the food cup was located. The percentage of correct choices (% Corr) was calculated with the following formula: $(\text{Baits}/\text{Visits}) * (\text{Baits} * 100/4)$. The calculated values distinguish between the performance of animals within trials where all baits were found (4 baits max) from trials where only 1, 2, or 3 baits were found. For example, if a rat finds all 4 baits without making an error it reaches a score of 100% correct choices $[(4/4) * (4 * 100/4)]$. On the other hand if it finds only 3 baits (of max 4) without making an error it reaches a score of 75 % correct choices $[(3/3) * (3 * 100/4)]$.

2.6. Quantification and Statistics. All data was collected automatically using Mazesoft Software (Version 8.1.9). Subsequently the data of each session (= 5 daily trials) was merged for every individual rat, and an overall statistical analysis was performed for each dependent variable using a 3-way repeated measures analysis of variance (ANOVA) with all sessions (1–5) as within-subjects factor and sex (male, female) and treatment (white light, blue light, and red light)

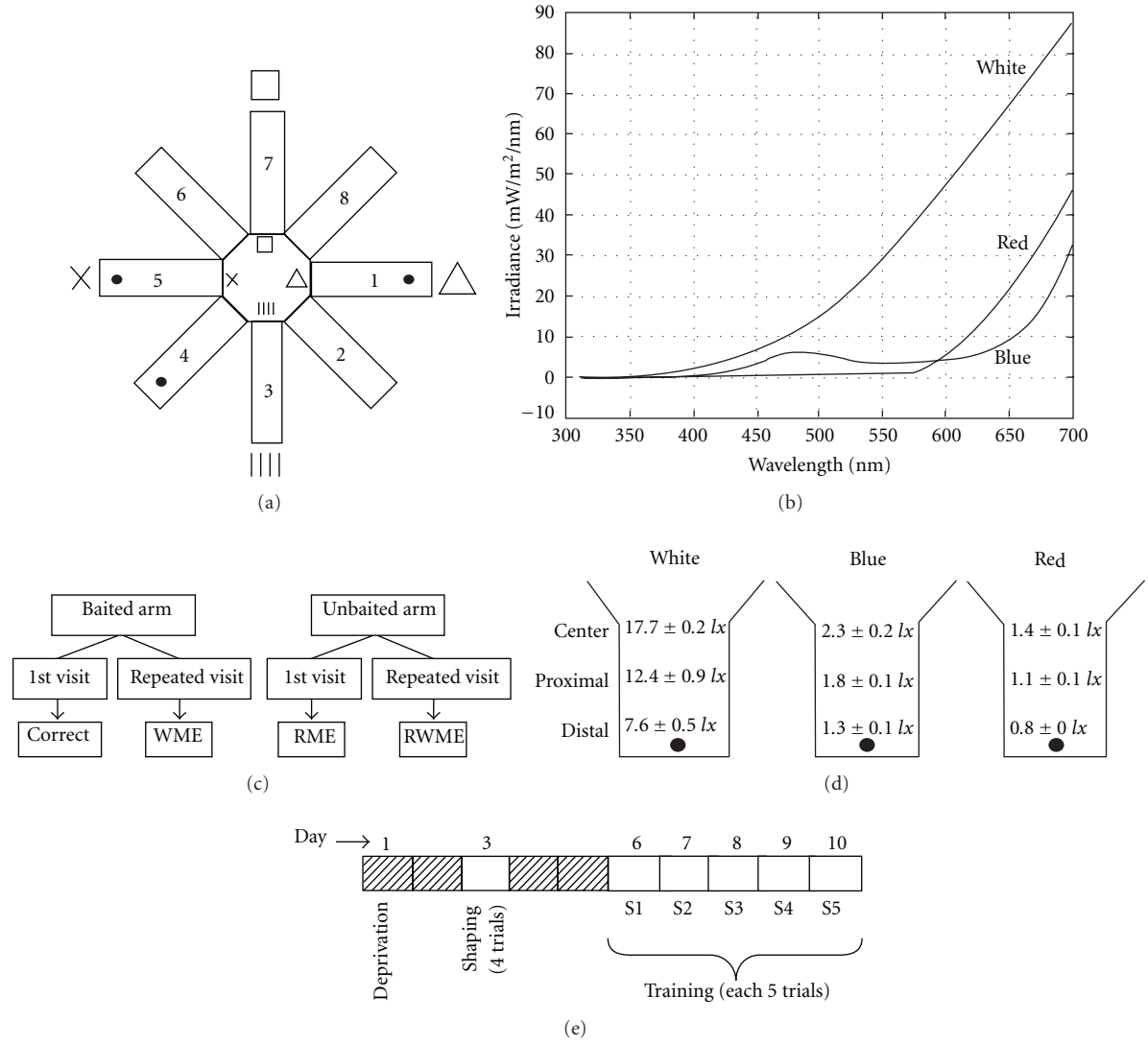

Figure 1: (a) Baiting pattern (black dots) and location of visual cues in the 8-arm radial maze. (b) Spectral irradiance distribution plotted against the wavelength [nm] of the used light sources (white, blue, and red). (c) Error definition (RME: reference memory errors; WME: working memory errors; RWME: reference/working memory errors). (d) Brightness of light in the center of the maze and in the proximal and distal arms of the maze given as mean ± SEM lux ($n = 3$). (e) Study design (S1–S5: session 1–5; shaded boxes: days without trials).

as between-subjects factors using SPSS software. Additionally a one-way analysis of variance (ANOVA) with a subsequent Fisher's LSD post hoc test was performed to compare session 5 of male and female rats within individual light exposure groups and to compare different light exposure groups within sexes. To analyze visits of marked (with visual cues) versus unmarked (without visual cues) arms a Poisson regression analysis was performed, including the effect of baited versus unbaited arms.

3. Results

An analysis of the differences between the individual sessions (using session 1 as a reference) revealed that control rats ($n = 26$; pool of equal male and female rats) showed a significant improvement in the spatial memory after session 3 (Figure 2(a)). The total number of errors significantly decreased after session 4 (Figure 2(b)) and the total time each rat explored the maze significantly decreased after session 3 (Figure 2(c)). Similarly all three types of errors (WME, RME, and RWME) decreased after sessions 3-4 (Figure 2(d)). A 3-way repeated measures ANOVA overall analysis showed a significant main effect of the within-subjects factor (session) over all investigated dependent variables (correct %, total errors, reference memory errors, working memory errors, reference/working memory errors, and visits). The main effect of the between-subjects factors (sex, treatment) and the sex-by-treatment interaction was not significant. The learning curves between male and female rats were statistically not different (data not shown).

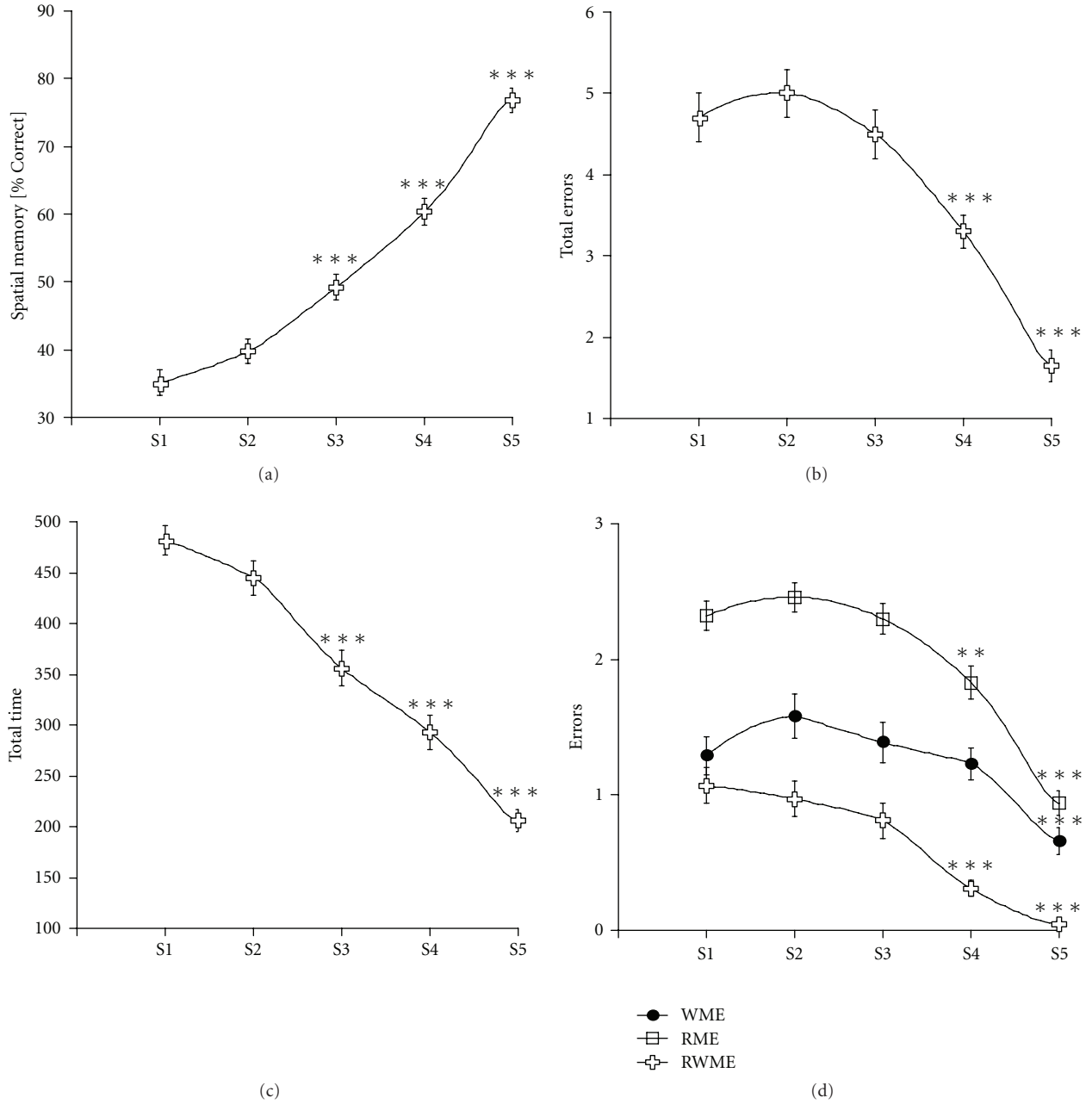

Figure 2: Spatial memory tests of control male and female rats ($n = 26$) in the 8-arm radial maze under dim white light. (a) Spatial memory corrected as percent, (b) total errors, (c) seconds spent in the maze, and (d) error types. Values are expressed as mean ± SEM. Statistical significance was performed by one-way ANOVA with a subsequent Fisher LSD post hoc test compared to session 1. ($^{***}P < .001$; $^{**}P < .01$). (S: session each 5 trials; RME: reference memory errors; WME: working memory errors; RWME: reference/working memory errors).

However, due to the main focus of our study further analysis showed a significant effect of the between-subjects factor sex between session 1 and 5 for the percentage of correct visits (data not shown).

3.1. Effects of Light on Memory Performance in Session 5. When rats were tested in the maze under dim white light, no differences were observed between male and female rats (Table 1) in all tested parameters. Exposure of rats with dim blue light significantly enhanced the total number of errors and the number of reference memory errors (RMEs) of female rats in session 5 (Table 1). No differences were found in all other tested parameters when male and female rats were exposed to blue light (Table 1). When rats were tested under dim red light, female rats exhibited an enhanced number of total number of errors, number of reference memory errors (RMEs), and number of visits (Table 1), while the correct choices were significantly reduced (Table 1). No differences were found in the number of working memory errors (WMEs), the number of reference/working memory

Table 1: Statistical analysis of the last session 5. Male and female Sprague Dawley rats were tested in a spatial memory task in an 8-arm radial maze under different lighting conditions. The performance of the rats was analyzed at the last training session (five) by a one-way ANOVA with a subsequent Fisher's LSD posthoc test. (Corr %: percentage of correct choices; total errors; RME: reference memory errors; WME: working memory errors; RWME: reference/working memory errors). Values are given as mean ± SEM. Differences between sexes are shown in the last column while differences between light exposure groups are shown within the respective column ($^*P < .05$; ns: not significant). Latency = time/visits.

Treatment	S5 all trails	Male	Female	P
White light	Corr %	66 ± 5	65 ± 6	ns
	Total Errors	2.9 ± 0.7	2.7 ± 0.5	ns
	RME	1.5 ± 0.3	1.5 ± 0.3	ns
	WME	1.1 ± 0.4	1.3 ± 0.3	ns
	RWME	0.3 ± 0.1	0.1 ± 0.1	ns
	Visits	6.9 ± 0.7	6.7 ± 0.5	ns
	Time	238 ± 35	170 ± 18	ns
	Latency	39 ± 7	26 ± 2	ns
Blue light	Corr %	76 ± 5^{ns}	62 ± 5^{ns}	ns
	Total Errors	1.7 ± 0.4^{ns}	3.0 ± 0.5^{ns}	.0487*
	RME	0.9 ± 0.2^{ns}	1.7 ± 0.3^{ns}	.0384*
	WME	0.6 ± 0.2^{ns}	1.0 ± 0.3^{ns}	ns
	RWME	0.2 ± 0.1^{ns}	0.3 ± 0.2^{ns}	ns
	Visits	5.7 ± 0.4^{ns}	7.0 ± 0.5^{ns}	ns
	Time	138 ± 9^{ns}	171 ± 15^{ns}	ns
	Latency	25 ± 1^{ns}	25 ± 2^{ns}	ns
Red light	Corr %	76 ± 5^{ns}	59 ± 5^{ns}	.0251*
	Total Errors	1.9 ± 0.5^{ns}	3.5 ± 0.6^{ns}	.0326*
	RME	1.0 ± 0.3^{ns}	1.8 ± 0.3^{ns}	.0467*
	WME	0.8 ± 0.3^{ns}	1.3 ± 0.3^{ns}	ns
	RWME	0.1 ± 0.1^{ns}	0.4 ± 0.2^{ns}	ns
	Visits	5.9 ± 0.5^{ns}	7.5 ± 0.6^{ns}	.0330*
	Time	142 ± 9^{ns}	178 ± 21^{ns}	ns
	Latency	25 ± 1^{ns}	24 ± 2^{ns}	ns

errors (RWMEs), the time spent in the maze, and the latency (time/visits) between male and female rats in session 5 when exposed to red light (Table 1). When light exposure groups were compared within the sexes no significant differences were found in all measured parameters (Table 1).

3.2. Effects of Visual Cues. To test for an effect of the variable "marked arm" (arm with or without visual cue), additionally to the effect of the variable "baited arm" (yes, no), on the number of visits to the individual arms a Poisson regression analysis was performed. The analysis revealed a highly significant effect of baiting (Table 2) but no significant effects of the variable "marked arm" (Table 2) or the interaction between baiting and "marked arm."

Table 2: Cross-table of marked versus unmarked arms. The cross-table shows the total (baited and unmarked; unbaited and marked) and the averaged (baited and marked; unbaited and unmarked) visits of four categories of arms at session 5 of all light exposure groups. Baited arms (1, 4, 5, and 7), unbaited arms (2, 3, 6, and 8), marked arms (with visual cues; 1, 3, 5, and 7) and unmarked arms (without visual cues; 2, 4, 6, and 8) (see also Figure 1(a)). Results of the Poisson regression analysis are shown in the cross-table for the effect of baited versus unbaited arms and for the effect of marked versus unmarked arms. ($^{***}P < .001$; ns: not significant).

Visits all	Marked arm	Unmarked arm	Σ
Baited arm	130	119	249
Unbaited arm	53	34	87^{***}
Σ	183	153^{ns}	$n = 336$

4. Discussion

In the present study we show that dim blue and red light suppressed the spatial memory performance of female rats in the 8-arm radial maze compared to male rats, while dim white light did not have an effect.

4.1. Spatial Memory in the 8-Arm Radial Maze. Two tests are well established to measure spatial memory, the Morris water maze and the 8-arm radial maze. The 8-arm radial maze allows to investigate learning behavior in a well-controlled environment [17]. Our test protocol was designed according

to Jarrard's error definition which allows to assess reference memory errors (RMEs), working memory errors (WMEs) as well as reference/working memory errors (RWMEs). The 3-way repeated measures ANOVA clearly showed a significant learning effect over time with a reduction of all types of errors. The learning effect was highly significant after sessions 3-4. Thus, to test the effect of different light exposures on male and female rats, we statistically compared the effects of session 5. Our experimental design included food-withdrawal to enhance motivation for search for pellets in the maze. Since all rats were treated the same way during all sessions it is likely that the motivation was not different between male and female rats. Interestingly, female rats exhibited an enhanced number of visits under red light, reflecting that female rats were more active than males. To facilitate navigation in the 8-arm radial maze high-contrast visual cues were attached above the doors of four maze arms. To analyze if the cues within the maze caused the rats to switch from a spatial allocentric strategy to a visual strategy to search for baited arms, we performed a Poisson regression analysis for arm visits in the last training session (session 5). The analysis revealed no significant preference of rats to choose an arm based on visual cues. Therefore, we assume that rats followed an allocentric spatial strategy to search for baited arms.

4.2. Effects of Gender on Spatial Memory. It is well established that the working memory in humans and specific brain areas are sexually dimorphic [18] and a large reliable male advantage for rats has been seen in the radial maze and water maze [11]. The prefrontal functions are sexually differentiated in humans [18] and emotionally-induced memory seems to be gender-differentiated in the amygdale [19]. But more importantly, the suprachiasmatic nucleus (shape, cell number) [12–14] as well as the hippocampus (spine density, connectivity, LTP), which is highly associated with learning and memory [10], are sexually dimorphic structures. In fact, the male and female hippocampi significantly differ in their anatomical structure (having a greater hippocampal volume), their neurochemistry and their reactivity to stressful situations [10]. Furthermore, it has been shown that the oestrus cycle has an influence on maze learning strategy in female rats [9, 10, 20, 21]. Sex hormones, such as oestrogens, can alter the excitability of hippocampal activity, influence NMDA receptor binding and neuronal plasticity and long-term potentiation [10]. Furthermore, it was shown that estradiol affects the vasopressinergic innervation of the lateral septum [22], a structure which has often been associated with mnemonic functions. A limit of this study is that the estrous cycle of the females was not tested and we cannot draw conclusions if high- or low-estradiol or progesterone levels may have contributed to the findings.

4.3. Effects of Wavelength on Spatial Memory. It is well established that the blue part of the visual light (446–484 nm) strongly influences brain activity as well as neuroendocrine functions, circadian rhythms, and neurobehavioral responses. Recently, it was shown that blue light stimulated the expression of the clock gene PER2 in humans [23]. In another study, Mehta and Zhu reported that red light primarily induced an avoidance-motivation and enhanced performance on a detailed-oriented task, while blue light primarily induced approach-motivation and enhanced performance on a creative-oriented task [24], indicating differential wavelength-dependent effects of light. More importantly, it was described that the circadian system is directly related to learning and memory by interacting with the hippocampal formation [25]. In our study, rats were exposed to the test-lighting conditions only for short durations and at low intensities. However, Vandewalle et al. showed that short duration (50 seconds) blue light exposures increased the activity in the hippocampus at light onset and in the brainstem and locus coeruleus during a working memory task [1, 2]. This finding clearly demonstrates a very acute effect of light on structures related to memory functions [1]. Furthermore, it was shown in humans that also low-intensity dim light is sufficient to affect the circadian system [1, 26, 27]. Our results go in line with previous studies, indicating acute effects of dim light on spatial memory.

4.4. Effects of Light on Different Errors. One major advantage of the 8-arm radial maze is to explore different memory errors: (1) reference memory errors (RMEs), which reflect "long-term memory" deficits, (2) working memory errors (WMEs, working memory correct), which reflect "short-term memory" deficits, and (3) reference working memory errors (RWMEs). RWMEs, also called working memory incorrect (WMI) errors, are not consistently defined. However, according to other groups RWMEs are often referred to as another form of working memory error [28–31]. Our data provide evidence that WME and RWMEs were both not affected by blue and red light exposure, indicating that blue and red light did not influence short-term memory. However, blue and red light affected the long-term memory as shown by significantly enhanced RMEs. Thus, we suggest that blue and red light may directly suppress memory consolidation in female rats; however, further detailed studies at the biochemical level are required.

4.5. Effects of Brightness on Spatial Memory. Sprague Dawley rats are a widely used animal strain in research. This strain is a nonpigmented rat strain and we have previously shown that high light intensity exposure (6100 Lux) results in loss of photoreceptors [32]. Such a high light intensity (2000 lux) also resulted in a massive stress-induced body weight loss in the pigmented rat strain Brown Norway [32]. It is well known that unusual light intensities result in behavioral disturbances, and humans working during night or a continuous 30-hour shift show reduced cognitive performance as well as differences in body temperature, melatonin, and cortisol levels [33]. In the present study, we used very low intensities (below 18 lux), which correlates to street lighting at night. Thus, we can exclude in our experiment stress-induced effects due to high light intensities. However, the light intensities of blue and red light were about 5–10 lux lower as with white light (equivalent to candle light).

Although we cannot exclude, it is unlikely that a shift of 10 lux has such a pronounced effect on female spatial learning.

4.6. Rats and the Reverse Cycle. Rodents are night active animals, thus it is uncommon to test during bright light. It is reasonable to ask if it makes sense to test rats during their sleep cycle and if this results in a different outcome than testing during their normal active wake (night) phase. The rat model has been found to be a well-used animal in all kinds of neurobiology and biochemistry research, and mainly all experiments are performed with rats sacrificed at bright light. Diurnal cycles of biogenic amines have been reported in several brain regions [34, 35]. Furthermore, some neuropeptides (e.g., vasoactive intestinal polypeptide) are regulated by light and have diurnal variations [32]. However, it has been shown that light exposure during the photoperiod does not phase shift a nocturnal species, but it does so when administered during the dark phase [36]. Beeler et al. observed occasional unsystematic interactions between circadian phase and both strain and sex [37]. Thus a reversed light exposure during the active night phase would not improve the experimental design. Anyhow, as we performed all experiments at daytime, we cannot fully exclude that the reverse cycle may influence working memory in the 8-arm radial maze.

4.7. Visual Acuity in Nonpigmented Rats. It is known that visual acuity is reduced in a nonpigmented rat strain, such as the Albino Srague Dawley rat strain compared to a pigmented strain such as for example, Brown-Norway rats [38]. However, since Sprague Dawley rats are widely used in scientific research including our own lab, we decided to test a nonpigmented rat strain in the spatial memory task. To improve visual acuity, additional visual cues were placed on the maze doors. Although wavelength-specific effects are likely mediated by the nonvisual photosystem [4, 7, 25, 39], we cannot exclude that red or blue light may influence visual acuity in the nonpigmented rats, although albino rats do not lack nonvisual photoreceptors. Finally rodents with rod and cone degeneration are still able to entrain their circadian rhythm [40]. Our results suggest that albino rats are susceptible for wavelength specific effects of light on memory, possibly influencing male and female rats in a different pattern.

In conclusion, our data show that dim blue and red light exposure impaired spatial memory performance of female rats during the last training session compared to male rats whereas dim white light did not influence memory performance. It is suggested that the wavelength influences learning of female rats in the 8-arm radial maze. However, further studies to determine hormonal stages and neurochemical parameters in the brain will be necessary.

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