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Paw preference is associated with behavioural despair and spatial reference memory in male rats

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ABSTRACT

Paw preference, one of the well-studied behavioural markers of asymmetry, has been associated with affective states and pathologies such as behavioural despair, a rodent model of clinical depression. However, a consistent differential effect of paw preference has not been observed for cognitive functions. In order to investigate the affective properties of paw preference together with its potential cognitive effects, we grouped male Wistar rats as left- or right-pawed, and tested them in the forced swim test and Morris water maze for behavioural despair and spatial memory performance, respectively. We found that left-pawed rats were significantly more susceptible to behavioural despair, while spatial learning performance of the two groups were not different over a five-day Morris water maze task. Left-pawed rats, however, displayed a better reference memory than the right-pawed ones on the subsequent probe trial when the hidden platform of the maze was removed. These findings indicate paw preference as a vulnerability factor for behavioural despair and reveal a previously unknown association between left-paw preference and reference memory performance as assessed in the probe trial of the Morris water maze.

1. Introduction

Cerebral asymmetry, defined as anatomical or functional dissimilarities between the two cerebral hemispheres, has been associated with differential stress response (Ocklenburg et al., 2016) and various stress-related psychopathology, including clinical depression (Hecht, 2010). It was shown that the left hemisphere is more vulnerable to the degenerative effects of stress hormones (Cerqueira et al., 2008). In another study, right hemisphere activation was associated with acute depressive symptoms (Herrington et al., 2010). Cerebral asymmetry is also observed in antidepressant treatment, which increased oscillatory synchrony in the left hemisphere (Rotenberg, 2008). Furthermore, metabolic activity in the left hemisphere was positively correlated with a therapeutic response (Rotenberg, 2008). In light of these clinical findings, behavioural manifestations of cerebral asymmetry emerge as a promising therapeutic target in stress regulation and treatment of depressive disorders.

Handedness is a well-studied behavioural marker of cerebral asymmetry associated with individual differences at the functional (Toga and Thompson, 2003), morphological (Galaburda et al., 1978) and molecular levels (Sun and Walsh, 2006). It was originally hypothesized that left-handed people experience higher levels of stress at birth (Bakan et al., 1973). This finding could not be replicated by later studies (Van Der Elst et al., 2011a; Van der Elst et al., 2011b). Similarly, certain studies failed to find any association between laterality and cerebral asymmetry (see Esteves et al., 2020b). While it cannot be deemed as a universal marker of brain asymmetry, handedness reflects central asymmetry that may correlate with neuroanatomical asymmetries that provide a potential explanation for observing a higher susceptibility to depression in left-handed individuals compared to the right-handed population (Elias et al., 2001).

Following handedness studies, animal research has established the differential effects of paw preference in various functions (see Ocklenburg et al., 2016). Paw preference in rodents was associated with cerebral asymmetry at the molecular (Zimmerberg et al., 1974), functional (Hamani et al., 2010), and behavioural levels (Castellano et al., 1989; Soyman et al., 2015). The tendency to prefer one paw over the other in rodents was also suggested to be a learned phenomenon as preference may be elicited by the initial rewarded trials during a paw preference test (Ribeiro et al., 2011). A large enough sample size would eliminate this possibility by equally distributing initial rewarded trials to both paws. The dominant theory, therefore, states that paw preference, as in

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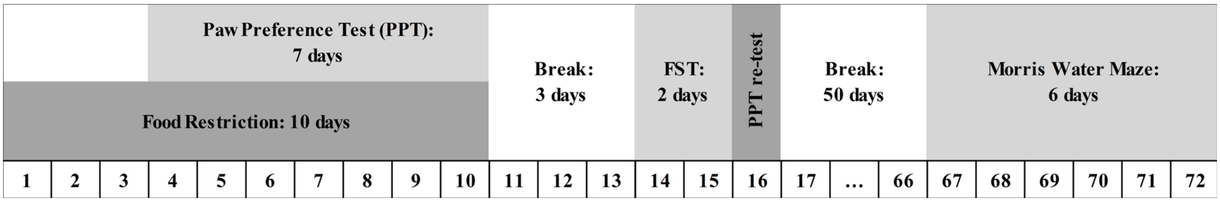

Fig. 1. Experimental timeline and the experimental days (below). Colours indicate food restriction (dark grey) and behavioural testing (light grey).

primate handedness, is not a simple behavioural adaptation, but a stable trait and a hardwired indication of cerebral asymmetry (Collins, 1985; Miklyaeva et al., 1991). Perhaps the strongest evidence comes from the differential effects of paw preference in animal models of depression. An earlier study in female rats found left-pawed rats to be significantly more vulnerable to behavioural despair compared to right-pawed ones, as induced by forced swim tests (FSTs; Soyman et al., 2015).

Since depressive symptoms are often comorbid with different types of cognitive impairment, utilizing cognitive paradigms is essential to understand how paw preference relates to depression (Sun and Alkon, 2004). A relatively recent study, using male Wistar rats, suggested that paw preference alters spatial memory performance in the Morris water maze (MWM) depending on the quadrant animals start swimming in (Budilin et al., 2015). Such a differential cognitive effect was not replicated in the aforementioned behavioural despair study utilizing the same spatial learning maze in female Wistar rats (Soyman et al., 2015). This contradiction may be the result of a sex difference arising from dissimilar lateralization. There are known differences between male and female rodents, indicating female animals to be more strongly lateralized (Betancur et al., 1991) and showing different levels of paw preference than males due to distinct neuronal correlates (Alonso et al., 1997; Sullivan et al., 2009). These sex differences in paw preference persist during induced stress (Ocklenburg et al., 2016; Sullivan et al., 2009), providing further support for paw preference as a reliable indicator of cerebral asymmetry.

Establishing paw preference as a predictor of stress-induced behaviour, in the absence of a major differential cognitive effect that may be comorbid with depression, provides support for the use of handedness as a marker of susceptibility in certain mood disorders. The present study investigated whether paw preference in male rats is a vulnerability factor for behavioural despair induced by forced swimming, and to what extent it correlates with spatial memory performance in the MWM.

2. Methods

2.1. Subjects

Adult male Wistar rats (272−360 g; n = 24) were individually housed in a temperature-controlled vivarium (21 ± 1 °C; ~50 % humidity; 12:12 day/night cycle, lights on at 7:00 AM) throughout the experimental procedure, excluding the 50 day-long break for which they were kept in cages of four. A food restriction protocol was applied prior to and during the paw preference test (PPT) for 10 days, during which animals were not given any food for 24 -hs every other day. During the intermittent days, animals were provided with *ad libitum* food and water. All procedures were approved by the Boğaziçi University Institutional.

Ethics Committee for the Local Use of Animals in Experiments and carried out by licenced personnel.

2.2. Experiments

2.2.1. Paw preference test

Food-deprived rats were introduced to the PPT box, where a bait could only be reached by using one paw, but not both, through a narrow tube. The preferred paw of the animal in each reach was recorded (see Collins, 1985). PPT was utilized every other day over a week (4 test and 3 inter/no-test days) with 50 bait reach trials per day. Animals were grouped as right-pawed, left-pawed or observed/potential ambidextrous according to their preferred paws based on the last two days of testing composed of a total of 100 trials. The preference strength was calculated for each rat by recording how many times the preferred paw was used in these 100 trials. The criterion to assign paw preference was to display ≥70 % preference strength, that is to use the same paw at least 70 times in 100 trials (see Soyman et al., 2015). An additional test day was conducted following the FSTs to assess the stability of the preferred paw (PPT re-test).

2.2.2. Forced swim test

An acrylic glass cylinder (height: 45 cm, diameter: 30 cm), filled to 30 cm height with water at 25 °C ± 0.1, was used for testing. Rats were forced to swim 15 min on the first day (FST1) and 5 min on the second day (FST2), in accordance with the original procedure (Porsolt et al., 1977). All sessions were recorded with a video camera for offline analyses. Behavioural despair was assessed by comparing the duration of immobility in the first 5 min of FST1 and FST2. This analysis method is utilized for assessing the effects of long-term manipulations or trait features, such as paw preference, as these may differentially affect the first, which is the induction, session of the FST (Drossopoulou et al., 2004; Brenes et al., 2009; Ecevitoglu et al., 2019). An FST index was also calculated by taking the ratio of immobility in FST2 to that in the first 5 min of FST1 (i.e. FST2/FST1 × 100).

2.2.3. Morris water maze

A circular acrylic glass pool (height: 60 cm, diameter: 120 cm), filled with water at 24 °C ± 0.1, was used to assess spatial learning and reference memory performance. The pool was surrounded by a number of fixed objects serving as visual cues. Spatial learning was assessed for five days, during which a transparent 10 × 10 cm platform was placed 2 cm beneath the water level. Each of these five training/test days consisted of five trials with 10-minute inter-trial intervals. Each trial started when the rat was placed in the pool from a randomly-chosen quadrant, and ended either when it found the hidden platform or at the end of 60 s, after which it was gently guided to the platform. Rats were allowed to stay on the platform for 10 s at the end of each trial. Learning was measured by the total swimming time until reaching the platform (escape latency). A 2-minute post-training probe trial was utilized next day by removing the hidden platform. The time spent within the quadrant where the platform was originally located indicates spatial reference memory. All sessions were recorded with a video camera.

2.3. Experimental procedure

All animals underwent a 10-day food restriction protocol. The PPT started on Day 4 and ended after 7 days together with food restriction. Once the rats were categorized based on their paw preference, they rested for three days and then tested in the FST for two consecutive days, 24 h apart. A paw preference re-test was applied after the last FST on Day 16. In order to minimize the stress and potential performance-related cognitive effects of the PPT and FST, animals were group-caged and rested for 50 days before being introduced to the MWM, which was run for 6 days including the probe trial day (Fig. 1).

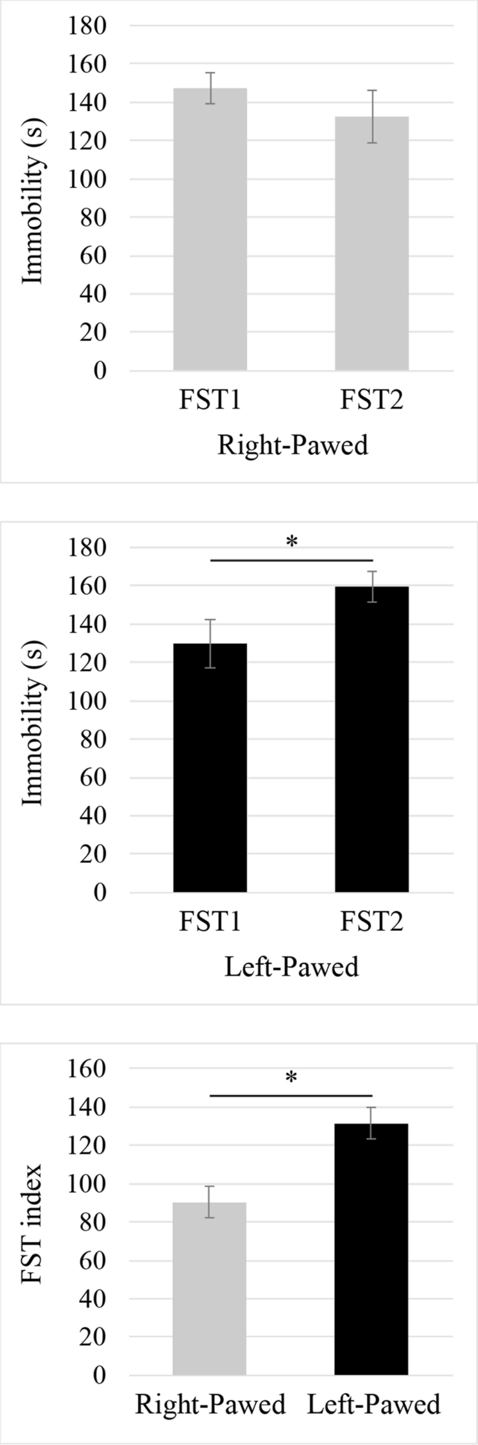

Fig. 2. Durations of immobility (mean ± SEM) in the first five minutes of FST1 and FST2 for right- (grey) and left-pawed (black) rats (upper two panels); also compared with the FST index (lower panel). Asterisks indicate statistical significance at $\alpha = 0.05$.

3. Results

PPT results revealed that 18 out of 24 rats displayed paw preference with a minimum preference strength of 94 % within the last two trials, indicating a much higher selectivity than the pre-determined 70 % criterion. Nine of these rats were right-pawed, while the other nine preferred the left-paw. Six rats that did not display dexterity according to the PPT criterion were categorized as observed/potential ambidextrous and excluded from further analyses. No animal showed a change in its preferred paw as assessed by the PPT re-test session ($F_{1,16} = 1.729$, $p = .207$ $\eta p2 = .098$; 2 × 2 two-way mixed ANOVA).

We examined the influence of lateralized function on behavioural despair by comparing the immobility score of the FST, and found a significant interaction with paw preference ($F_{1,16} = 8.001$, $p = .012$, $\eta_p^2 = .333$; 2 × 2 two-way mixed ANOVA; Fig. 2). There was a significant increase in the overall immobility of the left-pawed rats from FST1 ($M \pm SD = 130.00 \pm 37.45$) to FST2 ($159.89 \pm 23.35$; $F_{1,16} = 7.24$ $p = .016$, $\eta_p^2 = .311$). There was no such difference for the right-pawed rats, but a trend pointing to a decline in FST2 immobility (132.556 ± 40.41) as compared to FST1 (147.11 ± 24.02; $F_{1,16} = 1.72$, $p = .21$, $\eta_p^2 = .097$). A similar result was obtained with the FST index: left-pawed rats had significantly higher immobility compared to the right-pawed ones ($t_{16} = -2.76$, $p = .014$, 95 % CI = [9.532–72.854]), indicating behavioural despair (Fig. 2).

Next, we examined the potential effects of paw-preference on spatial learning and reference memory in the MWM. We found a significant effect of the training/test day, indicating that learning was achieved on the fifth day of the MWM ($F_{4,64} = 87.362$, $p < .001$, $\eta_p^2 = .845$; 5 × 2 two-way mixed ANOVA), in which the latency to locate the hidden platform was significantly lower for both groups (8.400 ± 2.474 and 7.933 ± 2.088, right and left-pawed rats respectively), as compared to their first day (37.489 ± 8.034 and 40.844 ± 10.978, right- and left-pawed rats, respectively; Fig. 3). There was no difference between the two groups regarding spatial learning performance across the five training/test days based on the escape latency ($F_{1,16} = 1.398$, $p = .254$, $\eta_p^2 = .080$; 5 × 2 two-way mixed ANOVA; Fig. 3).

We repeated these analyses by comparing the times spent in the quadrant with the platform (target quadrant). We first compared the absolute duration spent on the target quadrant until the animal located the platform and found a significant effect of the training/test day ($F_{4,64} = 25.632$, $p < .001$, $\eta p2 = .616$; 5 × 2 two-way mixed ANOVA). There was a significant difference between Day 1 ($9.727 \pm .643$) and Day 2 ($6.588 \pm .903$; post hoc analysis by Sidak correction, $p = .002$, 95 % CI = [1.038–5.240]); as well as between, Day 3 (5.649 ± 0.605) and Day 4 ($3.470 \pm .339$; post hoc analysis by Sidak correction, $p = .023$, 95 % CI = [.227–4.130]). Since differences in escape latency contaminate these results, we repeated the analyses by comparing the proportional target quadrant durations. This refers to the proportion of the time spent in the target quadrant to the total trial duration of each animal. The results did not change ($F_{4,64} = 14.051$, $p < .001$, $\eta p^2 = .468$; 5 × 2 two-way mixed ANOVA), pointing to a significantly better performance on Day 2 (40.127 ± 2.028) as compared to Day 1 ($25.109 \pm .980$; post hoc analysis by Sidak correction, $p < .001$, 95 % CI = [−20.680 – −9.358]). As in the original analyses, there was no difference between the two groups ($F_{1,16} = .670$, $p = .425$, $\eta p^2 = .040$; 5 × 2 two-way mixed ANOVA).

When spatial reference memory was assessed with an additional probe trial, we found that the left-pawed animals spent significantly more time in the quadrant where the hidden platform was originally located (53.200 ± 3.29), as compared to the right-pawed group (48.378 ± 5.83, $t_{16} = 2.16$, $p = .046$, 95 % CI = [.092–9.552]; Fig. 3). This points to a significantly better spatial reference memory in the left-pawed group.

There was no correlation between behavioural despair and spatial learning performance. Immobility scores of FST2 neither correlated with the last training/test day of the MWM, on which learning was achieved ($r = -.066$, $p = .793$) nor with the probe trial assessing reference memory ($r = .082$, $p = .746$). Similar results were obtained with the immobility indices and the same MWM parameters ($r = -.148$, $p = .558$; $r = .261$, $p = .295$, respectively for the last day of the MWM and the probe trial).

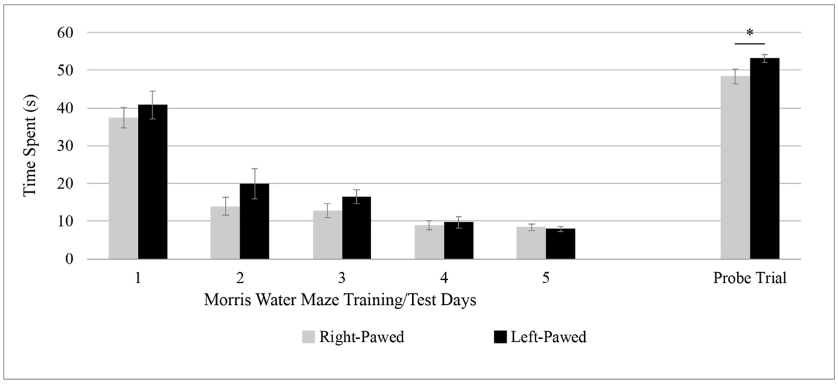

Fig. 3. Time spent (mean ± SEM) for reaching the platform (escape latency) during the five-day training/testing (left) and in the target quadrant during the probe trial (right) by right- (grey) and left-pawed (black) rats. Asterisk indicates statistical significance at $\alpha = 0.05$.

4. Discussion

Motor asymmetry, and its most common form handedness or paw preference, has been linked to cognitive (Budilin et al., 2015) and affective functioning (Soyman et al., 2015). In order to evaluate potential differential effects of paw preference in both domains, we utilized a rodent model of clinical depression together with a well-known spatial memory task following paw preference testing. Left-pawed rats showed significantly more immobility in the FST and performed better in the probe trial of the MWM, indicating a susceptibility to behavioral despair and better spatial reference memory.

In accordance with these findings, a study utilizing the Beck Depression Inventory with college students found that left-handed males displayed elevated depression scores compared to right-handed ones (Elias et al., 2001). A similar relationship between behavioural lateralization and depression-like behaviour was also observed in other species. Left-pawed female rats, for instance, are more susceptible to despair induced by forced swimming (Soyman et al., 2015).

Other forms of lateralized movement such as rotational behaviour (Carlson and Glick, 1991) and head-turning asymmetries (Soyman et al., 2018) have also been associated with depression-like behaviour in rats. In addition to observable functional laterality, hemispheric differences also determine the antidepressant response. Deep brain stimulation of the left, but not right, ventromedial prefrontal cortex has antidepressant effects in rats as observed in the FST (Hamani et al., 2010). It is now clear that both the hemispheric differences and observable lateralized function are differentially correlated with affective behaviour, including behavioural despair (Unal and Canbeyli, 2019).

It should be noted that the PPT forces rats to use only one paw in a trial. An alternative would be the Pawedness Trait Test (PaTRaT; Cunha et al., 2017), which allows animals to use both paws simultaneously. This paradigm would also reveal the degree of paw preference. In fact, two recent studies focused on preference strength in relation to cognitive abilities. A positive correlation was found between the degree of preference and problem solving skills in cats (Isparta et al., 2020), whereas preference strength was negatively associated with learning in wild grey squirrels (Leaver et al., 2020). Present study revealed a strong preference for both right- and left-pawed animals with a minimum preference strength of 94 % within the last two trials. Consequently, we were unable to check the correlation between preference strength and the severity of depression-like behaviour, measured as the total duration of immobility in the FST.

In this regard, an important consideration is the validity of the FST as a rodent model of clinical depression. The FST has been criticized as a poor measure of psychological despair and proposed as a learning paradigm in previous studies (De Pablo et al., 1989; Molendijk and de Kloet, 2015). According to this criticism, the actual measure of the FST, (im)mobility, can be an acquired behaviour. This issue is more critical for rats, which are placed in the water-filled FST cylinder for two consecutive days, as opposed to the single-day mouse FST. However, it must be remembered that the power of FST does not come from its theoretical basis, but its predictive power for antidepressant efficacy. As such, behavioral despair remains the method of choice in rodent depression research not necessarily for its validity, but reliability (Unal and Canbeyli, 2019). It is still true that a potential learning capacity/performance difference between left- and right-pawed rats that may confound the FST measure would have contributed to the results. We estimate that the contribution of such a potential difference in performance would be smaller than the substantial effects of an antidepressant treatment.

We did not find a difference between right- and left-pawed rats in spatial learning performance within the initial training/test days of the MWM. Similar learning curves were derived between the two groups as observed in a previous study (Budilin et al., 2015). However, the MWM revealed an important inter-group difference in spatial reference memory, assessed by an additional probe trial following the standard five-day task. Left-pawed rats performed significantly better in the probe trial, pointing to a major sex difference as female left- and right-pawed rats display similar levels of spatial reference memory in the same paradigm (Soyman et al., 2015). Comparing our results and the findings of another study using male Wistar rats (Budilin et al., 2015) with the earlier work in female rats (Soyman et al., 2015), we deduce that the cognitive effects of paw preference may also be more evident in males than females. It is well-established that males and females have different behavioural and physiological responses to stress (Ocklenburg et al., 2016), which may underlie the observed difference in spatial reference memory. In fact, the stressful nature of the MWM may have brought this subtle sex difference to surface. Water-based spatial learning tests constitute a popular choice in behavioural neuroscience due to their inherent motivational aspect. Yet, these tests induce stress, which by definition lead to sex-specific effects. Alterative spatial memory paradigms are needed for a comprehensive evaluation of the differential effects of paw preference with respect to sex differences.

The present study revealed a left-paw bias in behavioral despair induced by forced swimming. Left-paw preference, at the same time, was associated with better spatial memory performance in the probe trial of the MWM. Paw preference in rodents may not directly translate to human handedness. Asymmetrical plasticity may have differential weights on observed handedness or paw preference and lead to different physiological and behavioral outcomes in different species (Esteves et al., 2020a, 2020b). Furthermore, behavioral laterality such as handedness could not always be linked to structural laterality or cerebral asymmetry (Good et al., 2001; Guadalupe et al., 2014, 2016). Yet, several studies investigating the relationship between different forms of cerebral and/or motor asymmetry and psychopathology have found a differential association in terms of symptoms, susceptibility or therapeutic response (Baas, 2004; Berretz et al., 2020; Hecht, 2010; Ocklenburg et al., 2016). Results of the present study should therefore be evaluated within this framework, pointing out handedness as a potential vulnerability factor in clinical depression.

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CRediT authorship contribution statement

Alev Ecevitoglu: Investigation, Formal analysis, Writing - original draft. **Efe Soyman:** Investigation, Conceptualization, Methodology, Writing - review & editing. **Resit Canbeyli:** Conceptualization, Methodology, Supervision, Writing - review & editing. **Gunes Unal:** Conceptualization, Supervision, Project administration, Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.beproc.2020.104254.

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