Short Communication

Vibrating Tail, Digging, Body/Face Interaction, and Lack of Barbering: Sex-Dependent Behavioral Signatures of Social Dysfunction in 3xTg-AD Mice as Compared to Mice with Normal Aging

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Abstract. Modeling of Alzheimer's disease (AD), classically focused on the subject-environment interaction, foresees current social neuroscience efforts as improving the predictive validity of new strategies. Here we studied social functioning among congeners in 13–14-month-old mice with normal aging in naturalistic and experimental conditions and depicted behavioral signatures of dysfunction in age-matched 3xTg-AD mice. The most sensitive variables were vibrating tail, digging, body/face and self-grooming, that can be easily used in housing routines and the assessment of strategies. Sex-specific signatures (vibrating tail, digging, and grooming) defined female 3xTg-AD mice ethogram. All animals sleep huddled while barbering was only found in females with normal aging.

Keywords: Barbering, behavioral and psychological symptoms of dementia, Dalila effect, digging, ethogram markers, monitoring, sleeping behavior, social behavior, Social Interaction Test, Tube-dominance test

INTRODUCTION

While personalized medicine urges the depiction of the nuances of individual variability that underlies epidemiology, basic research classically focused on the individual specimen as the subject of study [1], now opens to the higher level of complexity of social behavior and communication.

Social behavior is a fundamental characteristic modulated by endogenous, genetic, and environmental factors. Deficits in social interaction are defined by endophenotypes and are present in various psychiatric disorders such as autism, schizophrenia, depression, and Alzheimer's disease (AD) with a strong impact on daily life of patients and caregivers [2–5]. Conversely, social factors are considered not only modulators of mental and physical health of people but also risk factors for symptoms of dementia [6].

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Although social interaction is considered a phenotype or endophenotype of AD, the underlying mechanisms and causes remain complex [7].

At the translational level, modeling behavioral and psychological symptoms of dementia (BPSD) in murine models of AD has been addressed using methodological approaches based on the interaction of the subject with the environment, but few involve the relation with other individuals [8]. Furthermore, social neuroscience efforts to fill the gap are also foreseen as important to improve the predictive validity of new preventive and/or therapeutic strategies for AD [9].

Therefore, the present work is aimed to explore social functioning (from affiliative behaviors and dominance to aggressive behaviors) among congeners in 13-14-month-old male and female mice with normal aging in naturalistic and experimental conditions, as well as to depict behavioral signatures of social dysfunction as a consequence of genetically-induced amyloid-β and tau pathologies in age-matched 3xTg-AD mice. At these ages, the 3xTg-AD model has extensively been described mimicking advanced stages of disease with hallmark amyloid and tau pathologies [10]. For that purpose, we evaluated behavioral interactions with congeners (group-sleeping, body/face, ano-genital, aggression), with the context (horizontal and vertical exploratory activities, digging) and self-actions (self-grooming and vibrating tail) that can be easily used in housing routines and the assessment of strategies.

MATERIALS AND METHODS

Animals

A total of forty-six 13–14-month-old homozygous male and female 3xTg-AD and their non-transgenic (NTg) mice, 7th breeding generations derived from the same genetic background (C57BL/6×129 sv), engineered at the University of California Irvine were used [10]. Subjects (group, n, mean age in months ± S.D.: male NTg, $n = 10$, $13 ± 0$; male 3xTg-AD, $n = 8$, $13 ± 0$; female NTg, $n = 14$, $13.57 ± 0.94$; female 3xTg-AD, $n = 14$, $13.71 ± 0.94$) were housed three to four per cage and maintained in Macrolon cages (35 x 35 x 25 cm) under standard laboratory conditions of food (A03 diet for breeding; A04 diet for maintenance, Panlab, SL, Barcelona) and water *ad libitum*, $22 ± 2°C$, a 12 h light:dark cycle and relative humidity 50–60%. Behavioral assessments were

performed blind to the experiment, in a counterbalanced manner. All procedures were in accordance with Spanish legislation on 'Protection of Animals Used for Experimental and Other Scientific Purposes' and the EU Directive (2010/63/UE) on this subject. The study complies with the ARRIVE guidelines developed by the NC3Rs and the aim to reduce the number of animals used.

Home cage sleeping behavior

Home cage group sleeping behavior was registered during 3 consecutive days and reported as the incidence of animals sleeping together, huddled (entire bodies being pressed up against each other) and/or dog-piled (similarly to dog-piling), in the same quadrant of their home cage [11].

Social interaction test

A dyad of two unfamiliar mice of the same genotype and sex were introduced in a standard home cage and video recorded for 5 min (modification of [12]). Behaviors were classified into social (social investigation, aggression, vibrant tail) and non-social (exploring, digging, self-grooming) interactions. We also scored the total number of episodes and their total duration. In order to depict the sequence of behavioral events, here we propose to plot the latencies for each genotype and sex as an ethogram tablature. There, self-grooming and vibrating tail are plotted as self-actions.

Barbering or Dalila effect

Barbering or Dalila effect, alopecia due to social interaction between animals, was scored according to 5-scores Kalueff scale [13]. The incidence per cage and the affected body area was also recorded in cm^2 [14, 15].

Tube-dominance test

In order to know if the Dalila effect was related to dominance, the social range of dyads was assessed in the Tube-dominance test [11]. Animals were placed at the opposite ends of a translucent acrylic tube (diameter: 4 cm, length: 25.5 cm), allowed to advance through it for a maximum of 120 s or until one of them ("dominant") forced the other ("subordinate") to get out of the tube.

Statistical analysis

Results are expressed as mean ± S.E.M. or incidence. Statistics using SPSS 15.0 as detailed in the legends, with significance considered at $p < 0.05$.

RESULTS

Home cage sleeping behaviors

All mice (100%) slept huddled, curled together, close to each other, in a quadrant of the cage, independently of the genotype or sex.

Social interaction test

The ethogram tablature (Fig. 1) showed a consistent sequence of actions in the NTg mice, with the only distinction of vibrating tail that was anticipated in the females. The ethogram started with exploration (horizontal and vertical), followed by first body/face social interaction done before the end of the first minute. In the second minute, ano-genital interaction and self-grooming were observed. Digging appeared around the third minute of the test, followed in males or preceded in females by vibrating tail. In the 3xTg-AD mice, the tablature showed sex and genotype differences. As compared to their NTg counterparts, males were delayed in the elicitation of social interactions, while vibrating tail was advanced similarly to NTg females. In contrast, female 3xTg-AD showed a very early elicitation of vibrating tail and an anticipated digging that was performed before the elicitation of social behaviors. Body/face and ano-genital interactions were consecutively performed, and grooming was delayed to the third minute of the test, as compared to all the other groups. These differences were found reflected in the respective variables of total duration and number of episodes of social (Fig. 2) and non-social (Fig. 3) behaviors elicited among congeners in the social interaction test (SIT). Incidence of aggression was 1/8 in male 3xTg-AD mice with a latency of 213 s, and absent in the other experimental groups. Overall, the most sensitive variables were vibrating tail (duration, episodes, and latency), digging (latency and episodes), body/face (episodes, duration, and latency), and self-grooming (latency) (all $F > 3.289$, $p < 0.001$).

Barbering or Dalila effect

Dalila effect was present only in the female NTg group, with an incidence of 0.40 ± 0.16, a severity score of 0.80 ± 0.35 and 0.25 ± 0.12 cm^2 of body affected area. The three variables showed significant differences as compared to null presence in 3xTg-AD (all $F < 2.170$, $p > 0.05$).

Tube-dominance test

First contact was faster in 3xTg-AD mice (1.21 ± 1.21 s versus. NTg: 2.00 ± 0.00 s, $p < 0.05$) but no differences were shown in the latency of withdrawn mice (1.42 ± 0.13 s versus NTg: 3.42 ± 2.33 s) or total duration of the test (16.00 ± 1.19 s versus NTg: 11.42 ± 2.06 s).

DISCUSSION

The present work identifies, for the first time, vibrating tail, digging, body/face interaction, and lack of barbering as variables that can be used as behavioral signatures of AD-social phenotype in the 3xTg-AD mice, with sex-specificity and their integration with non-social behaviors. We assessed a rank of social aspects, from affiliative behaviors and dominance to aggression, using experimental and naturalistic conditions that can be used for behavioral monitoring. Thus, we used social interaction and tube-dominance tests but also we recorded affiliative behaviors developed in the home cage such as sleeping behavior and barbering.

The quantitative and qualitative analysis of the ethogram elicited in the SIT evidenced that the expression of social behaviors (body/face contact and ano-genital contact, no aggressions) was very consistent in NTg mice, independently of sex. The behavioral repertoire started with a neophobia response toward the environment (horizontal and vertical exploration of the new cage), followed by the interaction with conspecifics, and afterwards by the expression of behaviors related to enhanced emotionality such as grooming behavior and digging. In contrast, the 'vibrating tail' appeared as a distinctive profile for female sex, as it was earlier expressed. This behavior, when elicited in rodents by systemic administration of glutamatergic agonist NMDA, is related to increased excitability [16]. In agreement with the increased vulnerability of 3xTg-AD to the
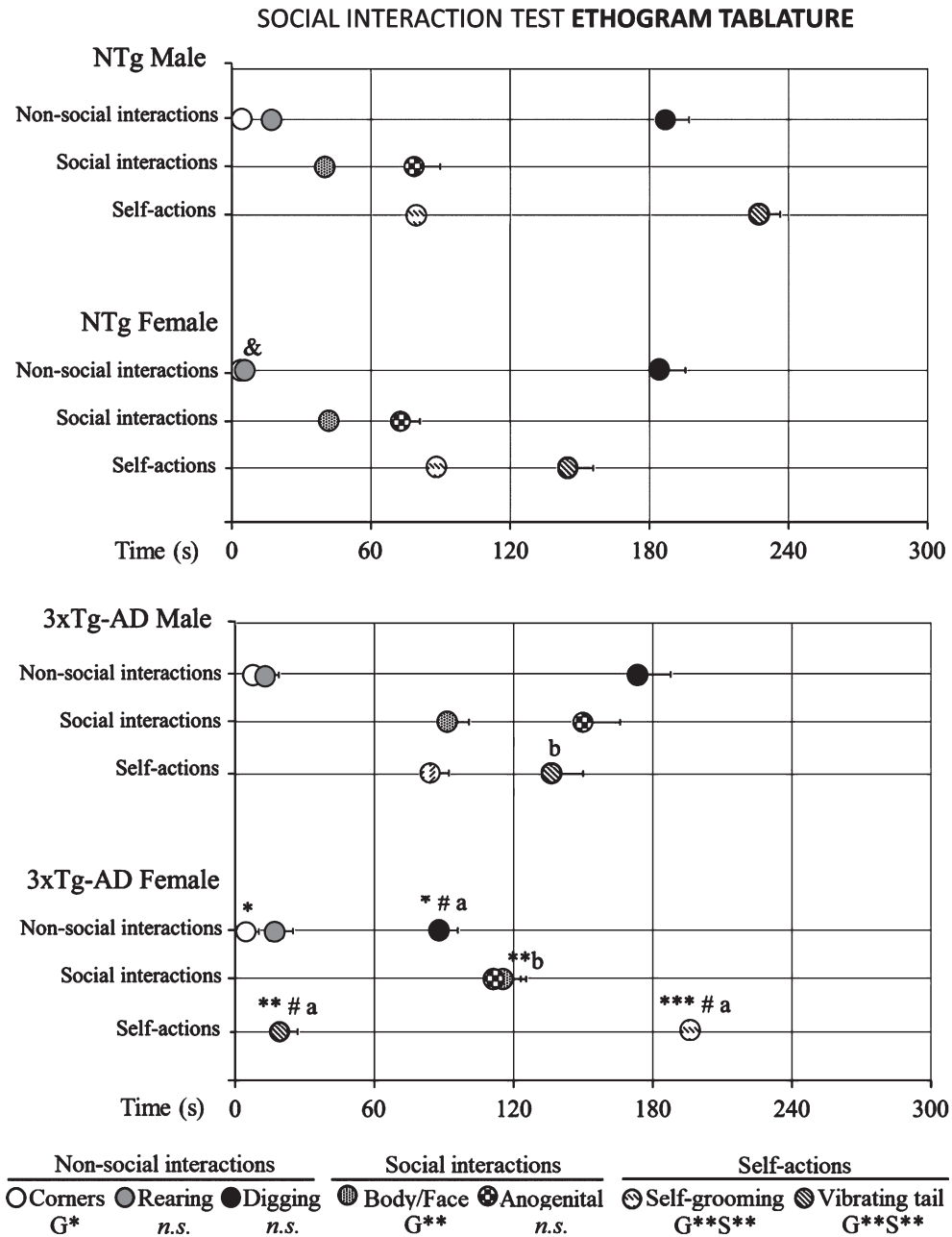
Fig. 1. Social interaction test ethogram tablature of 14-month-old male and female 3xTg-AD mice at advanced-stages of the disease and age- and sex-matched NTg mice with normal aging. Results are mean ± SEM of latency of events shown by NTg (male, $n = 10$; female, $n = 14$) and 3xTg-AD mice (male, $n = 8$; female, $n = 14$) in the social interaction test. Multivariate General Linear Modelling: G, genotype effect and S, sex effect *$p < 0.05$ and **$p < 0.01$, followed by Duncan's *post-hoc* test comparisons [a]$p < 0.05$ different all group and [b]$p < 0.05$ different to genotype. Student's *t*-test ***$p < 0.001$, **$p < 0.01$, and *$p < 0.05$ versus NTg mice. Student's *t*-test [&]$p < 0.05$ versus male NTg mice and, [#]$p < 0.05$ versus male 3xTg-AD mice.

occurrence of anxious-like behaviors in new environments [8], the ethogram in the SIT was found disrupted in the 3xTg-AD mice. The 'vibrating tail', also the most distinctive behavior of the female sex profile, was significantly enhanced and advanced on time. Thus, it was early expressed, in more occasions (episodes) and had longer total duration. These variables entitle vibrating tail as a selective and sen-
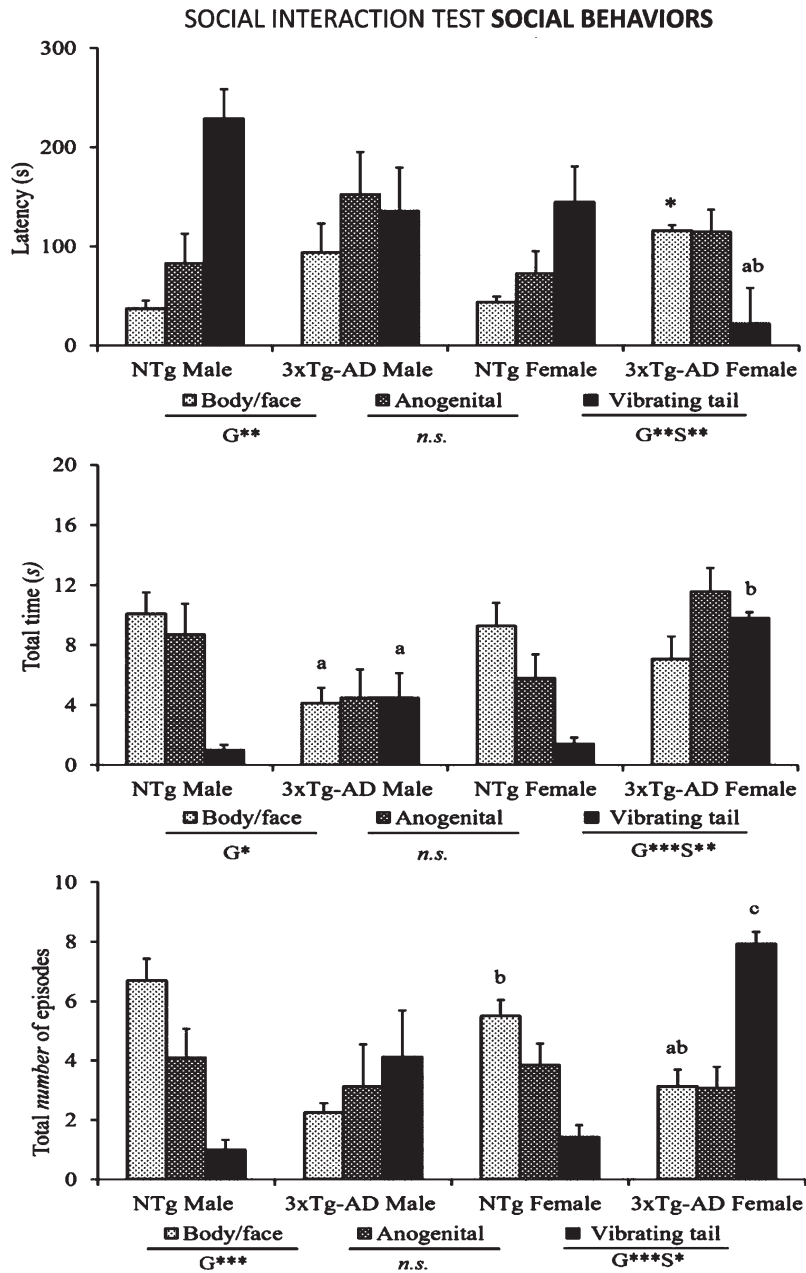
Fig. 2. Social interactions (body/face and ano-genital contacts) and vibrating tail shown in the SIT by 14-month-old male and female 3xTg-AD mice at advanced-stages of the disease and age- and sex-matched NTg mice with normal aging. Results are mean ± SEM of latency of events, total duration and total number of episodes. NTg (male, $n = 10$; female, $n = 14$) and 3xTg-AD mice (male, $n = 8$; female, $n = 14$) in the social interaction test. Multivariate General Linear Modelling: G, genotype effect and S, sex effect $*p < 0.05$ and $**p < 0.01$ and followed by *post-hoc* Duncan's test comparisons $*p < 0.05$ versus all the other groups, [a]$p < 0.05$ versus the NTg mice, same sex, [b]$p < 0.05$ versus male counterpart, [c]$p < 0.05$ versus male NTg mice.

sitive tool for sex-dependent expression of the social anxiety-like profile in 3xTg-AD mice.

Digging in the sawdust was sensitive to genotype and sex. In a precedent work, we showed that 12-month-old male 3xTg-AD mice showed increased marble-burying that was related to neophobia, modulable by handling, reversed by chronic treatment with risperidone [17] and modified by chronic caf-
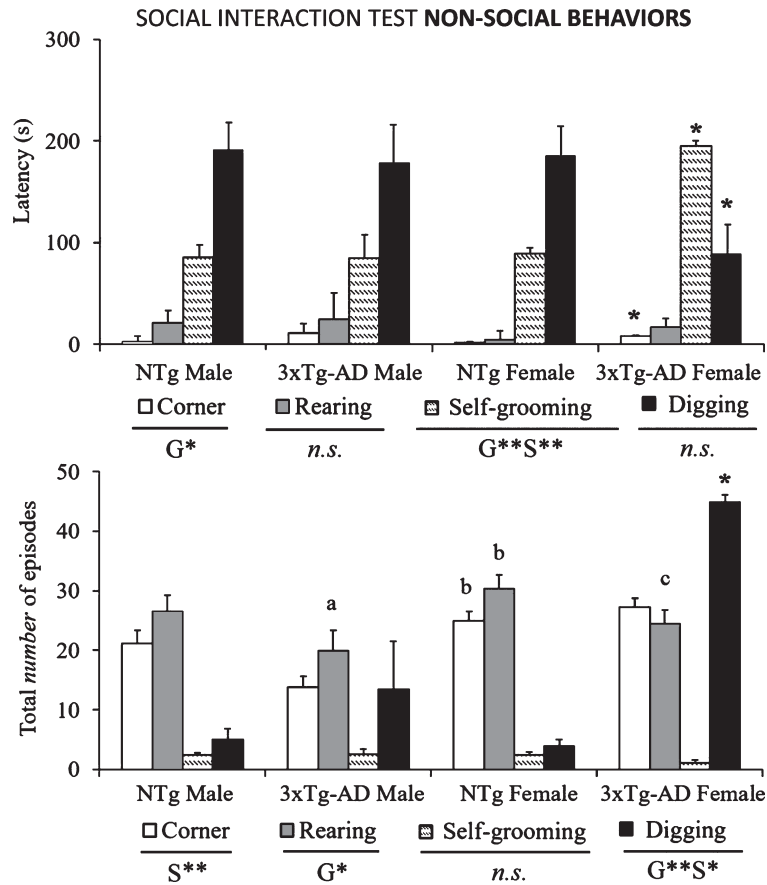
Fig. 3. Non-social interactions (rearings, corners, self-grooming, and digging) shown in the SIT by 14-month-old male and female 3xTg-AD mice at advanced-stages of the disease and age- and sex-matched NTg mice with normal aging. Results are mean ± SEM of latency of events and total number of episodes. NTg (male, $n = 10$; female, $n = 14$) and 3xTg-AD mice (male, $n = 8$; female, $n = 14$) in the social interaction test. Multivariate General Linear Modelling: G, genotype effect and S, sex effect *$p < 0.05$ and **$p < 0.01$ and followed by *post-hoc* Duncan's test comparisons *$p < 0.05$ versus all the other groups, [a]$p < 0.05$ versus the NTg mice, same sex, [b]$p < 0.05$ versus male counterpart, [c]$p < 0.05$ versus male NTg mice.

feine [18]. This behavior has been considered to serve to measure digging rather than evoke burying [19], while Deacon [20] typified marble burying and digging in mice as simple methods for *in vivo* identification of biological impacts.

Self-grooming was also affected in the SIT, in agreement with delayed grooming in 15-month-old male and female 3xTgAD assessed in an open-field test [21] but advanced in females when engaged in active copying-with-stress strategies [22]. Here, latency of self-grooming allowed to distinguish the female 3xTg-AD genotype. According to the 'action programs' described by Lat [23] for mice and rats when they habituate in the open-field, self-grooming emerges once the other behaviors or actions (fear-explorations) have been completed. Therefore, when

the previous actions are altered, as it is the case here, the latency of self-grooming reflects the previous sequence of behaviors, and could be consider less 'specific' by itself. For this reason, grooming was not chosen among the behaviors cited as relevant for the behavioral signature. With regards to social grooming in home-cage conditions, mutual grooming is considered an affiliative behavior. However, presence of barbering described as Dalila effect, more prevalent in females, illustrates a unidirectional behavior resulting of barber whiskers by plucking [15] done by one mouse (Dalila) that remains with its fur intact. There are several hypotheses about this phenomenon in rodents such as genetic, environmental, social hierarchies, stress, and certain disorders of obsessive-compulsive spectrum [13]. Here, the Dalila

effect was present only in the NTg females, while 3xTg-AD females exhibited similar performances in the tube-dominance test.

Common genetic mechanisms link sensorimotor gating deficits with abnormal social behavior. For instance, Dvl1 knock out mice modeling psychotic disorders show differences in whisker trimming, deficits in nest-building, less huddling sleeping, subordinate responses, and deficits in acoustic and tactile prepulse inhibition [11]. In the case of 3xTgAD mice, this spectrum is only partially observed as impaired individual [24] and group [25] nesting, some deficits in their prepulse startle response [26], social alterations when interacting with NTg mice [27], and here we report reduced social interaction with congeners in SIT and lack of whisker trimming. However, sleeping behavior was found intact.

These differences in social behavior of 3xTg-AD mice may be associated not only to their prominent anxious-like profile exhibited since young adulthood [8]. Several authors postulate it can be influenced by apathy, agitation, possible deficits social memory, all considered as first clinically symptomatic manifestations of AD [6, 28]. Bories et al. [27], the first to report both sex- and age-dependent alterations in social behavior in the 3xTg-AD mice, evaluated the deficits in terms of normal/enhanced/reduced patterns measured as sniffing, crawling over or under, following, escape behavior, and grooming the partner. In their social interaction paradigm, they tested 3xTg-AD versus NTg pairs of aged- and sex-matched animals, minimizing the occurrence of aggressive behaviors and anxiogenic situations, as also shown by no differences in grooming behavior observed during the SIT. In their work, the authors reported that male dyads of one 3xTg-AD mice with NTg partners showed similar number of social events in the SIT at 12 months of age but social disinhibition at 18 months. In contrast, females showed an advanced pattern with disinhibition followed by decreased sociability. Most importantly, as shown by correlation analysis, social changes were not related to genetically-induced amyloid-β or tau neuropathological hallmarks of disease. Instead, social changes were found correlated to an increase of both excitatory and inhibitory basal synaptic activity in the medial prefrontal cortex. Studies with other animal models such as mice APPswe/PS1 have also shown impairment in social interaction in the 3-chamber test at 6 months of age, with mutants being less willing to engage in social interaction than wild-type, whereas being hyperactive in the open-field and elevated plus-maze. They associated it with deficits in social memory [29, 30]. At the same age, male Thy1-hAPP$^{Lond/Swe+}$ mice assessed in this test also displayed reduced social interest, interpreted by decreased social memory or discrimination [31]. 23-month-old female Tg2576 mice are also impaired in social memory and open-field habituation tests [32].

The present work using a social paradigm of genotype and sex-matched dyads contributes to the growing efforts to study social behaviors in rodents [1,9] with special attention to its complexity in models of AD (i.e., [25, 27, 29–31]). This is important because several studies have shown that social environment (rearing conditions, enrichment, cohabitation, isolation, psychosocial stress) can be determinant and exert distinct impact in cognitive and BPSD-like symptoms as well as underlying neurobiological substrates and AD neuropathology [30, 33–35]. Finally, we propose that the identification of genotype- and sex-specific variables of behavior that can be used as signatures are of special interest for behavioral monitoring of animals in husbandry routines as well as in the follow-up during the assessment of preventive/therapeutic strategies, mainly in female sex which is the one at higher risk of developing the disease [36].

ACKNOWLEDGMENTS

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