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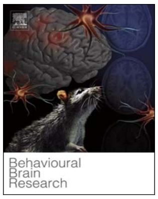

Short communication

Head-turning asymmetry: A novel lateralization in rats predicts susceptibility to behavioral despair

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ABSTRACT

Behavioral markers of laterality reflecting underlying neurobiological asymmetries between the cerebral hemispheres are related to differential susceptibility to mood disorders. In the present study, we investigated the strength and consistency of a novel behavioral lateralization, head-turning asymmetry, and its relation to behavioral despair in adult female Wistar rats. Head-turning biases were determined in a test where water-deprived rats had to turn their head to right or left to gain access to a water dispenser. This procedure was administered 4 times over 8 days. Four days after the head-turning test, rats were subjected to two forced swim tests separated by 24 h to examine the relationship between head-turning asymmetry and behavioral despair. Rats were administered one more head-turning test session after the second swim test to determine whether behavioral despair induction altered head-turning direction preferences. Results revealed significant correlations among head-turning test sessions indicating head-turning direction preference as measured with our method is a consistent behavioral lateralization. Although most rats were strongly lateralized, there was no bias in either direction at the population level. Importantly, we found that while rats with a left head-turning bias showed a significant increase in the duration of immobility from the first to the second swim test, right-biased rats performed similarly in the two swim tests. Behavioral despair induction did not change head-turning direction preferences. The present findings show that head-turning asymmetries are predictive of mood disorders in rats and may serve as the basis to elucidate the mechanisms relating hemispheric asymmetries to depression in humans.

Anatomical and functional differences between the two cerebral hemispheres are related to stress reactivity, emotion regulation, and depression [1–4]. Clinically depressed patients show increased activation in the right, relative to the left, prefrontal cortex in processing of emotional stimuli [5] and downregulating negative affect [6]. Furthermore, stroke patients with left frontal lobe damage, which leaves only the right frontal lobe intact, suffer from severe forms of depression as compared to people with damage to the right hemisphere [7], and stimulation of the right frontal, temporal, and insular brain regions for localization of seizures in epileptic patients leads to more negative affect than left-sided stimulations [8]. One of several behavioral markers of hemispheric asymmetries, handedness, is also shown to be related to depression. Left-handedness, a sign of atypical right hemispheric dominance for motor activities in humans, has a higher incidence among patients with mood disorders [9] and is associated with greater depression scores in the general population [10–12]. Recently, we demonstrated that this relationship is paralleled in an animal model such that adult female rats with consistent left paw preferences are more susceptible to forced swimming-induced behavioral despair compared to right-pawed rats [13]. This crucial finding indicates that the relationship between handedness and depression has a strong biological basis. Thus, a thorough examination of behavioral asymmetries in animal models will potentially provide a gateway into the detailed neurobiological mechanisms underlying the effects of lateralized brain functioning on depression.

Handedness in humans is related to another behavioral lateralization: head-turning asymmetry. A right head-turning bias in humans exists as early as during the final weeks of gestation [14], continues in supine lying patterns of newborns [15], and persists into the adulthood as assessed in the context of kissing [16]. Although the prevalence of this right-lateralization, 60–80% in the general population [16–20], is weaker than that of right-handedness in humans (~90%), head-turning direction preference is a consistent trait at the individual level [19]. In addition, there is a link between handedness and head-turning asymmetry such that individuals with a right head-turning bias while kissing, score higher in measures of right-handedness [18]. Despite its relation

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to handedness, neural underpinnings of head-turning asymmetry, as well as its relation to emotional processing, remains unknown. In rodents, strong and consistent paw preference is prevalent at the individual level with no clear population bias for either direction [13]. Several other individual-level behavioral lateralities such as drug-induced or spontaneous nocturnal rotation behavior have also been documented in relation to neurobiological differences between the two cerebral hemispheres [21,22]. One study assessed the spontaneous head and tail movements in neonatal rat pups in the first day of life and reported a population-level rightward bias for head movements [23], in parallel to findings in human newborns. However, there has been no report of the existence and consistency of a head-turning asymmetry in adult rodents, similar to the one observed in humans, up to date.

In the present study, our goal was twofold: (1) to test whether a consistent head-turning asymmetry exists among adult female rats and (2) to examine the relationship between these head-turning biases and susceptibility to behavioral despair. Based on documented head-turning asymmetries in humans and the relationship between paw preference and depression in rats, we hypothesized that rats show consistent head-turning direction preferences and left head-turner rats are more susceptible to behavioral despair than the right head-turners.

Twenty naïve adult female Wistar rats (2–4 months of age, 136–210 g at the beginning of the experiment) housed in same-sex cages of 4 in a vivarium (22 ± 2 °C, 12 h:12 h L:D) were used in the present study. The phase of the estrous cycle was not controlled since it does not modulate the forced swim test immobility behavior in adult female Wistar rats [24]. The rats had free access to food and water throughout the experiment except during head-turning tests when they were water-deprived for 24 h before each session. All protocols used in the current study were approved by the Bogazici University Ethics Committee on Animal Maintenance and Experimentation.

To determine head-turning asymmetries, we developed an apparatus with one plexiglass wall that features a window with a height of 2 cm and a width of 8.5 cm, placed 12.5 cm from the floor. A water dispenser was placed just outside this window such that rats had to stand up on hind legs and extend their heads to reach it. The window was narrow so rats had to tilt their heads to left or right to gain access to the water dispenser (Fig. 1A, Video 1). This simple drinking behavior did not require any motor learning and thus tested rats' innate head-turning direction preferences without an external influence. This procedure was administered in 4 separate sessions of 30 min over 8 days. Since drinking is a continuous behavior, the times spent drinking while the head was turned to left and right were recorded separately. The total time spent drinking within a session was 183 ± 14 s (Mean ± SEM). Each rat's right head-turning percentage score was computed for each session separately as well as across the 4 sessions by taking the ratio of the drinking duration while the head was turned to right to the total drinking duration as a percentage. Following the criterion used for paw preferences [13], the rats were classified as left or right head-turners if they preferred one direction equal to or more than 70% of the total drinking time.

Four days after the last head-turning test session, rats were subjected to two consecutive forced swim tests separated by 24 h. Swim tests were performed in a plexiglass cylinder with a height of 45 cm and a diameter of 30 cm, filled with water (25 ± 0.1 °C) up to the height of 30 cm. Animals were allowed to swim for 15 min and 5 min in the first and second swim tests, respectively. Durations of immobility in the first 5 min of the first test and in the second test were measured. Increased immobility in the second swim test compared to the first is a sign of behavioral despair [25]. Thus, for each rat, a behavioral despair index was calculated by taking the ratio of the duration of immobility in the second swim test to the immobility duration in the first swim test as a percentage. The day following the second swim test, rats were subjected to one more head-turning test session to determine whether behavioral despair induction altered head-turning direction preferences.

One rat did not show any drinking behavior in the first two head-turning test sessions and was excluded from further procedures; so, all statistical analyses were based on 19 rats. Right head-turning percentages in all sessions, durations of immobility in the second swim test, and the behavioral despair indices were all non-normally distributed as indicated by Shapiro-Wilk tests (all $W < 0.873$, all $p < 0.017$); thus, nonparametric tests were used for all statistical analyses. The consistency of head-turning asymmetries across sessions was assessed via Spearman correlations. To test whether there was a population-level asymmetry in head-turning, the median right head-turning percentage value was compared to 50% (no asymmetry) using a one sample Wilcoxon signed-rank test. The degree of head-turning laterality for the preferred direction was compared between the left and right head-turner groups via a Mann-Whitney U test. The effects of behavioral despair induction on the head-turning biases were assessed via two

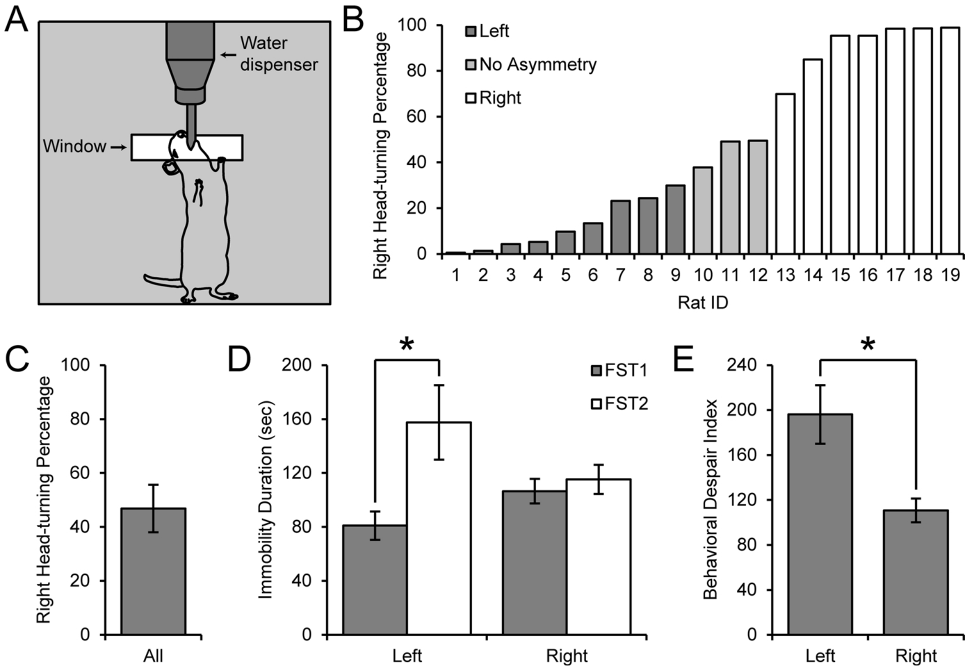

Fig. 1. The assessment of head-turning asymmetry and its relation to behavioral despair. (A) The schematic representation of the head-turning test apparatus and an example rat showing a right head-turning bias. (B) Right head-turning percentages of individual rats. (C) Mean right head-turning percentages of all rats in the study. (D) Mean immobility durations in the initial five min of the first swim test (FST1) and the second swim test (FST2) for the left and right head-turner groups. (E) Mean behavioral despair indices for the left and right head-turner groups. Error bars depict standard errors of the means. Asterisks indicate significant differences.