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Age-dependent decline in learning and memory performances of WAG/Rij rat model of absence epilepsy

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Abstract

Recent clinical studies revealed emotional and cognitive impairments associated with absence epilepsy. Preclinical research with genetic models of absence epilepsy however have primarily focused on dysfunctional emotional processes and paid relatively less attention to cognitive impairment. In order to bridge this gap, we investigated age-dependent changes in learning and memory performance, anxiety-like behavior, and locomotor activity of WAG/Rij rats (a valid model of generalized absence epilepsy) using passive avoidance, Morris water maze, elevated plus maze, and locomotor activity cage. We tested 5 month-old and 13 month-old WAG/Rij rats and compared their performance to age-matched Wistar rats. Results revealed a decline in emotional and spatial memory of WAG/Rij rats compared to age-matched Wistar rats only at 13 months of age. Importantly, there were no significant differences between WAG/Rij and Wistar rats in terms of anxiety-like behavior and locomotor activity at either age. Results pointed at age-dependent learning and memory deficits in the WAG/Rij rat model of absence epilepsy.

Keywords: Anxiety, Learning, Locomotor Activity, Memory, Rats, WAG/Rij, Wistar

Introduction

Growing number of studies started to indicate that epilepsy is not restricted to recurrent seizures and emphasize that neuropsychological symptoms are part of its clinical profile [1,2]. Furthermore, emotional and cognitive dysfunction impacts academic performance and social life not only in drug-resistant epilepsy but also benign epileptic syndromes including absence epilepsy, a neurological disorder that lacks structural deficits and responds well to treatment [2-7]. In addition to neuropsychiatric comorbidities, recent studies investigated the time course of neurocognitive impairments in epileptic patients [8-12]. For instance, Hermann et al. reported progressive cognitive abnormalities in temporal lobe epilepsy patients over a 4-year period compared to age- and sex-matched healthy controls [9]. In another study, Hommet et al. compared adolescents and young adults in complete recovery from benign childhood epilepsy with centrotemporal spikes (BECTS) and childhood absence epilepsy (CAE) [8]. They

found that patients with CAE showed decline in intellectual performance. Furthermore, brain-imaging studies demonstrated that the brain regions implicated in behavior, cognition, and language had different developmental characteristics in CAE [11,12]. These studies overall emphasize the importance of studying age-related aspects of epilepsy for a better understanding of its multi-faced nature and the development of effective tools for tracking and preventing its progression.

In order to elucidate the relation between behavioral/cognitive impairment and epilepsy, research studies have often used models of acquired epilepsy such as kindling or status epilepticus [13-18]. These models, in which limbic structures are affected, are characterized by convulsive seizures. On the other hand, research on genetic models of absence epilepsy has primarily focused on emotional dysfunction and paid relatively less attention to cognitive impairment [19-22]. Moreover, although genetic models are particularly well-suited for detecting and tracking developmental dynamics, age-related behavioral and cognitive alterations in these models remain unexplored.

Wistar-Albino-Glaxo from Rijswijk (WAG/Rij) rats, a strain of Wistar origin, is a widely used, valid genetic

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model of generalized absence epilepsy [23]. Electrophysiologically and behaviorally well-defined absence seizures occur in every member of WAG/Rij rats [23]. Spike-wave complexes (SWD) begin to emerge on the epidural records of two month-old WAG/Rij rats and their frequency and duration increase with age [23]. SWD activity has been suggested to be closely related to depression-like symptoms observed in this model [19,24]. Unlike the depression-like behavior however, the evaluation of the absence epilepsy models in terms of anxiety-like behaviors has not revealed consistent strain differences [25].

The well-documented impact of epilepsy and depression on learning and memory processes, and the existence of relatively few cognitive characterizations of animal models of absence epilepsy in the literature motivated our study. We examined learning and memory performance of 5 months and 13 months old WAG/Rij rats and age-matched Wistar controls in passive avoidance and Morris water maze, two tasks that are well-characterized in terms of their behavioral, neuroanatomical, and neurochemical bases. We further evaluated the locomotor activity and anxiety-like behavior of 5 m and 13 m WAG/Rij and age-matched Wistar rats using locomotor activity cage and elevated plus maze, respectively. Results revealed age-dependent differences between WAG/Rij and Wistar rats in emotional and spatial memory in the absence of clear differences in terms of anxiety-like behavior and locomotor activity.

Materials and methods

Animals

Subjects were 4–6 months old (5 m) and 12–14 months old (13 m), male WAG/Rij and Wistar albino rats. Animals were maintained under standard laboratory conditions on a 12/12-h light/dark cycle (lights on at 7:00 AM). Tap water and food pellets were provided *ad libitum*. Around half of the rats were tested on all behavioral tests on different days. Sixty four rats were tested in locomotor activity cage, 43 rats in elevated plus maze, 71 rats in passive avoidance, and 66 rats in Morris water maze. All experiments were conducted between 09:00 AM and 12:00 PM. All procedures were conducted in accordance with the Regulation of Animal Research Ethics Committee in Turkey (July 6, 2006, Number 26220). Ethical approval was granted by the Kocaeli University Animal Research Ethics Committee (Project number: HADYEK 28, Kocaeli, Turkey).

Procedure

Locomotor activity

Locomotor activity was assessed using an animal activity monitoring system (Commat Ltd., Turkey) composed of a Plexiglas chamber connected to a computer and

monitored by an open field activity software. The Plexiglas chamber (40 cm × 40 cm × 35 cm) was equipped with pairs of infrared photo beams and detectors that were mounted horizontally every 2.5 cm and vertically every 4.5 cm. Interruptions of photocell beams were detected and recorded by the software. Total locomotor activity was expressed as the sum of stereotypic, ambulatory, and vertical activity. Activity was monitored continuously for 10 minutes following acclimatization to the test room illuminated with two 36-W overhead fluorescent bulbs (light intensity 190–220 lx in center of the room and 18–45 lx on the cage floors) for a period of one hour.

Elevated plus maze

Anxiety-like behavior was evaluated in the elevated plus maze apparatus. Maze was made of wood and consisted of two open arms (50 cm × 10 cm) and two closed arms (50 cm × 10 cm, surrounded by a 40-cm high black wall) connected by a central square (10 cm × 10 cm). Maze was elevated to a height of 50 cm. Rats were placed individually in the central square facing a closed arm and allowed to explore the maze freely for 5 minutes. A rat was considered to have entered an arm when all four limbs were inside the arm. The apparatus was cleaned with ethanol solution after each test. The time spent in closed arms and open/closed arm entries were recorded.

Passive avoidance

In passive avoidance test, animals learn to inhibit a previously exerted behavior (i.e., moving from the light chamber to the dark chamber). Rats were tested in a step-through type passive avoidance apparatus (Ugo Basile model 7551, Italy). The apparatus (measuring 22 cm × 21 cm × 22 cm) consisted of a light and a dark compartment separated by a guillotine door.

1. *Pre-acquisition trial*: On day one (training trial), rats were placed individually in the light compartment and allowed to explore this compartment. The door between the two compartments was opened after 30 s. During this stage, the animal could freely move into the dark compartment.
2. *Acquisition trial*: The acquisition trial was conducted 15 min after the pre-acquisition trial. Rats were placed in the light compartment. Following a 30 second-long adaptation period, the door separating two compartments was opened. After the rat completely entered the dark compartment (four paws in), the door automatically closed, and an electric foot-shock (0.5 mA) was delivered for 3 seconds via the grid floor. Animals were then removed from the dark compartment and returned to their home cages. The time taken to enter the

dark compartment was recorded. Any animal failing to cross from the light to the dark compartment within 300 s was discarded from the experiment. Between each training session, both compartments were cleaned to remove olfactory cues.

3. *Retention trial*: Memory was evaluated 24 h post-training by returning the animals to the light compartment and recording their latency to enter the dark compartment (four paws in). No foot-shock was applied in this trial. If a rat did not enter the dark compartment within 300 s, it was returned to its cage and a maximum latency of 300 s was recorded for that rat. The latency to enter the dark compartment served as a measure of retention performance of step-through avoidance responses.

Morris water maze test

The water maze was a circular pool (150 cm in diameter) filled with water (25°C). Small black plastic pieces were placed in the pool in order to make the platform invisible [26]. The pool was located in a dimly lit sound-proof test room with a number of extra-maze visual cues.

Maze was divided into four quadrants and three equally spaced points around the edge of the pool were used as starting positions. The order of the release positions was varied throughout the experiment. An escape platform (10 cm diameter) was located in one of the quadrants 1 cm below the water surface during acquisition sessions. Rats were trained in the Morris water maze for five daily sessions (3 trials per session). Five consecutive daily sessions were all performed between 9.00-12.00 h.

For each acquisition trial, a rat was placed in the pool from one of the three locations (randomly chosen) with its head facing toward the wall of the pool. A trial was initiated with the release of the rat in the pool. After the rat had found and climbed onto the platform, the trial was terminated and the mean escape latency was recorded. The maximum trial length was 60 s. If a rat had not climbed onto the platform within 60 s, the trial was terminated and the experimenter guided the rat by hand to the platform. In these cases, an escape latency of 60 s was recorded.

The inter-trial interval was 30 s. During the inter-trial interval the rat was left on the escape platform before starting the next trial. Following the inter-trial interval, the rat was placed in the pool again from a different location and upon its release the next trial began. At the end of each session, the rat was returned to its cage. The escape latency typically declines during acquisition as the animal learns the location of the hidden platform.

Twenty-four hours after the final acquisition session, a 'probe trial' was used to assess rats' retention of the

location of the hidden platform. During this trial, the platform was removed from the maze and the rat was allowed to search the pool for 60 s. During this period, animals are expected to spend relatively more time searching the quadrant that previously contained the hidden platform compared to other three quadrants.

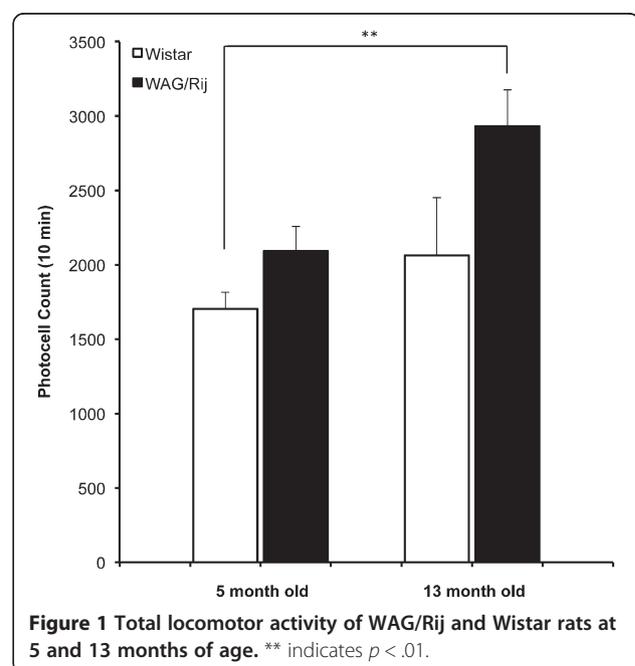
Data analysis

Data from the locomotor activity cage, elevated plus maze, passive avoidance, and probe trials of Morris water maze (separately for two different age groups) were analyzed by one-way ANOVA. Turkey's HSD was used for post-hoc analysis of significant overall differences. Data from the acquisition trials of Morris water maze were analyzed by a two-way mixed design ANOVA (strain x test day) separately for two different age groups. Data are depicted graphically in terms of average \pm SEM. An alpha level of .05 was chosen for statistical significance.

Results

Locomotor activity

Figure 1 shows the total locomotor activity of 5 m and 13 m WAG/Rij and Wistar rats. There was a significant overall difference between the four groups in terms of total locomotor activity, $F(3,60) = 4.96$, $p < .01$. Post-hoc analysis revealed a significant difference only between 5 month-old Wistar and 13 month-old WAG/Rij rats ($p < .01$). There were no significant differences between WAG/Rij and age-matched Wistar rats either at 5 months ($p = .71$) or 13 months of age ($p = .07$).



Elevated plus maze

Figure 2 shows the performance in elevated plus maze separately for different behavioral indices. Time spent in closed arms differed significantly between the four groups, $F(3,39) = 2.89$, $p < .05$ (Figure 2A). Post-hoc analysis revealed that WAG/Rij rats spent less time in closed arms than age-matched Wistar rats only at 13 months of age ($p < .05$) and not at 5 months of age ($p = .88$). There was no overall significant differences between the four groups in terms of time spent in open arms, $F(3,39) = 1.46$, $p = .24$ (Figure 2B) or the ratio of time spent in open arms to time spent in open or closed arms, $F(3,39) = 1.44$, $p = .25$.

There were significant overall differences between the four groups in terms of the number of closed arm entries, $F(3,39) = 7.98$, $p < .001$ (Figure 2C), open arm entries, $F(3,39) = 4.83$, $p < .01$ (Figure 2D), and total number of arm entries, $F(3,39) = 7.27$, $p < .001$ (Figure 2E). Post-hoc analysis revealed a significantly higher number of open arm entries of 13 month-old WAG/Rij rats compared to 5 and 13 month-old Wistar rats (both $ps < .05$). Post-hoc analysis also revealed almost

significantly higher number of open arm entries of 5 month-old WAG/Rij rats compared to 5 month-old Wistar rats ($p = .057$) and 13 month Wistar rats ($p = .054$). 5 and 13 month-old WAG/Rij rats exhibited higher number of closed arm and total arm entries than 5 and 13 month-old Wistar rats (all $ps < .05$). There were no significant differences between the four groups in terms of the ratio of open arm entries to the number of entries to open or closed arms, $F(3,39) = 1.12$, $p < .35$ (Figure 2F).

Passive avoidance

Day 1. There was a significant overall difference between the four groups in terms of time they took to enter the dark compartment, $F(3,67) = 4.87$, $p < .01$ (Figure 3A). Post-hoc analysis revealed that 5 and 13 month-old WAG/Rij rats entered the dark compartment earlier than 13 month-old Wistar rats (both $ps < .05$). There was no significant difference between WAG/Rij and Wistar rats at 5 months of age ($p = .22$).

Day 2. There was a significant overall difference between the four groups in terms of time they took to

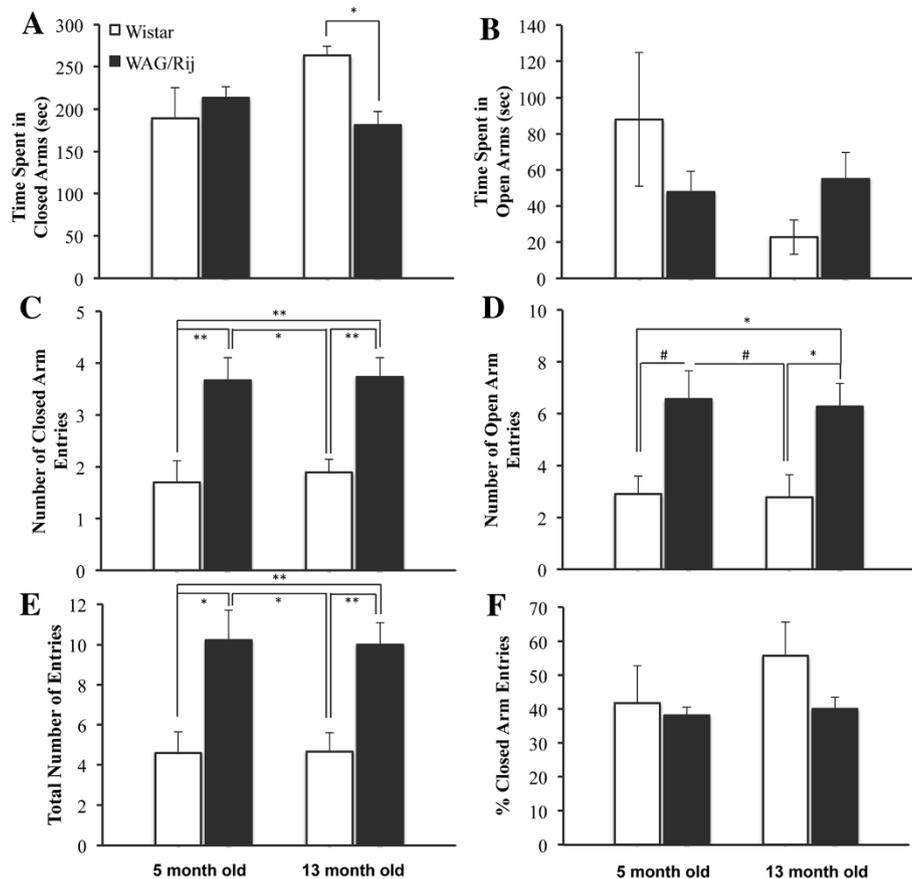
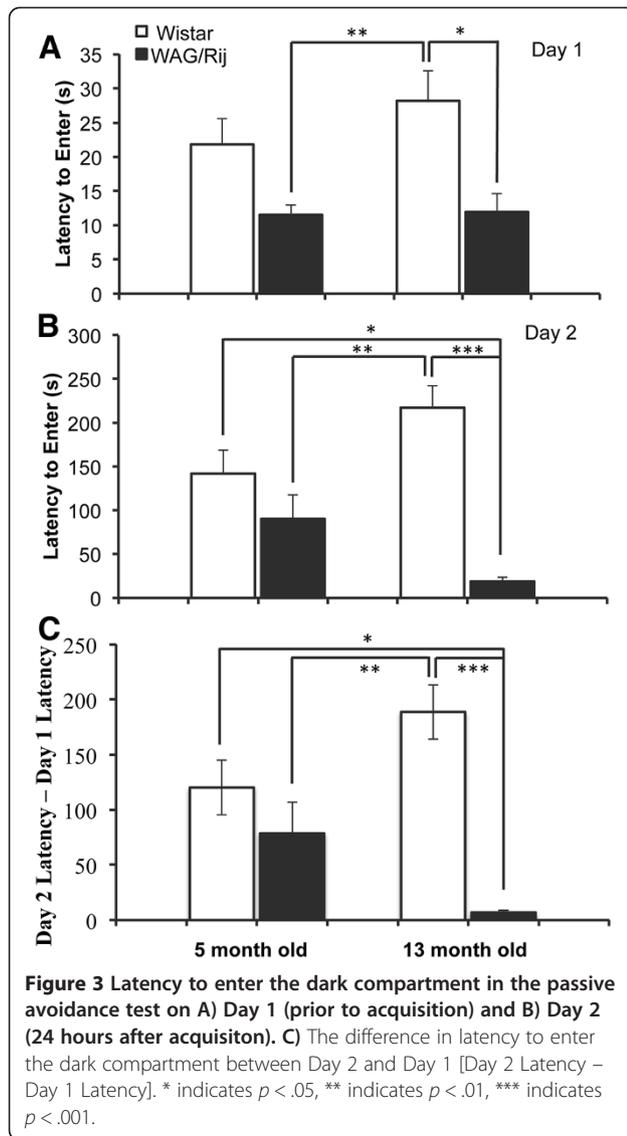


Figure 2 A) Time spent in closed arms, B) Time spent in open arms, C) number of closed arm entries, D) number of open arm entries, E) total number of arm entries, and F) percentage of closed arm entries in WAG/Rij and Wistar rats at 5 and 13 months of age.

* indicates $p < .05$, ** indicates $p < .01$.

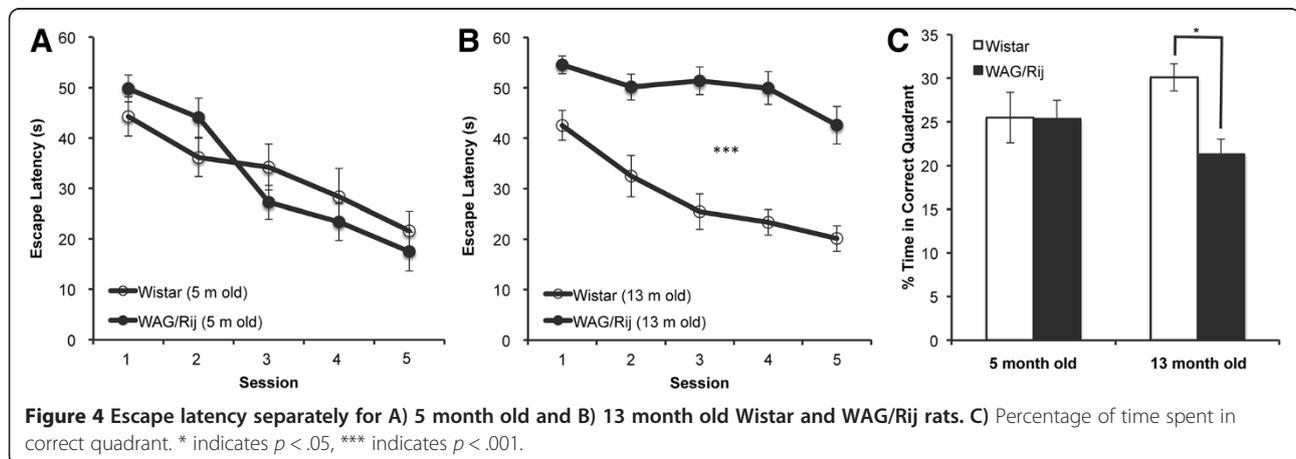


enter the dark compartment, $F(3,67) = 10.62$, $p < .001$ (Figure 3B). Post-hoc analysis revealed that 13 month-old WAG/Rij rats entered the dark compartment earlier than both 5 and 13 month-old Wistar rats (both $ps < .05$) and that 5 month-old WAG/Rij rats entered the dark compartment earlier than 13 month-old Wistar rats ($p < .01$). There was no difference between WAG/Rij and age-matched Wistar rats at 5 months of age ($p = .48$).

Day 2-Day 1: The same analyses were conducted on the difference between latency to enter the dark compartment on Day 2 and latency to enter the dark compartment on Day 1 [Latency(Day 2)-Latency(Day 1)]. This analysis showed an overall significant difference between the four groups, $F(3,67) = 9.40$, $p < .001$ (Figure 3C). Post-hoc analysis revealed a smaller difference score for 13 month-old WAG/Rij rats compared to both 5 and 13 month-old Wistar rats (both $ps < .05$) and for 5 month-old WAG/Rij rat compared to 13 month-old Wistar rats ($p < .01$). There was no significant difference between WAG/Rij and age-matched Wistar rats at 5 months of age ($p = .63$).

Morris water maze

Figure 4A & 4B shows the escape latency as a function of training sessions separately for four different groups (2 strain \times 2 age). At 5 months of age, there was no significant difference between WAG/Rij and Wistar rats in terms of escape latency, $F(1,29) = .02$, $p = .90$. As expected, training significantly decreased the escape latency, $F(4,116) = 24.30$, $p < .001$. There was no strain by training interaction, $F(4,116) = 2.29$, $p = .06$. At 13 months of age, WAG/Rij rats were slower at finding the platform compared to age-matched Wistar rats, $F(1,33) = 61.03$, $p < .001$. As in the case of 5 m groups, training significantly decreased the escape latency, $F(4,132) = 10.23$,



$p < .001$. There was no strain by training interaction, $F(4,132) = 2.4, p = .053$.

Since we could not evaluate the swimming speed and had not tested rats on a cued platform session, we repeated the analysis after normalizing escape latencies on each session by the corresponding escape latencies observed on the first session. Results of this analysis corroborated our findings based on absolute escape latencies. There was no difference between WAG/Rij and Wistar rats at 5 months of age, $F(1,29) = 2.50, p = .13$. There was a significant effect of training on normalized escape latencies, $F(3,87) = 14.68, p < .001$ and there was no significant strain by training interaction, $F(3,87) = 2.22, p = .09$ at 5 months of age. At 13 months of age, WAG/Rij rats exhibited significantly longer normalized escape latencies than age-matched Wistar rats, $F(1,33) = 6.90, p < .05$. Training significantly decreased the normalized escape latencies, $F(3,99) = 4.37, p < .01$ at 13 months of age. There was no significant strain by training interaction, $F(3,99) = 1.04, p = .38$ at this age group.

There was an overall significant difference between the four groups in terms of the percentage of time spent in the correct quadrant, $F(3,62) = 3.19, p < .05$ (Figure 4C). Post-hoc analysis showed that WAG/Rij rats spent less time in the correct quadrant compared to Wistar rats only at 13 months of age ($p < .05$) and not at 5 months of age ($p = .99$).

Discussion

WAG/Rij rats exhibited worse emotional and spatial memory performances in passive avoidance and Morris water maze tests compared to their aged-matched Wistar controls at 13 months but not at 5 months of age. Importantly, these cognitive deficits were observed in the absence of clear differences in anxiety-like behavior and locomotor activity. For instance, WAG/Rij rats did not exhibit different levels of anxiety-like behavior (i.e., time spent in open arms or the ratio of time spent in open arms to time spent in open or closed arms) in the elevated plus maze or different levels of locomotor activity in the activity cage compared to their age-matched Wistar controls. These results overall suggested an age-dependent decline in the learning and memory performances of WAG/Rij rat model of absence epilepsy (compared to Wistar controls) that cannot be accounted for by differential levels of anxiety and locomotor activity.

The idiopathic generalized epilepsy, characterized with typical absence seizures, has been assumed to be a type of benign epilepsies. However, recent studies led to a change in this assumption except for the responsiveness of these conditions to anti-epileptic treatment [11,12,27]. Clinical studies carried out with absence epileptic patients indicate presence of cognitive impairments

including general cognitive decline [28], visiospatial dysfunction [28,29], linguistic problems [26], non-verbal and short-term verbal memory impairment [26,29] as well as attentional, emotional and behavioral alterations [9,29-32]. Several of these studies have been conducted with non-medicated patients with newly emerging seizures [9,29]. In humans, several variables including medical treatment and social factors make it difficult to detect the onset and track the progression of cognitive impairments [33].

In animal models of absence epilepsy, cognitive functions have received surprisingly little attention. In one of these studies, WAG/Rij rats were tested on the hole board and radial arm maze, and exhibited a partial decline of the reference memory without the working memory impairment [34]. Bazyan et al. (2000) also showed that WAG/Rij rats performed worse than controls in the passive avoidance test [35]. In the same study, although WAG/Rij rats performed better than controls early in training in the active avoidance test, their performance worsened during latter trials [35]. These results emphasize the task-specificity of memory performance in the absence epilepsy models. None of these studies however, have addressed the possible age-dependent dynamics in memory performance.

Our study clearly demonstrates that memory impairment became evident in WAG/Rij rats even over the course of a limited age range (i.e., 5 m/young adulthood vs. 13 m/middle-aged). One plausible causal basis of this age-dependent decline in memory performance of WAG/Rij rats in the light of previous studies is their differential spike-wave discharge (SWD) activity compared to age-matched Wistar rats. For instance, previous studies showed an age-dependent increase in the frequency of absence seizures in WAG/Rij rats; SWD activity starts between 2–3 months of age and reaches hundreds a day by 12 months of age, the age group tested in this study [23,36]. SWD activity does not only appear in these inbred absence epilepsy models but also in g/Cpb rats [37], APO-SUS [38], and Long Evans [39] rats. Importantly, these rat models too exhibit impaired performance on different memory and/or emotional tasks [37,38,40]. SWD activity was further observed in all members of the outbred Wistar rats within the 15–23 m age range [41] and can be detected even earlier in this strain [42]. Again consistent with SWD-based account, Wistar rats exhibit poor performance in passive avoidance and water maze tests within the older age range characterized by SWD activity [43-45]. Thus, the behavioral results of the current study combined with electrophysiological findings of previous studies point at a possible relation between SWD activity and age-dependent memory impairment of WAG/Rij rats. Note that since we did not record EEG in this study, this relation only remains to

be a plausible account that needs to be substantiated by data. Thus, future studies are needed to establish the relation between SWD activity and memory performance by recording EEG from rats tested in learning and memory assays.

Despite these previous findings that suggest a potential relationship between SWD activity and cognitive dysfunction, results obtained from GAERS (genetic absence epilepsy rats from Strasbourg) appear to conflict this relation. The SWD activity emerges earlier, occurs more frequent and with longer duration in GAERS, another genetic rat model of absence epilepsy [23]. Thus, under an SWD-based account GAERS would be predicted to exhibit poorer memory performance earlier than observed here. Contrary to this prediction, GAERS rats performed better than controls in the two-way active avoidance test [46]. The disparity between the effect of brain lesions on two-way active avoidance and other memory task performances suggest that this contradiction might be task-specific.

For instance, hippocampal, septohippocampal or reticular thalamic nucleus lesions, which had detrimental effects on performances in many memory tasks, have been shown to enhance two-way active avoidance performance [47-51]. Based on this disparity, it has been suggested that two-way active avoidance performance entailed complex aversive learning, and that it could be facilitated by reduced emotionality, decreased cholinergic innervation, and increased behavioral disinhibition [50,52]. The study of GAERS rats in other memory tests would help elucidate whether their enhanced performance in two-way active avoidance is task specific or not.

A neuroanatomical perspective would contribute to the understanding of the dynamics that underlie our behavioral results. Limbic structures including amygdala, hippocampus, and parahippocampal cortical areas are particularly implicated for the performance on the two memory tasks used in this study [53-56]. These structures were evaluated previously by electrophysiological, molecular, and functional methods in the absence epileptic rats. Electrophysiological studies have shown that limbic areas were silent during thalamocortical SWD activity [57,58]. On the other hand, other studies reported the presence of the metabolic and molecular changes [59-62]. Support for functional changes in the limbic structures of absence epileptic rats originate from kindling studies. Kindling, which is a model of epileptogenesis for acquired epilepsies, shares some of the similar mechanisms with long-term potentiation (LTP) [57]. In fact, it is considered to be a pathological form of neuroplasticity [63,64]. Development of kindling has been shown to be more difficult in rats with absence epilepsy and different degrees of resistance to kindling progression have been shown in these animals in amygdala,

hippocampus, and perirhinal cortex [65-67]. If resistance to kindling in these rat models indeed generalizes to the formation of LTP in the corresponding limbic structures, this could predict worse learning and memory performance in absence epilepsy rat models.

Finally, the performance of rats in these tests might be altered by other factors such as emotional state, motivation and/or impulsivity. For instance, in a recent study [18] of two models of temporal lobe epilepsy in two different strains, researchers found that lower anxiety scores (as assessed by open arm related measures) in EPM was related to lower performance on the Morris water maze. Although we did not observe any differences between WAG/Rij and Wistar rats in terms of anxiety-like behavior as canonically assessed by open arm related measures, WAG/Rij rats spent less time in closed arms compared to age-matched Wistar rats at 13 months of age. This result might imply weaker safety-seeking tendencies of WAG/Rij rats and might indeed be relevant to their lower performance on passive avoidance and Morris water maze, which are tasks with aversive components. Contrary to these arguments however, van der Staay et al. (2009) demonstrated that emotional reactivity as assessed by open field and elevated plus maze activities did not mediate learning and memory performance in tasks with aversive components such as Morris water maze and passive avoidance [68].

In our study, WAG/Rij rats did not exhibit different levels of locomotor activity in the activity cage however they exhibited higher total number of arm entries in EPM at both ages. Although, these differences might be argued to have mediated the performance on passive avoidance and Morris water maze, this reasoning cannot fully account for the age-dependence of poorer performance on these memory tasks. In other words, differences between WAG/Rij and Wistar rats in terms of arm entries was comparable between the two age groups whereas cognitive impairment appeared specifically at 13 months of age. The same argument also holds for the possible relation between number of arm entries and time-spent in closed arms; the between-strain differences for the former measure was not age-dependent whereas age-dependency of between-strain differences held for the latter. Furthermore, although previous studies argued for a relation between higher levels of activity in elevated plus maze and open arm exploration [69], its relation to closed arm exploration has not been discussed.

We did not test rats on a cued-learning trial in order to control for possible factors (other than spatial memory) that might have mediated the observed performances. However, note that analysis of the escape latencies normalized by the escape latency of the first session also revealed similar results. We observed that WAG/Rij rats at 13 months of age jumped of the

platform upon being placed on it by the experimenter after the trial cut-off duration. This behavior was not observed with any Wistar rats or 5 months old WAG/Rij rats. Further studies should evaluate the swimming speed and other potentially confounding factors.

In conclusion, this study shows an age-dependent decline in the learning and memory performance of WAG/Rij rats compared to age-matched Wistar rats in the absence of clear differences in anxiety-like behavior and locomotor activity. More detailed studies are needed to understand the electrophysiological correlates of these behavioral alterations as well as the relation between the neuroanatomical and neurochemical components of this disturbance and other emotional/behavioral comorbid situations.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AK, TU, FA, and NA designed the experiments. AK and TU conducted the experiments. AK and FB analyzed the data. AK, TU, FB, and NA drafted the manuscript. All authors read and approved the final manuscript.

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