THE ROLE OF ENDOGENOUS CIRCADIAN OSCILLATORS ON HIPPOCAMPAL-DEPENDENT LEARNING IN AN ANIMAL MODEL OF SOCIAL JET LAG

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Abstract

Discrepancies between weekday and weekend sleep schedules have led to the concept of "social jet lag", which is suggested to negatively impact circadian rhythms via disruption of the light entrainable oscillator (LEO). The current study used an animal model of social jet lag, herein coined the social jet lag manipulation (SJM), to examine the effects of circadian rhythm disruption on hippocampal-dependent memory. Further, it examined if having access to the food entrainable oscillator (FEO) could counteract any observed deficits. While receiving one (FEO access) or multiple (no FEO access) meals per day, rats were exposed to either a 12:12 light-dark cycle or the 32-day SJM. Following the manipulation schedule, rats were trained on the non-hippocampal dependent stimulus response (SR) task and the hippocampal-dependent Morris water maze task. There were no differences observed between group performance on the non-hippocampal SR task. SJM and control rats also showed equal acquisition and retention of the hippocampal-dependent water maze task, leaving the question of whether FEO can counteract LEO disrupted circadian rhythms to be further investigated. The current study demonstrates the importance of further investigation into models of circadian rhythm disruption and the possible ameliorative effects of access to the FEO.

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Table of Contents

List of Tables

List of Figures

The Role of Endogenous Circadian Oscillators and Hippocampal-Dependent Learning in an Animal Model of Social Jet Lag

Circadian rhythms are biological patterns which are responsible for the regulation of many bodily processes including, but not limited to, hormone secretion, body temperature, and the sleep-wake cycle (Gillette, Abbott, & Arnold, 2012; Li et al., 2016). The system begins at a molecular level within the brain and tissues peripheral to the central nervous system. These cellular networks of the circadian system act on the biological mechanisms which contribute to cognitive and behavioural expression. The resulting rhythms oscillate, driven by genes which form an autoregulatory feedback loop (Mohawk, Green, & Takahashi, 2012). This includes activator genes such as CLOCK and BMAL1, which target *Per1*, *Per2*, *Cry1*, and *Cry2* genes to form a negative-feedback complex (Mohawk et al., 2012). This negative-feedback cycle takes approximately 24 hours, which is why circadian rhythms are often discussed in terms of a 24-hour period (Mohawk et al., 2012).

The "master clock" or dominant pacemaker is considered to be the suprachiasmatic nucleus (SCN), located within the anterior hypothalamus (Zelinski, Hong, & Mcdonald, 2014). It accommodates as many as 20,000 neurons which have been suggested to each exhibit circadian oscillator expression (Mohawk et al., 2012). Due to its preeminent status, it maintains control over many behavioural processes and the synchronization of auxiliary oscillators within the body (Mulder, ReckMan, Gerkema, & Van der Zee, 2015). Its robust impact on numerous brain areas is due to its widespread projections across many regions. These projections include, but are not limited to, the

medial preoptic area, dorsal medial hypothalamus (DMH), locus coeruleus, paraventricular nucleus, and amygdala (Gillette, Abbott, & Arnold, 2012).

Clock gene expression exists both internal and external to the SCN, with some peripheral tissues requiring input from the SCN, and others capable of independent expression (Mohawk et al., 2012; Welsh, Yoo, Liu, Takahashi, & Kay, 2004). Regardless of the influence of the SCN, oscillators require cues, or information to entrain to in order to maintain their clock-like rhythm. *Zeitgebers* are external cues that synchronize the internal clock with the external environment (Schulz & Steimer, 2009). One oscillator in particular which is reliant on the SCN is the light entrainable oscillator (LEO), which uses a *Zeitgeber* known as the light-dark cycle for entrainment (Mistlberger, 2011). The SCN receives retinal inputs via the retino-hypothalamic tract through intrinsically photoreceptive retinal ganglion cells (ipRGCs), which express the photopigment melanopsin (Mohawk et al., 2012). These photoreceptors collaborate with rod and cone photoreceptors to interpret information about the light-dark cycle which allows for circadian entrainment (Mohawk et al., 2012). The importance of the tract to circadian timing is supported by the alterations observed in the retino-hypothalamic pathway among individuals with glaucoma, in favour of preserving circadian synchrony (Chiquet et al., 2006).

As previously mentioned, there are also clocks peripheral to the SCN which do not require direct influence from the SCN to maintain synchrony. One such oscillator is the food entrainable oscillator (FEO), whereby the availability of food acts as a *Zeitgeber* (Mistlberger, 2009). The anatomical location of the FEO is currently unclear, however, it has been suggested that the DMH may play a critical role in entrainment to food

availability (Gooley, Schomer, & Saper, 2006; Herzog & Muglia, 2006). As suggested by rodent models, rats are said to have access to the FEO when they are provided with one to two meals at the same time each day (Luna-Illades, Carmona-Castro, & Miranda-Anaya, 2014). By doing so, rats are able to entrain to and anticipate meal times, often displaying what is called food-anticipatory activity (FAA) (Luna-Illades, Carmona-Castro, & Miranda-Anaya, 2014; Mistlberger, 2009; Silver & Kriegsfeld, 2014). Anticipatory behaviour is shown as a spike in activity levels within the hour of the expected meal, which may also include an increase in body temperature and hormone release (Verwey & Amir, 2009). Gaining access to the FEO has been suggested to be advantageous among animal models of cognitive ability, specifically, spatiotemporal variability of stimuli, or time-place learning (TPL) (Wall et al., 2019). Rats who were granted access to the FEO by being provided with one meal at the same time each day, were better able to learn the location of a food reward that was contingent on time of day, when compared to rats which were provided with several meals at variable times throughout the day (Wall et al., 2019). The emerging concept of chrononutrition, or the relation between circadian rhythms and metabolism, is evidence to support the presence and importance of the FEO in humans (Johnston, Ordovás, Scheer, & Turek, 2016). For example, human studies suggest that scheduled meal times may offer benefits to glycemic control and regulate clock gene expression in adipose tissues (Johnston, Ordovás, Scheer, & Turek, 2016; Wehrens et al., 2017).

As a result of modern-day technological advances, stressors, and voluntary bedtime restriction emerging as a commonplace in today's society, individuals have found themselves in situations where their circadian rhythms are disrupted, resulting in

desynchrony (Hirotsu, Tufik, & Andersen, 2015; Spiegel et al., 2015). It has been suggested that these advancements such as 24-hour work operations, and electronics, namely, television and smartphones are largely implicated in the deficits observed in circadian functioning, which ultimately, play a role in several health concerns (Shochat, 2012) including, but not limited to, cardiovascular disease, obesity, and diabetes (Rutters et al., 2014; Zelinski, Deibel, & McDonald, 2014). In the case of cardiovascular disease, it has been suggested that both cardiac function and dysfunction are reliant on time-dependent oscillations of the gene expression within the cells of the myocardium (Martino & Young, 2015). With disturbance to circadian timing comes a higher risk of adverse cardiovascular events, with poorer outcomes (Martino & Young, 2015). In addition, disruption to circadian rhythms such as exposure to light at night has effects on antioxidant melatonin secretion and production, with decreased efficacy correlating with premature aging and cancer development (Zelinski et al., 2014).

The effects of arrhythmic circadian functioning in humans is not limited to physical health complications but can also contribute to the development and/or exacerbation of mental health conditions, such as mood disorders like depression (Benca et al., 2009; Rutters et al., 2014). It has been suggested that blue light from LED backlit devices may be a contributing factor to the adverse symptoms of mental illnesses due to its influence over sleep, such as, disruptions to melatonin production and subjective sleepiness (Bauer et al., 2018; Münch et al., 2017). Additionally, more severe stages of common mental illnesses such as mood disorders are associated with sleep disturbances, including sleep phase delay (Scott et al., 2016). Similarly, it has been proposed that addressing disturbances to sleep schedules among patients with obsessive-compulsive

disorder may prove protective against the development of comorbid mental illnesses and increase the efficacy of treatment options (Paterson, Reynolds, Ferguson, & Dawson, 2013).

One commonly discussed catalyst of circadian rhythm disruption is jet lag. It has been suggested that chronic jet lag in humans, as seen, for example, among airline staff, induces physiological stress with increased cortisol levels correlating with cognitive impairments and decreased hippocampal volume (Cho, 2001). Animal models have supported these suggestions by assessing the effects of the light-dark cycle manipulation, using a single 8-hour phase advance. This single shift elicits a spike in brain-derived neurotrophic factor (BDNF) within the hippocampus, implying that acute disruption is enough to impose physiological change within the brain (Sei et al., 2003), and affirming the need for further investigation into the relationship among sleep disruptions and brain functioning.

Another model of chronic circadian disruption among humans is shift work. Shift work, for many individuals, results in a reduction of alertness during working hours, and poor sleep quality in the daytime (Burgess, Sharkey, & Eastman, 2002). Health risks associated with working night-time shift work are plentiful. Cancer rates are so highly correlated with shift work, that it has been classified as a probable carcinogen by the International Agency for Research on Cancer (Erren et al., 2010). For example, among those who are lifetime night shift workers, or undergo many consecutive night shifts, there is an increased risk of developing breast cancer (Hansen, 2017). Furthermore, shift workers are 40% more likely to develop cardiovascular related disease states (Bøggild, & Knutsson, 1999). There are lifestyle changes associated with adaptation to shift work,

such as, night time eating, which may contribute to the increase in disease risk (Zelinski et al., 2014). Such lifestyle changes, in combination with metabolic changes, correlate with an increased preference for high fat and high sugar foods (Zelinski et al., 2014). As a result, shift work is considered to be a risk factor for increased body mass index (BMI), which is associated with the development of many circadian related diseases such as diabetes (Zelinski et al., 2014). In addition to physiological concerns, cognitive ability is also related to circadian disruption as a result of shift work. Shift work is said to impair cognition whereby there may be safety consequences for both the individual, and other members of society (Marquié, Tucker, Folkard, Gentil, & Ansiau, 2015). For instance, when compared to day-shift nurses, night-shift nurses show signs of slower cognitive competency at the end of their shifts (Molzof et al., 2019).

Animal models of shift work also reveal that circadian disruption aligns with cognitive impairments (Craig & McDonald, 2008; McDonald et al., 2013; Zelinski et al., 2014). Using a series of photoperiod shifts, circadian rhythm disruption has been found to interfere with hippocampal-dependent learning and memory (Zelinski et al., 2014). Exposure to the phase shifts resulted in deficits in retention of spatial memory for both male and female rats. Notably, compared to acute disruption, chronic photoperiod shifting paradigms have been shown to result in greater deficits to hippocampal-dependent memory, suggesting that long-term implications of circadian disruption may pose more of a threat to cognitive ability (Craig & McDonald, 2008).

However, shift workers are not the only group of individuals who experience disruption due to lifestyle choices. Previously mentioned societal pressures have led to a concept referred to in the literature as ‘social jet lag’ (Haraszti, Ella, Gyöngyösi,

Roenneberg, & Káldi, 2014; Roenneberg et al., 2004; Wittmann, Dinich, Merrow, & Roenneberg, 2006). Social jet lag refers to the discrepancies observed in sleep times throughout the week (Haraszti et al., 2014; Roenneberg et al., 2004; Wittmann et al., 2006). For example, university students often experience social jet lag due to late night studying or socializing some nights and going to bed early other nights.

Many others in the greater population experience social jet lag as a result of simply going to bed and waking up earlier throughout the weekdays and staying up and sleeping in later on the weekends. This is often due to an individuals' lifestyle obligations not being in alignment with their natural chronotype. Chronotype refers to the behavioural exhibition of an individual's internal circadian clock depicted through a preference for sleep and wake times (Kalmbach et al., 2017). It is often referred to as a dichotomy of evening or morning chronotype, with those expressing an evening chronotype left more vulnerable to social jet lag than those expressing a morning chronotype (Roenneberg et al., 2004; Wittmann et al., 2006). It has been suggested that social jet lag is a common concern, with many individuals reporting at least an hour of social jet lag (Roenneberg, Allebrandt, Merrow, & Vetter, 2012). Previously described health implications of circadian disruption also remain true for those with social jet lag. Specifically, women who have greater than one hour of social jet lag report more severe menstrual symptomology when compared to their non-social jet lag counterparts independent of total sleep duration, which is indicative of the relationship between social jet lag and reproductive health (Komada et al., 2019). Additionally, similar to shift workers, social jet lag is associated with increased BMI, suggesting that this circadian phenomenon is a risk factor contributing to the global obesity epidemic (Roenneberg et

al., 2012). In addition to health-related concerns, social jet lag has also been correlated with cognitive deficits. Among undergraduate students, social jet lag has been correlated with poorer academic performance (Díaz-Morales & Escribano, 2015; Haraszti et al., 2014). For example, lower GPA scores are associated with irregular sleep schedules throughout the week, while students who report regular weekday sleep schedules maintain higher GPA scores (Hysing, Harvey, Linton, Askeland, & Sivertsen, 2016).

Together, research in this area suggests that our society would benefit from the implementation of interventions to ameliorate the negative impacts resulting from social jet lag (Lund, Reider, Whiting, & Prichard, 2010; Matthew, Li, Hale, & Chang, 2019). However, there is a dearth of experimental data on social jet lag, including a lack of animal models which would allow for more intricate assessment of the biological mechanisms and the resulting deficits underlying this emergent phenomenon.

With this in mind, the current study developed a novel approach to examine the effects of circadian rhythm disruption in an animal model of social jet lag. Similar to previous animal models of shift work using photoperiod shifting paradigms, the current model used a novel lighting manipulation coined the Social Jet Lag Manipulation (SJM) (Table 1). This paradigm was designed to illustrate typical sleep patterns of social jet lag as a means of examining its effects on hippocampal-dependent learning and memory. The current study also examined whether access to the FEO could ameliorate any observed deficits associated with exposure to the lighting manipulation.

To accomplish the aims of the current study, rats were divided into four groups based on meal and lighting conditions. Rats either received the SJM (SJM groups), or a control (C groups) 12:12 light-dark lighting condition. Rats were further sub-divided by

meal group: rats assigned to the 1-meal per day group (1M) received their total daily allotment of food at 16:30 each day, allowing access to the FEO, while rats assigned to the multiple meal group (MM) received their total daily allotment of food dispersed throughout 1-3 random times a day, inhibiting access to the FEO due to the lack of meal time predictability. As a result, the groups consisted of SJM-1M; SJM-MM; C-1M; and C-MM. Following SJM-groups' exposure to the lighting manipulation, all groups were trained on a hippocampal-dependent Morris water maze task to assess the effects of the circadian oscillators on learning. Simultaneously, all groups were trained on a hippocampal-independent stimulus-response (SR) task to ensure that circadian rhythm disruption does not produce global memory deficits.

Based on the previous literature described, it was hypothesized that acquisition of the hippocampal-dependent Morris water maze task would be impaired due to disruption of the LEO as a result of exposure to the SJM, but not the hippocampal-independent SR task. Additionally, it was hypothesized that access to the FEO would be advantageous in acquisition of the tasks, as shown by 1M groups out-performing MM groups. Consequently, it was hypothesized that the C-1M group would achieve the highest performance on the task, with the SJM-MM group demonstrating the most impairment as a result of circadian desynchrony.

Method

Subjects

Thirty-two male Long Evans rats (approximately 185 g upon arrival) were obtained from Charles River Laboratories (QC, Canada). Upon arrival, rats were singly housed in individually ventilated cages (32 cm x 35 cm x 18 cm) containing corncob

bedding (Netco, New York, NY), Crink-l'Nest (The Anderson, Maumee, Ohio), a Nylabone (Nylabone Products, Neptune, NL), a wooden block and a piece of tubing for enrichment. Additional enrichment included two Plexiglas enrichment boxes (Box A: 59.5 x 59.5 x 59.5 cm; Box B: 53.5 x 43.5 x 43 cm) which contained, corncob bedding (Netco, New York, NY), plastic running wheel (PetSmart, CA), Froot Loops (Kellogg, CA), and various stimulating toys (e.g., ladders, dangling toys). Rats were assigned to enrichment pairs and placed in a box with their partner for 20 minutes at variable times, daily, to eliminate entrainment to the activity. Rats received standard rat diet (PMI Nutrition International, St. Louis, MO), as well as *ad libitum* access to water while placed on a food restriction paradigm so as to gain 10g per week. Additionally, rats were housed in a temperature-controlled room maintained on a 12:12 light-dark cycle with lights on at 7:00 a.m. until the onset of the lighting manipulation.

Rats were randomly assigned to one of four groups based on lighting and meal conditions. SJM-1M (n = 8) received their total daily allotment of food at 4:30 p.m. every day so as to provide access to the FEO, and the social jet lag lighting manipulation. C-1M (n = 8) also received their total daily allotment of food at 4:30pm every day, but the standard 12:12 lighting conditions. SJM-MM (n = 8) received their total daily allotment of food in separate meals (2-3 multiple meals) at varying times throughout the light cycle, so as to not provide access to the FEO. They also received the social jet lag manipulation. C-MM (n = 8) also received their total daily allotment of food at multiple varying times throughout the light cycle, and the standard 12:12 lighting. The social jet lag lighting schedule encompassed a total of 32 days prior to the start of behavioural testing, with Day 1 beginning on a Saturday (Table 1). All procedures used throughout the duration of the

experiment were approved by Memorial University's Institutional Committee on Animal Care and were in accordance with the Canadian Council on Animal Care guidelines.

Apparatus

Elevated Plus-Maze. Two wooden mazes painted grey consisting of two open arms (15 cm x 122 cm) and two enclosed arms (15 cm x 122 cm x 50 cm) were elevated 75 cm from the floor. The testing room contained several visual cues such as counters, chairs, and doors which remained consistent throughout testing. A curtain was placed between both apparatuses so as to eliminate distractions between the rats during testing.

Stimulus-Response (SR). This apparatus was a plus maze (75 cm elevated) made of wood and painted white with four extending arms (53 cm x 15.5 cm). At the end of each arm was a depressed food cup in which a Froot Loop (Kellogg, CA) could be placed as a means of reinforcement. A wire mesh stimulus was placed over the correct arm extending to where the Froot Loop was placed. Small bags made of nylon containing Froot Loops were placed under each arm to mask olfactory cues. The testing room contained several visual cues such as windows, a sink, multiple doors, cabinets, and shelving, all of which were consistent throughout the experiment.

Morris Water Maze. The water maze was a circular pool made of Plexiglas on a metal frame (178 x 178 cm), maintained 28 cm from the floor on wheels. The pool was 170 cm in diameter and 60 cm in depth. The amount of water in the pool was maintained at approximately 10 cm below the top of the pool. The temperature of the water was maintained at approximately 21° C throughout the duration of the experiment. To account for visual cues within the pool, the water was visibly opaque by adding white, non-toxic

paint (Michaels, CA). The escape platform consisted of white tubing and was weighed down with sand. The platform was 11 cm in diameter and remained approximately 2 cm below the surface of the water throughout each trial of the experiment. The training room contained several visual cues such as cabinets, lamps, and posters, which remained consistent throughout testing. Two lamps were used in lieu of overhead lighting so as to accommodate requirements for video data collection.

Procedure

Upon arrival, rats were given four weeks to adjust to a 12:12 LD cycle, and the restricted feeding regime. After the four weeks, the rats in the social jet lag condition then began the 32-day light manipulation schedule. The day following termination of the lighting manipulation, rats began behavioral tests of hippocampal-independent (SR task) and hippocampal-dependent (Morris water maze) tasks. Training on the tasks began at approximately 09:00 each day. Rats were run on the SR task until they reached criterion (18 out of 20 correct trials). The Morris water maze task followed a rapid acquisition paradigm consisting of an acquisition phase, massed training phase, and a competition phase for a total of seven days. In between each phase the rats completed a no platform probe to assess learning of the location of the escape platform.

Elevated Plus-Maze (EPM). The EPM is used as a measure of anxiety-like behaviours among subjects to determine if there are differences in behaviour between groups, indicative of stress. Each rat received a five-minute trial on the final day of the lighting manipulation, the day before the start of training on the behavioural tasks. Rats were brought to the testing room on two carts such that equal numbers of each condition were in various positions on the cart. Both carts were left in an ante room for 30 minutes

to accommodate for any possible stress from the transportation from the colony room to the testing room (i.e., use of an elevator). Following the acclimation period, each rat received one trial. Two researchers were present for the testing phase and ran one rat each at a time. The rat was placed in the center of the EPM, facing an open arm to explore for five minutes. A rat was said to have entered an arm when its entire body, minus its tail was in an arm. Between each rat the maze was cleaned with Peroxiguard hydrogen peroxide solution. Trials were video recorded and were coded at a later time for time spent in open and closed arms, and frequency of entry into each arm.

Stimulus-Response (SR) Task. Prior to testing, each rat received three days of habituation. Once testing began, each rat received eight trials on the task per day. Upon reaching criterion (18 out of 20 correct first arm entries), rats were removed from the task.

Habituation. Prior to the start of habituation, Froot Loops were placed in the rats' home cages to introduce them to the new food. Three days prior to the start of the testing phase, rats received habituation trials consisting of five minutes a trial to acclimate them to the task. On the first day, Froot Loop dust, consisting of small pieces of Froot Loops and powder was scattered over the entirety of the maze to encourage exploration of the maze. On the second day, Froot Loop dust was placed in the end half of each arm closest to the food cups. On the third day, a half of a Froot Loop was placed in each food cup. By the end of habituation all rats were eating the Froot Loops from the maze.

Testing Phase. Rats were transported to the training room in groups of five or six and were arranged in chronological order along a counter. Rats received each trial in turn, with the inter-trial interval of approximately 10 minutes at the beginning of training and

decreased as rats were removed from the task after reaching criterion. Lights were on and a radio was playing during all trials to provide background noise, alleviating external disturbances.

During the testing phase, wire mesh was placed on a pseudorandomly chosen arm and half a Froot Loop was placed in the coinciding food cup. A rat was then placed on a different pseudorandomly chosen start arm, facing the experimenter. Arms were assigned so that each arm acted as the start or correct arm an equal number of times, and so that a rat would not start on the same arm on consecutive trials. Rats also would not start on the same arm as the mesh was located. Rats were considered to have made a choice when their entire body minus their tail entered an arm. A trial was recorded as being correct if a rat entered the target arm as its first arm choice. Latency to reach the Froot Loop was also recorded. For the first 20 trials, rats were permitted to make incorrect choices, however if the rat did not eat the Froot Loop within 120 seconds, it was removed from the maze. After 20 trials, the rats were removed upon making an incorrect first choice.

Morris Water Maze. The procedure for behavioral testing followed the rapid acquisition paradigm, similar to what was outlined by Craig and McDonald (2008). Following the SR task, rats were brought to the testing room where they were transferred into individual testing cages lined with paper towels. The room was dimly lit to accommodate requirements for video recording and a radio was turned on during all trials.

Acquisition Phase. Rats were brought into the testing room in groups of five or six. Each rat received eight trials a day for four days in the acquisition phase. At the start of each trial the rat was carried counterclockwise around the maze to one of four

counterbalanced release positions and trained to swim to a fixed platform in Quadrant C (Figure 1). The latency to the escape platform was recorded manually, and via video recording. Each trial was a maximum of 60 seconds. If after 60 seconds the rat had not reached the platform, the experimenter placed it on the platform for 10 seconds. The water was thoroughly agitated between trials to mitigate olfactory cues. Twenty-four hours following the last acquisition trial, rats were given a no platform probe. This consisted of one 60 second trial with the escape platform removed. For this trial, release was from Positions 1 or 2 (Figure 1).

Massed Training Phase. Rats were brought into the testing room in groups of four to allow for training to take place in under two hours for each rat. Each rat received 16 trials within those two hours. The procedure for massed training remained the same, with the exception of the escape platform now being placed in Quadrant A (Figure 1). Twenty-four hours following massed training, rats were given another no platform probe, following the same procedure as the previous probe, with the exception of the release positions which were 3 or 4 (Figure 1).

Competition Phase. Rats were brought into the testing room in groups of five or six. The competition phase consisted of one day, with rats receiving eight trials. The procedure remained the same as the acquisition phase, including the return of the escape platform to Quadrant C (Figure 1). Twenty-four hours following the competition phase, rats were given the third and final no platform probe, with release Positions 1 or 2 (Figure 1).

Results

Elevated-Plus Maze (EPM)

The ratio of time spent and frequency of arm entries for each group in the open versus closed arms of the maze are shown in Figure 2.

A between subjects ANOVA revealed that there was no main effect of lighting condition for the ratio of time spent in the open arms (time spent in the open arms/time in all of the arms) (Figure 2A), (SJM condition $M = .433$, $SD = .114$; Control condition $M = .456$, $SD = .103$), $F(1, 28) = .331$, $p = .570$, partial $\eta^2 = .012$. No main effect of meal time was found for ratio of time in open arms (1M condition $M = .443$, $SD = .131$; MM condition $M = .446$, $SD = .081$), $F(1, 28) = .003$, $p = .956$, partial $\eta^2 < .001$, and no interaction $F(1, 28) = .875$, $p = .357$, partial $\eta^2 = .030$.

Similarly, an ANOVA determined that there was no main effect of lighting condition for ratio of frequency of open arm entries (frequency of entry of open arms/frequency of entry of all arms) (Figure 2B), (SJM condition $M = .456$, $SD = .063$; Control condition $M = .459$, $SD = .052$), $F(1, 28) = .031$, $p = .861$, partial $\eta^2 = .001$, nor was there a main effect of meal condition (1M condition $M = .4635$, $SD = .067$; MM condition $M = .452$, $SD = .0469$), $F(1, 28) = .320$, $p = .576$, partial $\eta^2 = .011$, and no interaction $F(1,28) = .070$, $p = .793$, partial $\eta^2 = .003$.

Stimulus-Response Task (SR)

The SR task is used as a measure of hippocampal-independent learning. To assess performance on the task, acquisition data were grouped into seven blocks of eight trials (See Figure 3A). A between-within ANOVA established a significant linear effect of Block, $F(1, 22) = 49.631$, $p < .001$, partial $\eta^2 = .693$, indicative of task acquisition by all groups. There were no significant differences in acquisition of the task among lighting

conditions, $F(1, 22) = .001$, $p = .977$, partial $\eta^2 < .0005$, nor among the meal conditions, $F(1, 22) = 1.136$, $p = .298$, partial $\eta^2 = .049$. Likewise, there was no interaction, $F(1, 22) = .366$, $p = .551$, partial $\eta^2 = .016$.

To determine if there were any differences in how quickly rats learned the task, the number of trials to criterion was analyzed. Criterion was designated as 18 correct trials out of 20. The average trials to criterion among groups can be found in Figure 3B. An ANOVA determined there was no main effect of lighting condition, (SJM condition $M = 65.81$, $SD = 12.76$; Control condition $M = 61.94$, $SD = 14.125$), $F(1, 28) = .732$, $p = .400$, partial $\eta^2 = .025$. There was also no main effect of meal condition, (1M condition $M = 68.50$, $SD = 12.204$; MM condition $M = 59.25$, $SD = 13.259$), $F(1, 28) = 4.169$, $p = .051$, partial $\eta^2 = .130$, and no interaction between lighting and meal, $F(1, 28) = .933$, $p = .342$, partial $\eta^2 = .032$.

Water Maze Task

The water maze task followed a rapid acquisition paradigm to determine if there were group differences in latency to locate the hidden platform. This was followed by rapid acquisition to a new platform location within the same pool, and a competition test to challenge both platform representations. To quantify this, we used latency to the platform and distance travelled as measures of acquisition for all platform trials. For the non-platform probes following each phase, we used latency to the correct quadrant, time spent in the correct quadrant, and total distance travelled in the analysis.

Acquisition phase. To assess performance, acquisition data from this phase were organized into four blocks of eight trials (eight trials per day for four days) (See Figure

4). Latency to the platform was analyzed using a between-within ANOVA which revealed a significant linear effect of Block, $F(1, 28) = 396.046$, $p < .001$, partial $\eta^2 = .934$ indicating that all groups acquired the task over time. There were no significant differences in platform latencies among lighting conditions, $F(1, 28) = .830$, $p = .370$, partial $\eta^2 = .029$, nor among the meal conditions, $F(1, 28) = .070$, $p = .794$, partial $\eta^2 = .002$. There was, however, a significant interaction of lighting by meal conditions, $F(1, 28) = 7.683$, $p = .01$, partial $\eta^2 = .215$. One-way ANOVA determined a significant effect of lighting condition among the 1M meal group, $F(1, 14) = 8.098$, $p = .013$, partial $\eta^2 = .366$, (SJM condition $M = 14.677$, $SD = 3.544$; Control condition $M = 19.488$, $SD = 3.150$), which indicated that when provided access to the FEO, the SJM group acquired the task more quickly than the control group. However, among the MM meal group there was no significant effect of lighting, $F(1,14) = 1.489$, $p = .243$, partial $\eta^2 = .096$, (SJM condition $M = 18.610$, $SD = 4.656$; Control condition $M = 16.199$, $SD = 3.088$). When analyzing distance travelled, a between-within ANOVA revealed that there were no significant differences in average distance travelled during a trial among lighting conditions, $F(1,28) = .548$, $p = .465$, partial $\eta^2 = .019$. There was no significant effect of meal condition, $F(1,28) = .202$, $p = .657$, partial $\eta^2 = .007$, and there was no significant interaction, $F(1,28) = 3.682$, $p = .065$, partial $\eta^2 = .116$.

Probe 1. Probe 1 was a non-platform trial, whereby the quadrant which previously housed the platform in the acquisition phase was considered the correct quadrant.

Latency to correct quadrant. Analysis for latency to the correct quadrant can be found in Figure 5A. An ANOVA revealed there was a main effect of lighting for latency

to reach the correct quadrant, $F(1, 28) = 4.881$, $p = .035$, partial $\eta^2 = .148$, (SJM condition $M = 3.676$, $SD = 1.116$; Control condition $M = 4.538$, $SD = 1.215$) with the SJM group reaching the correct quadrant in less time than the control group. There was no main effect of meal, $F(1, 28) = 1.622$, $p = .213$, partial $\eta^2 = .055$ (1M condition $M = 3.859$, $SD = 1.299$; MM condition $M = 4.356$, $SD = 1.140$) and no interaction $F(1,28) = 3.928$, $p = .057$ partial $\eta^2 = .123$.

Time spent in correct quadrant. Analysis for the time spent in the correct quadrant can be found in Figure 5B. An ANOVA revealed there was no main effect of lighting for time spent in the correct quadrant, $F(1, 28) = .243$, $p = .626$, partial $\eta^2 = .009$, (SJM condition $M = 30.350$, $SD = 7.245$; Control condition $M = 31.527$, $SD = 6.419$). There was no main effect of meal, $F(1, 28) = .038$, $p = .847$, partial $\eta^2 = .001$ (1M condition $M = 30.708$, $SD = 7.394$; MM condition $M = 31.173$, $SD = 6.296$) and no interaction $F(1, 28) = 2.897$, $p = .100$ partial $\eta^2 = .094$.

Total distance travelled. Analysis for the total distance travelled can be found in Figure 5C. An ANOVA revealed there was no main effect of lighting for total distance travelled among trials, $F(1, 28) = .882$, $p = .375$, partial $\eta^2 = .028$, (SJM condition $M = 16.949$, $SD = 2.541$; Control condition $M = 16.214$, $SD = 1.940$). There was no main effect of meal, $F(1, 28) = .612$, $p = .440$, partial $\eta^2 = .021$ (1M condition $M = 16.901$, $SD = 2.409$; MM condition $M = 16.262$, $SD = 2.119$), and no interaction $F(1, 28) = .177$, $p = .677$ partial $\eta^2 = .006$.

Massed training phase. For this phase, the platform location was moved to Quadrant A (See Figure 1). The latency to this new platform location and total distance

travelled within a trial were measured (See Figure 6). When analyzing latency to the platform, a between-within ANOVA determined a significant linear effect of trial, $F(1, 28) = 122.200$, $p < .001$, partial $\eta^2 = .814$, which indicated that all groups acquired the task. There was no significant difference in platform latencies among lighting conditions, $F(1, 28) = .922$, $p = .345$, partial $\eta^2 = .032$. There was also no effect of meal condition, $F(1, 28) = .814$, $p = .375$, partial $\eta^2 = .028$, nor a significant interaction, $F(1, 28) = .234$, $p = .632$, partial $\eta^2 = .008$. When analyzing distance travelled, a between-within ANOVA revealed that there were no significant differences in average distance travelled during a trial among lighting conditions, $F(1, 28) = .545$, $p = .466$, partial $\eta^2 = .019$. There was no significant effect of meal condition, $F(1, 28) = .989$, $p = .328$, partial $\eta^2 = .034$, and there was no significant interaction, $F(1, 28) = .219$, $p = .644$, partial $\eta^2 = .008$

Probe 2. Probe 2 was a non-platform trial, whereby the quadrant which previously housed the platform in the massed training phase was considered the correct quadrant.

Latency to correct quadrant. Analysis for the latency to the correct quadrant can be found in Figure 7A. An ANOVA revealed there was no main effect of lighting, $F(1, 28) = .013$, $p = .911$, partial $\eta^2 < .0005$, (SJM condition $M = 9.314$, $SD = 9.897$; Control condition $M = 9.658$, $SD = 7.143$). There was no main effect of meal, $F(1, 28) = .703$, $p = .409$, partial $\eta^2 = .025$, (1M condition $M = 8.205$, $SD = 4.272$; MM condition $M = 10.767$, $SD = 11.282$), nor was there an interaction $F(1, 28) = 1.227$, $p = .277$ partial $\eta^2 = .042$.

Time spent in correct quadrant. Analysis for the time spent in the correct quadrant can be found in Figure 7B. An ANOVA revealed there was no main effect of lighting for time spent in the correct quadrant, $F(1, 28) = .205$, $p = .654$, partial $\eta^2 = .007$,

(SJM condition M = 19.569, SD = 6.519; Control condition M = 18.531, SD = 6.018). There was no main effect of meal, $F(1, 28) = .001$, $p = .978$, partial $\eta^2 < .0005$ (1M condition M = 19.081, SD = 5.496; MM condition M = 19.019, SD = 7.007), nor was there an interaction $F(1, 28) = 1.227$, $p = .277$ partial $\eta^2 = .042$.

Total distance travelled. Analysis for the total distance travelled can be found in Figure 7C. An ANOVA revealed there was no main effect of lighting for total distance travelled among trials, $F(1, 28) = .068$, $p = .797$, partial $\eta^2 = .002$, (SJM condition M = 1578.559, SD = 350.366; Control condition M = 16.115, SD = 3.540). There was no main effect of meal, $F(1, 28) = .668$, $p = .421$, partial $\eta^2 = .023$, (1M condition M = 16.468, SD = 2.861; MM condition M = 15.432, SD = 4.013), and no interaction $F(1, 28) = .177$, p = .602, partial $\eta^2 = .010$.

Time spent in previously correct quadrant. Analysis for the time spent in the previously correct quadrant can be found in Figure 7D. An ANOVA revealed there was no main effect of lighting for time spent in the previously correct quadrant (Quadrant C), $F(1, 28) = .001$, $p = .971$, partial $\eta^2 < .0005$, (SJM condition M = 8.610, SD = 3.140; Control condition M = 8.574, SD = 2.022). There was no main effect of meal, $F(1, 28)$ = .057, $p = .813$, partial $\eta^2 = .002$, (1M condition M = 8.707, SD = 2.520; MM condition M = 8.478, SD = 2.751), and no interaction $F(1,28) = .453$, $p = .507$, partial $\eta^2 = .016$.

Competition phase. For this phase, the platform location was moved back to the original platform location in Quadrant C. The latency to this platform location and total distance travelled within a trial was measured over eight trials (See Figure 8). When analyzing latency to the platform, a between-within ANOVA determined a significant

linear effect of trial, $F(1, 28) = 44.877$, $p < .001$, partial $\eta^2 = .616$, which indicated that all groups acquired the task over trials. There was no significant difference in platform latencies among lighting conditions, $F(1, 28) = .673$, $p = .419$, partial $\eta^2 = .023$. There was, however, a significant effect of meal condition, $F(1, 28) = 5.211$, $p = .030$, partial $\eta^2 = .157$, with the average latency to the platform greater among the 1M condition ($M = 17.511$, $SD = 5.265$), than the MM condition ($M = 12.611$, $SD = 6.892$). There was no significant interaction, $F(1, 28) = 1.944$, $p = .174$, partial $\eta^2 = .065$. When analyzing distance travelled, a between-within ANOVA revealed that there were no significant differences in distance travelled during a trial among lighting conditions, $F(1, 28) = .703$, $p = .409$, partial $\eta^2 = .024$. There was no significant effect of meal condition, $F(1, 28) = 3.876$, $p = .059$, partial $\eta^2 = .122$, and there was no significant interaction, $F(1, 28) = 1.866$, $p = .183$, partial $\eta^2 = .062$.

Probe 3. Probe 3 was one non-platform trial, whereby the quadrant which previously housed the platform in the acquisition and competition phases was considered the correct quadrant.

Latency to correct quadrant. Analysis for latency to the correct quadrant can be found in Figure 9A. An ANOVA revealed there was no main effect of lighting for latency to reach the correct quadrant, $F(1, 28) = .699$, $p = .410$, partial $\eta^2 = .024$, (SJM condition $M = 7.157$, $SD = 4.647$; Control condition $M = 5.966$, $SD = 3.111$). There was no main effect of meal, $F(1, 28) = .548$, $p = .465$, partial $\eta^2 = .019$, (1M condition $M = 6.033$, $SD = 3.704$; MM condition $M = 7.089$, $SD = 4.209$) and no interaction $F(1, 28) = .326$, $p = .573$, partial $\eta^2 = .012$.

Time spent in correct quadrant. Analysis for the time spent in the correct quadrant can be found in Figure 9B. An ANOVA revealed there was no main effect of lighting for time spent in the correct quadrant, $F(1, 28) = 1.870$, $p = .182$, partial $\eta^2 = .063$, (SJM condition $M = 18.430$, $SD = 5.547$; Control condition $M = 21.585$, $SD = 7.669$). There was no main effect of meal, $F(1, 28) = 1.202$, $p = .282$, partial $\eta^2 = .041$, (1M condition $M = 18.743$, $SD = 6.004$; MM condition $M = 21.272$, $SD = 7.445$) and there was no interaction $F(1, 28) = 2.353$, $p = .136$, partial $\eta^2 = .078$.

Total distance travelled. Analysis for the total distance travelled can be found in Figure 9C. An ANOVA revealed there was no main effect of lighting for total distance travelled among trials, $F(1, 28) = .081$, $p = .778$, partial $\eta^2 = .003$, (SJM condition $M = 17.194$, $SD = 2.869$; Control condition $M = 16.847$, $SD = 3.799$). There was no main effect of meal, $F(1, 28) = .487$, $p = .491$, partial $\eta^2 = .017$, (1M condition $M = 17.447$, $SD = 3.271$; MM condition $M = 16.595$, $SD = 3.412$), and no interaction $F(1, 28) = .064$, $p = .802$, partial $\eta^2 = .002$.

Time spent in previously correct quadrant. Analysis for the time spent in the previously correct quadrant can be found in Figure 9D. An ANOVA revealed there was no main effect of lighting for time spent in the previously correct quadrant (Quadrant A), $F(1, 28) = .501$, $p = .485$, partial $\eta^2 = .018$, (SJM condition $M = 16.535$, $SD = 6.410$; Control condition $M = 14.937$, $SD = 6.193$). There was no main effect of meal, $F(1, 28) = .528$, $p = .474$, partial $\eta^2 = .018$, (1M condition $M = 16.556$, $SD = 7.052$; MM condition $M = 14.916$, $SD = 5.444$), and no interaction $F(1, 28) = .716$, $p = .405$, partial $\eta^2 = .025$.

Discussion

The current study used a novel approach to examine the effect of circadian rhythm disruption on hippocampal-dependent learning and memory in an animal model of social jet lag. To do this, a social jet lag lighting manipulation was developed to mirror typical sleep habits characteristic of social jet lag in humans. Using this lighting manipulation, it was thought that the LEO would be disrupted due to inconsistent cues from the light-dark cycle. Furthermore, the role that access to the FEO may have in potentially counteracting impairment from social jet lag was also examined.

It was hypothesized that rats that were exposed to the SJM would display impairments on the hippocampal-dependent water maze task, but not on the hippocampal-independent SR task, to demonstrate that circadian rhythm disruption does not impair global cognitive ability. Additionally, it was hypothesized that having access to the FEO would be advantageous and ameliorate deficits from circadian misalignment due to the SJM.

As hypothesized, exposure to the SJM did not have an effect on the hippocampal-independent SR task. Both the SJM and control groups were successful at acquiring the task with no significant differences among the groups. This was unsurprising, as the SR task relies on the dorsolateral-striatum (Featherstone & McDonald, 2004) and was included as a measure of non-global memory impairment to confirm that circadian rhythm disruption does not produce a global memory deficit. However, it appeared as though there was a trend in the direction that 1M group required more trials to reach criterion, therefore, moving forward replicating the task to see if there is an effect could prove beneficial.

The results from this study did not support the hypothesis that exposure to the SJM would result in impairments to performance in hippocampal-dependent tasks. Both the SJM group and the control group performed equally on the rapid acquisition water maze task for all of the phases of the task and probes. However, during the acquisition phase, the SJM-1M group demonstrated a faster latency to the platform location. Additionally, during the competition phase of the rapid acquisition task, the 1M group was slowest to relearn the platform location. It is possible that this was due to a stronger representation of the previous platform location in the 1M group, which created greater confusion during the competition phase, resulting in slower relearning time. These findings are contradictory to previous research using animal models which demonstrate spatial learning impairment following a light manipulation paradigm (Craig & McDonald 2008). Furthermore, previous research on FEO access has indicated that rats who receive one meal at the same time each day outperform their multiple meal counterparts on a TPL task (Wall et al., 2019). Rats with access to the FEO have also shown faster acquisition on a water plus maze, and greater retention of the platform location during a no-platform probe (Lewis et al., 2019).

Unfortunately, because there were no impairments in the SJM group, we were unable to determine if having FEO access would ameliorate negative effects of the lighting manipulation. This leaves the compensatory role of the FEO on circadian rhythm disruption unknown. It is possible that the SJM used in this animal model was not severe enough to cause misalignment of the circadian clock. Previous animal models of shift work use photoperiod shifts involving a phase advance of three hours each day (Craig & McDonald 2008; McDonald et al., 2013; Zelinski et al., 2014), which may be viewed as a

more aggressive paradigm. Therefore, future studies on the topic of circadian disruption may examine the ameliorative effects of the FEO using other lightning manipulations, such as, McDonald and colleagues' photoperiod shifting paradigm. Further, it may be worth being cognisant of the time of day training and testing takes place. The current study performed behavioural training and testing at approximately the same time each day. Previous research has suggested that cognitive tasks which require a great deal of attention have the potential to act as a *zeitgeber* (Gritton, Stasiak, Sarter, & Lee, 2013) and therefore in the case of the current study possibly counteract impairments due to the SJM.

That being said, actograms produced from running wheels in a previous experiment (Lewis et al., 2019) using the same lighting manipulation used in the current study suggests that rats exposed to the SJM do demonstrate characteristic free running behaviour, which is an indicator of circadian misalignment. Therefore, it may be postulated that it is not that the SJM is not severe enough to elicit profound impairment, but that perhaps, the duration of the paradigm was too short. Craig and McDonald (2008) suggested that a 16-day photoperiod phase advance was to be considered acute, and not long enough to show lasting impairment on the Morris water maze task. However, that same paradigm at 64 days duration was considered chronic disruption, and rats showed deficits in hippocampal-dependent learning and memory. Therefore, it is reasonable to suggest that the current study duration of 32 days was also not long enough to meet the threshold for the impairment that is observed at the chronic level of disruption. Future studies on the subject should consider extending the current SJM to a duration that is considered chronic, such as the 64-day definition provided by Craig and McDonald

(2008). This would inform the question of whether the SJM is not eliciting impairment due to duration of the paradigm.

The results from the present study's EPM data show that there are no significant differences between groups, which indicate that stress is not a confound associated with this lighting manipulation. There are previous studies which use aforementioned aggressive phase shifts (Craig & McDonald, 2008; Zelinski et al., 2014) which do not report stress measures. Circadian disruption, however, is often considered a stressor as it modifies the release of stress hormones, such as, catecholamines and glucocorticoids (Koch, Leinweber, Drengberg, Blaum, & Oster, 2016). This is particularly pertinent to the hippocampus as it is highly sensitive to glucocorticoids, and increased levels can lead to hippocampal degradation (Conrad, 2008). It has been shown that as intensity or duration of stress increases, the greater the negative consequences on hippocampal functioning, including learning and memory (Kim, Pellman, & Kim, 2015). Other lighting manipulations are often either more severe, or longer in duration, making it possible that stress may play a role in the observed deficits in hippocampal-dependent learning and memory, which was not a factor in the current study.

Furthermore, there are few studies such as the current study and Craig and McDonald (2008) which investigate the effects of circadian disruption on hippocampal impairment in the anterograde direction. Due to the limited number of studies in this direction, it is difficult to determine if the current study's null results or the Craig and McDonald (2008) finding was spurious in nature. However, previous studies have trained rats on behavioural tests prior to administration of a lighting manipulation and found that retention was impaired at recall (McDonald et al., 2013; Zelinski et al., 2014). Perhaps, it

is true that hippocampal impairment is most vulnerable in the retrograde direction. The effects of lighting manipulations on retrograde learning and memory has been well-documented, crediting reentrainment patterns for the amnesic deficits (Fekete, Van Ree, & De Weid, 1986; Fekete, Van Ree, Niesink, & De Weid, 1985; Tapp & Holloway, 1981). In order to further examine this in the context of this study, a follow up to the current study is proposed. This involves using the current SJM to investigate if exposure to the lighting manipulation after training on the hippocampal-dependent water maze task impairs recall of the task during a no platform probe. In addition to the SJM, rats would be grouped based on meal (1M group; MM group), to examine if access to the FEO can ameliorate deficits in recall due to exposure to the SJM. The results of such an experiment could offer insight into the question of whether anterograde hippocampal memory or retrograde hippocampal memory is most vulnerable to circadian disruption.

As social jet lag becomes more widespread within today's society, it remains vital to continue to research these variables within vulnerable populations. With reference to the implications that social jet lag may pose on learning and memory, some populations worth looking into in particular are adolescents and undergraduate students. Adolescents typically show much later chronotypes than older age groups, henceforth, often undergo insufficient sleep throughout the week due to school, and as a result, sleep longer on the weekends (Martin et al., 2016; Roenneberg et al., 2004). Preliminary data from an ongoing study in our research group looking at adolescents' sleep and meal schedules as they correlate with performance on a cognitive task, suggest that adolescents that skip meals are more likely to demonstrate poor performance on a cognitive task.

It is also true that while adolescents are particularly at risk for social jet lag, so are post-secondary students, particularly if they too have an evening chronotype (Roenneberg et al., 2004; Wittmann et al., 2006). This is the rationale behind a currently ongoing pilot study of undergraduate students, also assessing their sleep and meal schedules to see if regularity of these variables correlates with improved performance on cognitive tasks.

In conclusion, it is clear that while circadian rhythm research is receiving much needed attention, there is still a great deal of work to be done. With societal pressures continuing to increase and technology steadily advancing it is important to continue to research the effects these changes are having on the body, and what we can do to attempt to combat the negative repercussions. It is important that this research involves both human studies and animal models to get an all-encompassing story of the effects of circadian rhythm disruption on health, disease, and cognition.

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Table 1

Social Jet Lag Manipulation (SJM) Schedule

Day	Lights On	Lights Off
Saturday	11:00	03:00
Sunday	12:00	24:00
Monday	07:00	23:00
Tuesday	09:00	23:00
Wednesday	09:00	24:00
Thursday	07:00	22:00
Friday	08:00	01:00

Note. Day 1 of the SJM was a Saturday. This manipulation repeated for 32 light changes. Therefore, the total duration of the lighting manipulation was 32 days.

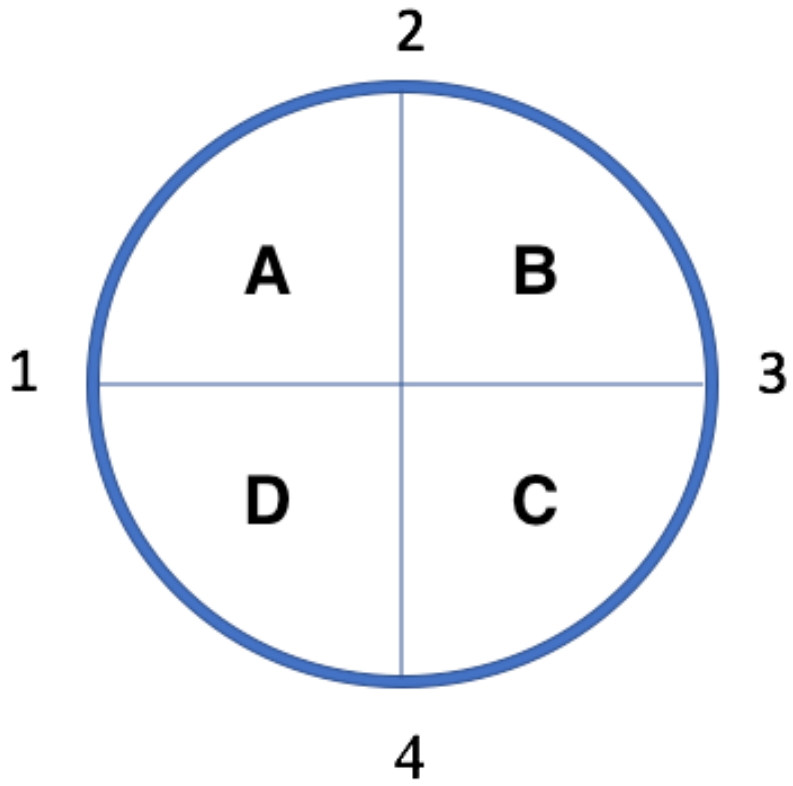

Figure 1. Visual representation of the Morris water maze apparatus with quadrants and release positions. During the acquisition phase, the escape platform was in Quadrant C. During the massed training phase, the escape platform was in Quadrant A. During the competition phase, the escape platform was in Quadrant C. The escape platform was removed from the arena during no-platform probes.

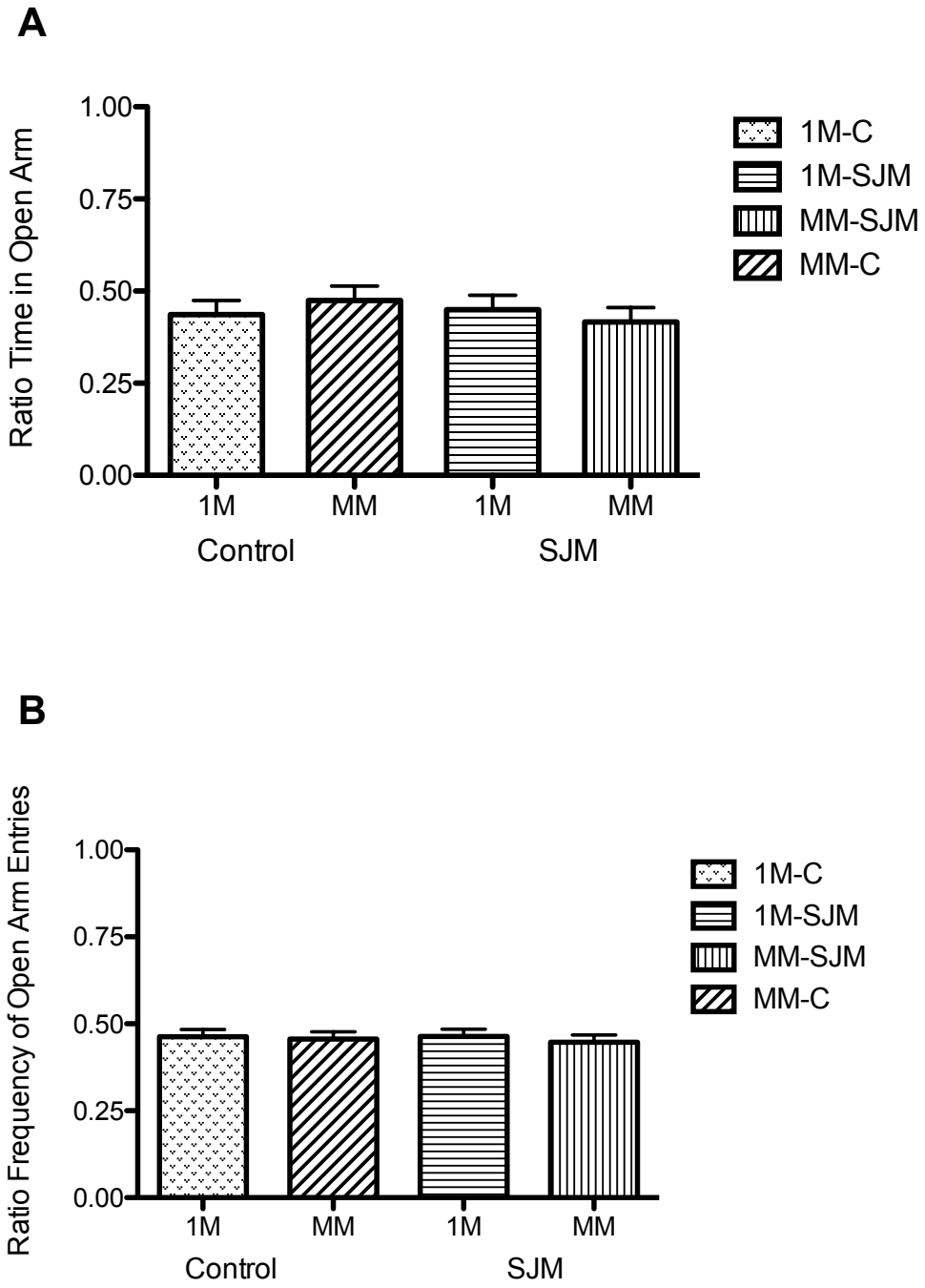

Figure 2. Average (±SEM) ratio of time spent in the open arms/time spent in all of the arms (A) and ratio of frequency of open arm entries/all arm entries (B) per group on EPM.

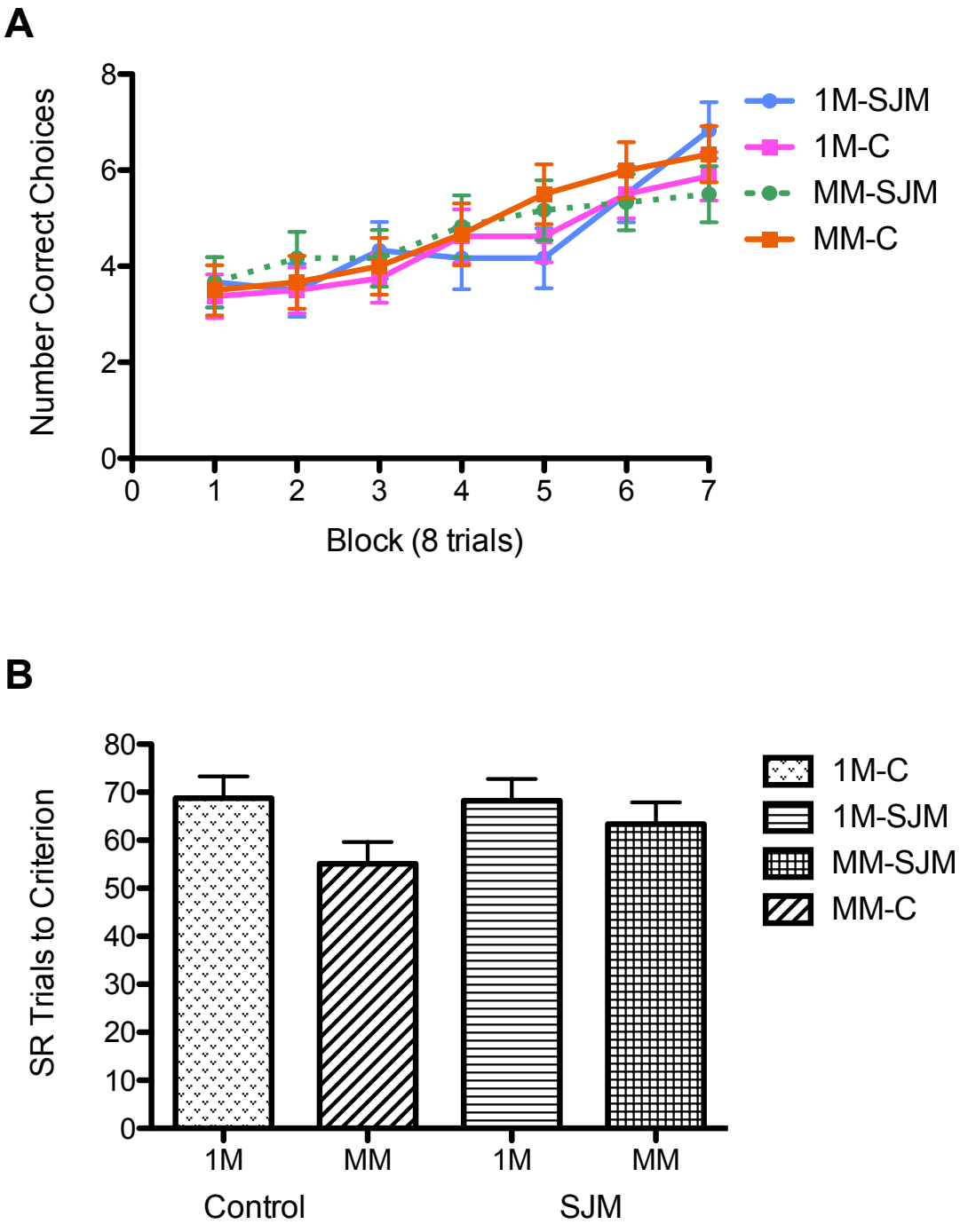

Figure 3. A) Acquisition of SR task across groups by 7 blocks of 8 trials B) Average (±SEM) trials to criterion (18/20) on the SR task.

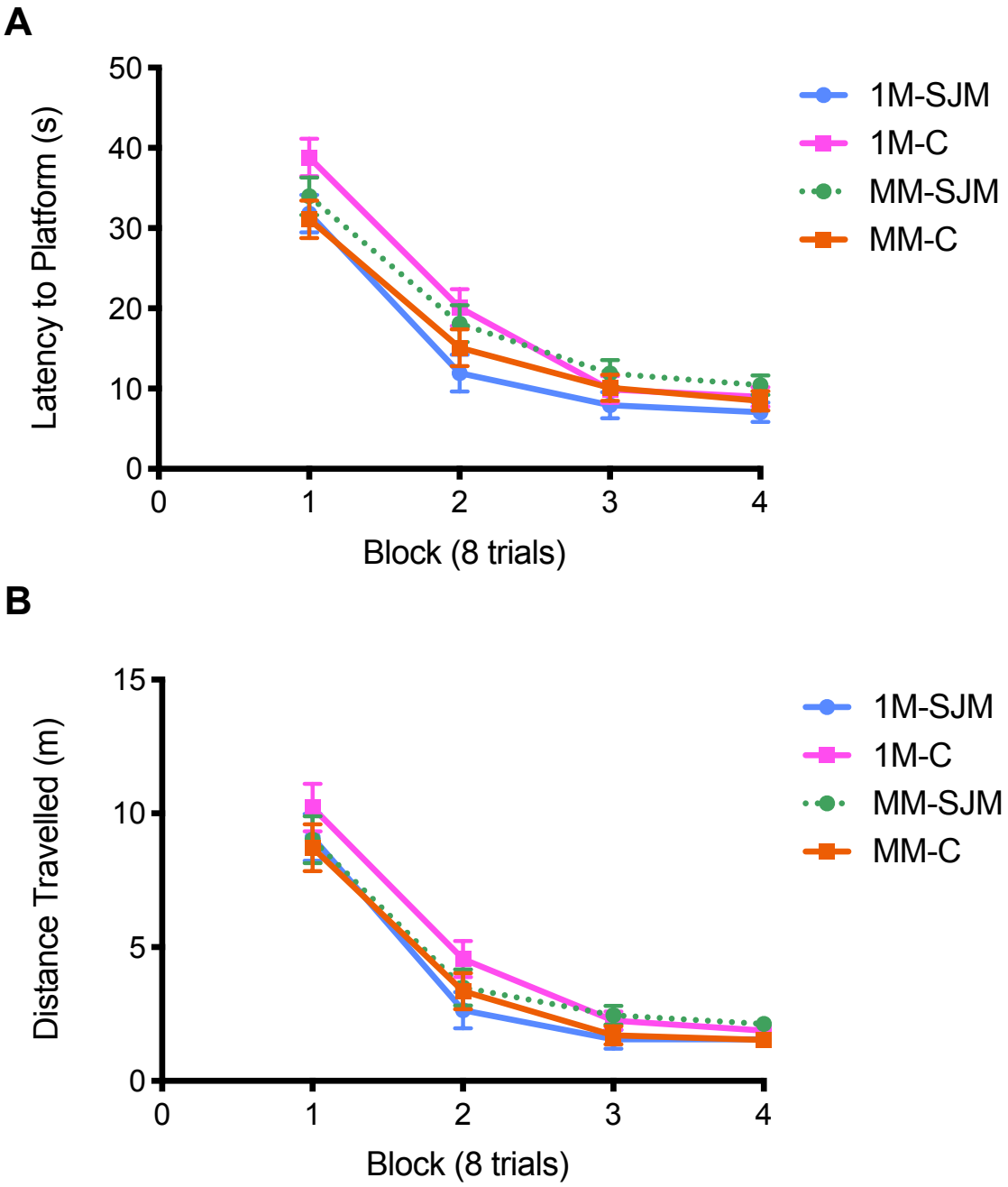

Figure 4. (A) Acquisition of escape platform during the acquisition phase of the rapid acquisition WM task according to latency in seconds across groups by 4 blocks of 8 trials. (B) Average distance travelled in a trial per group in metres during the acquisition phase by 4 blocks of 8 trials.

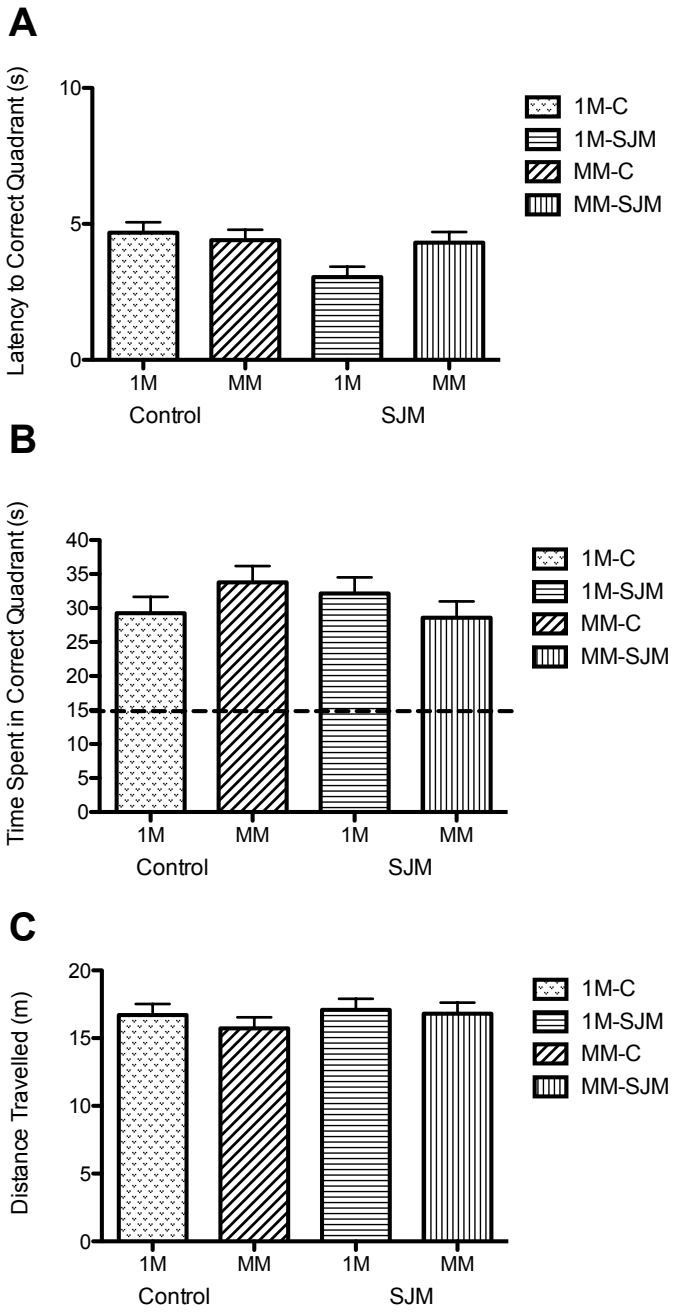

Figure 5. (A) Average (±SEM) latency in seconds to the correct quadrant per group during Probe 1 of the WM task. (B) Average (±SEM) time in seconds spent in the correct quadrant per group during Probe 1 of the WM task. The dotted line represents chance. (C) Average (±SEM) distance in meters travelled per group during Probe 1 of the WM task.

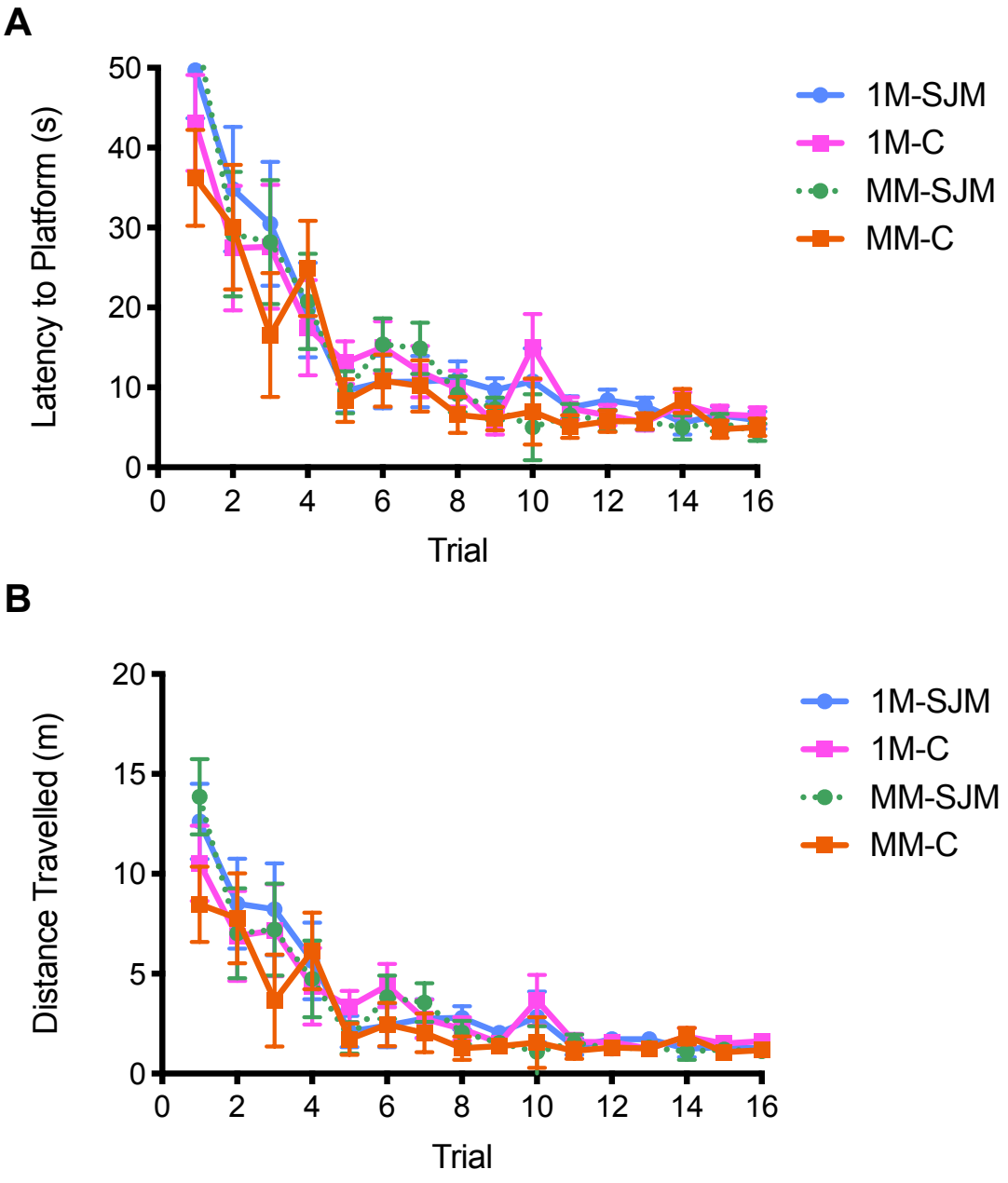

Figure 6. (A) Acquisition of escape platform during the massed training phase of the rapid acquisition WM task according to latency in seconds across groups by trial. (B) Average distance travelled in a trial per group in metres during the massed training phase.

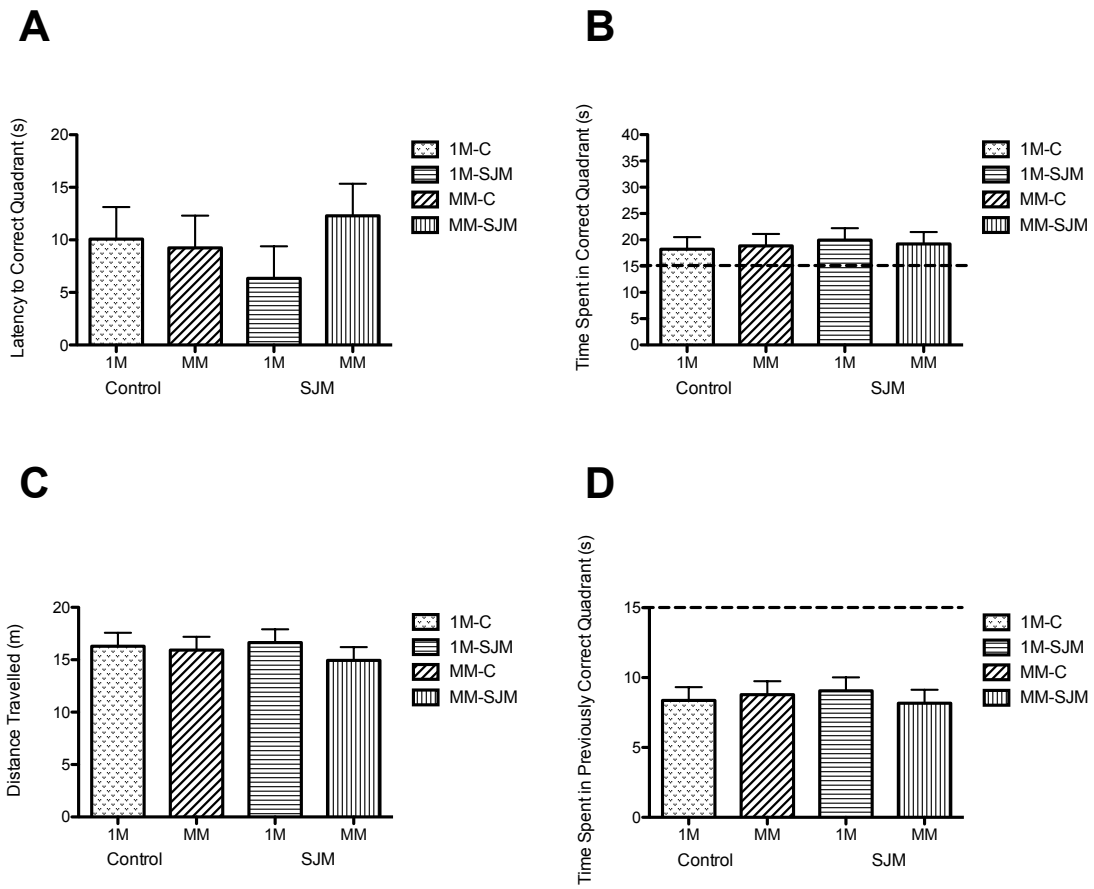

Figure 7. (A) Average (±SEM) latency in seconds to the correct quadrant per group during Probe 2 of the WM task. (B) Average (±SEM) duration in seconds spent in the correct quadrant per group during Probe 2 of the WM task. The dotted line represents chance. (C) Average (±SEM) distance in meters travelled per group during Probe 2 of the WM task. (D) Average (±SEM) time spent in the previously correct quadrant in seconds per group during Probe 2 of the WM task. The dotted line represents chance.

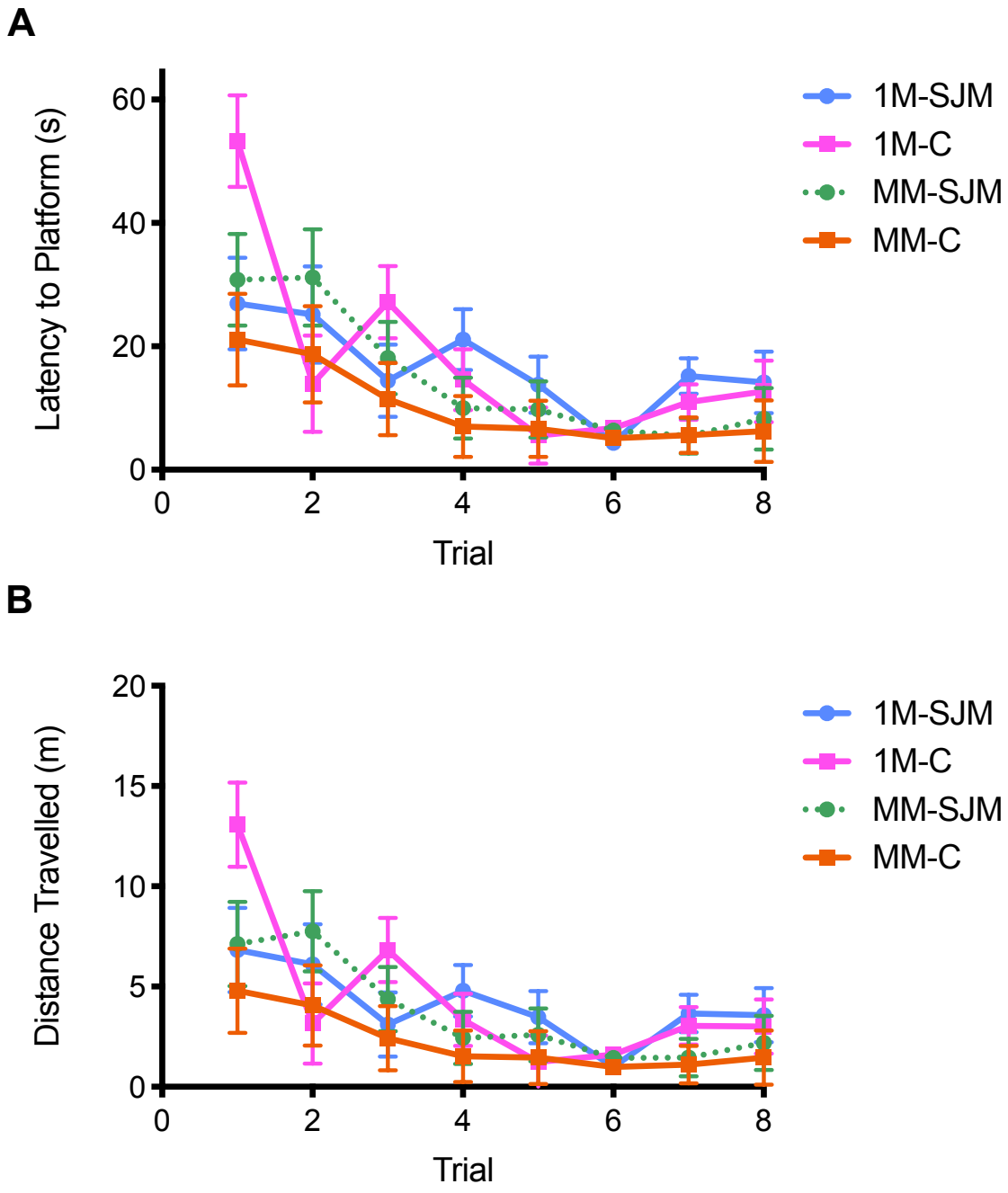

Figure 8. (A) Acquisition of escape platform during the competition phase of the rapid acquisition WM task according to latency in seconds across groups by trial. (B) Average distance travelled in a trial per group in metres during the competition phase.

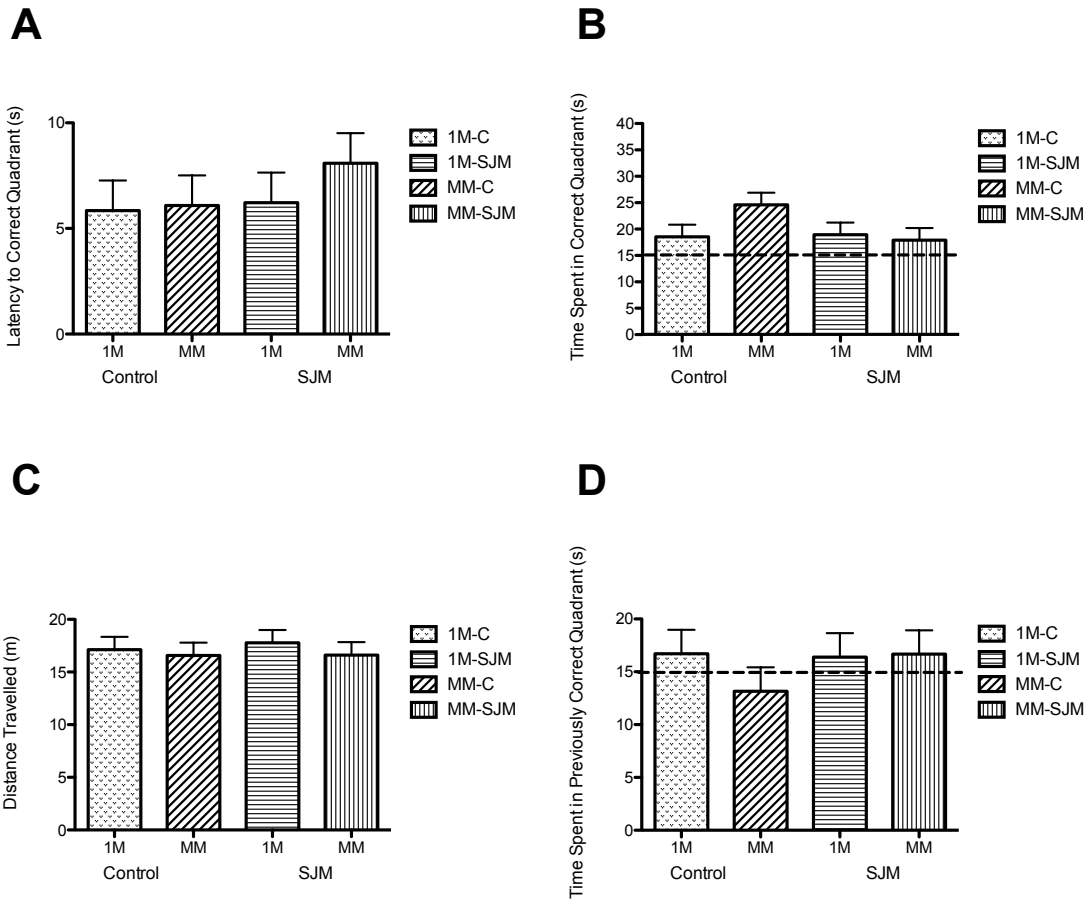

Figure 9. (A) Average (±SEM) latency in seconds to the correct quadrant per group during Probe 3 of the WM task. (B) Average (±SEM) duration in seconds spent in the correct quadrant per group during Probe 3 of the WM task. The dotted line represents chance. (C) Average (±SEM) distance in meters travelled per group during Probe 3 of the WM task. (D) Average (±SEM) time spent in the previously correct quadrant in seconds per group during Probe 3 of the WM task. The dotted line represents chance.