Behaviour Profile Characterization of PS19 and rTg4510 Tauopathy Mouse Models: A Systematic Review and a Meta-Analysis.

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Highlights

- This study discusses the behavioural profiles of the PS19 and rTg4510 mouse models.

- The PS19 mice exhibit anxiety-like behaviour, cognitive and locomotor alterations.

- rTg4510 mice demonstrate locomotion and cognitive changes.

- Establishing baseline behavioural profiles is recommended.

Abstract

The rTg4510 and PS19 mouse models are widely used in tauopathy research. Alzheimer's disease (AD) is the most prevalent among tauopathies. Behavioural tests are frequently used to assess emotional, cognitive, and motor behaviours in mouse models of AD. Cognitive deficits begin to manifest in rTg4510 mice around 3 months of age and in PS19 mice around 6 months. However, it's widely recognized that behavioural outcomes can vary due to environmental factors, health status, and husbandry practices, causing phenotypic differences between facilities. This study aims to consolidate current knowledge of the behavioural phenotypes of these two mouse models. We conducted a comprehensive literature review using keyword searches with Boolean operators across databases up to January 2024. Additional studies were included from manual searches. A total of 23 articles were reviewed for rTg4510 mice and 52 for PS19 mice. We extracted methodological details and key findings from each study. Results for rTg4510 mice show consistent findings regarding locomotion, memory and learning, and neurological dysfunction. However, the limited studies on motor and balance behaviour revealed no significant differences, while anxiety-like behaviour showed some inconsistencies. PS19 mice demonstrate more robust results for anxiety-like behaviour, memory and learning, and locomotion, while findings for balance and coordination are more inconsistent. Although there is overall coherence in certain aspects of the behavioural profiles of these tauopathy mouse models, it is crucial to recognize experimental heterogeneity and profile behavioural baselines to optimize the testing of both genetic and pharmacological interventions.

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Keywords: behaviour, dementia, mice, PS19, rTg4510, tauopathy

1. Introduction

The main function of tau in normal conditions is to maintain the stability of microtubules (Weingarten et al., 1975). Tau is encoded by the microtubule-associated protein tau (MAPT) gene, that by an alternative splicing of pre-mRNA produces six protein isoforms, which present different C-terminal repeat domains (3R or 4R) (Andreadis et al., 1992; Goedert et al., 1989). In pathological conditions, tau is hyper-phosphorylated, misfolded, and abnormally accumulated into neuronal inclusions termed neurofibrillary tangles (NFTs) (Goedert et al., 1988, 2017; Trejo-Lopez et al., 2022; Wischik et al., 1988). This intracellular tau aggregation is associated with several neurodegenerative disorders, known as tauopathies (Orr et al., 2017; Trejo-Lopez et al., 2022).

Of all the tauopathies, Alzheimer's disease (AD) is the most prevalent (Prince et al., 2015). In addition to tau pathology, neuronal loss, amyloid-β plaques, and neuroinflammation (i.e., astro-/microgliosis) are a feature of AD (Jankowsky & Zheng, 2017). However, NFT load, rather than amyloid-β burden, correlates most clearly with cognitive deterioration in AD patients (Giannakopoulos et al., 2003).

AD is a chronic and progressive neurological disease with higher incidence rate in the population over 65 years old (Calabrò et al., 2021). Due to the aging population, the prevalence of dementias is increasing (Prince et al., 2013; H. Wang et al., 2016), having a major impact on patients and their caregiver's quality of life (Sousa et al., 2010). Consequently, a major effort has been ongoing to find a drug able to slow down or stop the progression of AD (Huang et al., 2020, Breijyeh & Karaman, 2020; Calabrò et al., 2021; Cummings et al., 2014). However, AD pathology remains far from being fully understood, due to its complexity and multifactorial nature (Kong et al., 2023; Querfurth & LaFerla, 2010; Xia et al., 2023). To identify potential drugs able to fight this disease, a common approach in drug discovery is to use animal models that mimic a disease phenotype to test efficacy and safety of compounds before going to clinical trials (Brown et al., 2021; Parikh et al., 2018; Van Dam & De Deyn, 2011; Xia et al., 2023). The importance of rodents is well established in biomedical research, and mice are the vertebrates most often used in research (Bryda, 2013). Nevertheless, due to the complexity of the disease it can be challenging to find the correct model. There are a variety of models, covering the main known features of AD, such as, amyloid plaques,

NFTs, and neurodegeneration (for more details see (Jankowsky & Zheng, 2017)), that facilitate the understanding of different parts of a complex mechanism.

To study the impact of tau accumulation, several tau transgenic models have been developed. Tau isoforms are disease-specific (i.e., accumulation of specific tau isoforms occurs in different tauopathies) and species-specific (e.g., adult rodents only express 4R isoforms) (Bachmann et al., 2021; Cherry et al., 2021). rTg4510 and PS19 mouse models overexpressing human 4R isoforms are most often used (Jankowsky & Zheng, 2017). Although AD patients show 3R and 4R isoforms in their NFTs, no tau mutations have been linked to AD, and therefore these models employ mutations which cause frontotemporal dementia (FTD) (Jankowsky & Zheng, 2017). Thus, while these models do not have construct validity derived from AD specific mutations, they display pathology in the form of tau accumulation that resembles AD (face validity).

Despite expressing the same human tau protein, these models differ in three key aspects: the specific tau mutation (P301L in rTg4510 vs. P301S in PS19), the promoter system (CaMKIIα in rTg4510 vs. PrnP in PS19), and the insertion site (on chromosome 12 in rTg4510 vs. on chromosome 3 in PS19). The insertion sites are crucial in understanding the phenotypes of these models. Gamache and colleagues (2019) found that the pathology of neurodegenerative diseases observed in rTg4510 mice were impacted due to an unexpected disruption of the coding sequence of endogenous genes. In addition, strain background could also be a non-tau factor that affects neurodegeneration (Sahara & Yanai, 2023).

The rTg4510 mouse is bi-transgenic and is generated by crossing responder line mice carrying the human mutant MAPT transgene downstream of a tetracycline operon-responsive element with activator line mice which carry a tetracycline-controlled transactivator under control of the CaMKIIa promoter. The resulting progeny express human tau^{P301L} unless it is inactivated by dosing with doxycycline (Ramsden et al., 2005)**. The CamKIIa promoter results in human tau expression which is forebrain restricted and at approximately 13 times the level of endogenous tau. In the original papers describing this model** (Ramsden et al., 2005; SantaCruz et al., 2005) **neurofibrillary tangle deposition was observed in the cortex from around 4 months of age and in the hippocampus from around 5.5 months. Cortical cell loss was observed from around 8.5 months and gross forebrain atrophy**

from 10 months (Spires et al., 2006)**. Astrogliosis and microgliosis have been reported to occur from around 2.5 months of age** (Helboe et al., 2017)**.**

The PS19 mouse model incorporates a single mutant human MAPT transgene under the control of the PrnP promoter. Expression of human tau is approximately fivefold higher than endogenous tau and occurs in the brain and spinal cord. In the original paper on this model, neurofibrillary tangle-like inclusions occurred in the cortex, hippocampus, amygdala, brain stem and spinal cord from around six months of age. Neuronal loss and brain atrophy follow at around 8 months. Microgliosis is seen from around 3 months of age, predominantly in white matter and precedes astrogliosis (Yoshiyama et al., 2007)**.**

Since rTg4510 and PS19 mice models are widely used in research on tauopathies, it is fundamental to have a clear characterization of the phenotype. Behavioural tests are often conducted to characterized animals' phenotype regarding emotional, cognitive, and motor behaviours (Kraeuter et al., 2019). There are claims in the literature that cognitive deficits occur in these mice (from about 3 months in rTg4510 mice and from about 6 months in PS19 mice). However, as is widely known, behaviour tests are often sensitive to changes in environment, as husbandry features, such as cage changes, light/dark cycle, noise, among others; so phenotypic differences in mouse strains are often seen between animal facilities (Alves et al., 2020; Saré et al., 2021). Therefore, having an overview of the main findings in these models can help researchers identify the most appropriate mouse model, behavioural tests, and optimal timepoints for studies aimed at evaluating potential therapies.

This meta-analysis and systematic review compile, for the first time to our knowledge, the current state of knowledge regarding the behavioural phenotype of these two tauopathy mouse models, providing an overview of their behavioural profiles. The tauopathy model mice used in this review are: a) PS19 (B6;C3-Tg mice (Prnp-MAPT*P301S)PS19Vle/J) (Yoshiyama et al., 2007) and b) rTg4510 (129S6.Cg-Tg(Camk2a-tTA)1Mmay/JlwsJ) (Ramsden et al., 2005; SantaCruz et al., 2005).

2. Methods

2.1. Search strategy and study selection

The article selection was conducted using a systematic strategy. To find the articles, the search equation “("rTg4510" OR "Tau P301L") OR ("PS19" OR "P301S") AND behaviour” was conducted in the following databases: PubMed, Scopus, and EBSCOhost. Articles were searched up to 09 January 2024.

The articles were independently reviewed by two authors (RLA and IV) using the following exclusion criteria (exclusion criteria 1): (a) studies not conducted on rodents; (b) not published in English; (c) not primary source research articles (i.e., reviews, dissertations or book chapters); (d) studies not assessing behaviour in their results. Peer agreement was assessed using Cohen's kappa test (k = 0.966). A second set of exclusion criteria (exclusion criteria 2), involving full-analysis, was conducted by the same authors, excluding articles that: a) did not use the intended strains (i.e., rTg4510 and PS19 mice); b) did not focus on emotional, cognitive and motor behaviour (e.g., social behaviour); c) did not compare results with an appropriate control (e.g., comparing the effects observed in treated mice (whether administered the drug or the vehicle) versus naïve mice; d) conducted behaviour assessments within less than 30 days after any procedure (e.g., intraperitoneal injection, oral gavage). Criteria c) and d) were implemented to avoid misinterpretation of results, as even mild procedures can lead to behaviour changes, particularly if behaviour is tested immediately after a procedure (Gerdin et al., 2012; Li et al., 2022; Saré et al., 2021). Any disagreements not resolved by consensus during this article selection process were addressed by a third senior author (DH). Additionally, to ensure the quality of publications, we verified whether articles were published in peer-reviewed journals.

2.2. Data collection and Analysis

Quantitative meta-analysis using IBM SPSS Statistics 29 software, was applied to data from only the PS19 mouse strain, as more comprehensive data suitable for analysis were available. We examined several behavioural tests, and the selection was based on the consistency of these behavioural studies and their respective variables across the analysed studies. To minimize variability across studies, the following criteria were applied: a) Open-Field: total distance travelled was the selected measure, with tests completed within a maximum duration of 15 minutes. b) Y-Maze: alternation behaviour

was measured, with tests completed within a maximum duration of 15 minutes. c) Contextual Fear Conditioning – measure selected: freezing behaviour measured 24 hours after conditioning. d) Rotarod: Latency to fall was measured, with the speed of the rotating rod gradually increased. Studies employing a constant speed were excluded. e) Morris Water Maze – reference memory was assessed by measuring the time spent in the target quadrant. Studies reporting time to platform were excluded from analysis.

Descriptive statistics (mean, standard deviation, sample size), necessary for conducting meta-analysis, when not reported in the articles, were obtained using the WebPlotDigitizer software (https://automeris.io/WebPlotDigitizer/) or by contacting the authors. **If this information was not available, the articles were excluded from the meta-analysis.** Continuous outcome measures were analysed by a random model with restricted maximum likelihood estimation. Effect size was assessed using Hedges' g (adjusted for standard error). Subgroup analyses were conducted based on the age of the animals (< 7 months or ≥ 7 months), as the onset of pathology in PS19 mice is known to occur later. This means that PS19 mice will be compared with their respective control groups at two different age points. The degree of heterogeneity between studies was determined by I^2 statistic: low (I^2: <25%), low to moderate (I^2: 25–50%), moderate to substantial (I^2: 50–75%), or substantial (I^2: >75%) (Higgins & Thompson, 2002) and *Q* statistics. Funnel plot was used to visually verify publication bias. Egger's tests were used to estimate the severity of publication bias. *p*-value <0.05 was considered statistically significant.

3. Results

3.1. Study Selection

Following the electronic search, a total of 529 records were identified. Duplicates were excluded. After the analysis following exclusion criteria 1, a total of 170 papers were excluded. After a second analysis (using exclusion criteria 2), 117 articles were removed. Additionally, 13 papers were included through manual search. In the end, a total of 75 articles were systematically reviewed (Figure 1) (Page et al., 2021).

Figure 1 – PRISMA flow diagram of study selection process.

3.2. Study characteristics

In total, 23 articles were used to characterize emotional, cognitive, and motor behaviours in rTg4510 mice (Table 1), and 52 articles focused on PS19 mice (Table 2).

3.2.1. rTg4510 behavioural profile

After reviewing the pool of 23 studies, we decided not to proceed with the meta-analysis due to lack of information available and instead conducted a systematic review of the selected papers for this strain. Among these 23 studies, 11 (48%) analysed both males and females, five (22%) included only males, five (22%) did not specify the sex used, one (4%) analysed females and males separately, and one (4%) included only females.

Anxiety-like behaviours - The Elevated Plus Maze, Elevated Zero Maze, Open Field, and Dark-Light test are validated and common methods used to assess anxiety-like behaviour in mice, by exposing them to mildly aversive or anxiety-inducing environments (Hölter et al., 2015). The six studies (26%) examining this behaviour have shown highly inconsistent results across different age groups. In the Open-Field test and Elevated Zero Maze, **rTg4510 mice did not show** significant differences in the time in the centre or open arms compared to WT mice (Anglada-Huguet et al., 2023; Rodriguez & Lippi, 2022; Rodriguez Ospina et al., 2022), except for two studies where rTg4510 mice showed a decrease in time spent in the centre area (i.e., showing an increase of anxiety-like behaviour) (Criado-Marrero et al., 2021; Xolalpa-Cueva et al., 2022). On the other hand, Cook and colleagues (2014) using the Elevated Plus Maze and Dark-Light tests, found an increase in the time spent in the open arm (at 6 and 10 months of age) and the light chamber (at 6 months of age), respectively (i.e., showing a decrease of anxiety-like behaviour).

Neurological dysfunction/well-being - Assessing nesting behaviour is a non-invasive tool that can reflect neurological dysfunction, including cognitive and motor impairments, as well as overall well-being (Kraeuter et al., 2019). The Marble/Burrowing test can assess natural burrowing behaviour and general activity levels, as well as anxiety-like behaviour and obsessive-compulsive disorder (Kraeuter et al., 2019; Pond et al., 2021). Like nesting behaviour, these tests can also indicate alterations in cognitive and motor functions and well-being (Gjendal et al., 2019). Five studies (22%) were identified

that assessed burrowing and nesting behaviour. Three studies showed a reduction in nesting scores after 4 months of age (Anglada-Huguet et al., 2023; Hernandez et al., 2019; Rodriguez & Lippi, 2022). When analysed before 4 months of age, no significant differences were observed (Hernandez et al., 2019; Xolalpa-Cueva et al., 2022). However, Barabas and colleagues (2022) report that females already exhibited impaired nesting behaviour before 4 months of age. The three studies found indicate a reduction in burrowing behaviour between the ages of 4 and 7 months (Anglada-Huguet et al., 2023; Hernandez et al., 2019; Rodriguez & Lippi, 2022).

Locomotion - The Open-Field test, allowing animals to freely explore an arena, is commonly used for evaluating locomotor behaviour (Kraeuter et al., 2019). We found 12 studies (52%) assessing locomotor behaviour. In all studies, except two (Anglada-Huguet et al., 2023; Wes et al., 2014) which assessed animals after and within 4 months of age, there appears to be an increase in activity (i.e., distance travelled) in rTg4510 mice compared to WT mice (Blackmore et al., 2017; Cook et al., 2014; Criado-Marrero et al., 2021; Foster et al., 2019; Jul et al., 2015; Rodriguez Ospina et al., 2022; Rostgaard et al., 2023; X. Wang et al., 2018; Wes et al., 2014), suggesting an association with a hyperactivity profile. Results in the first 4 months of age mostly show no differences (Cook et al., 2014; Fuller et al., 2024; Xolalpa-Cueva et al., 2022) except for one showing an increase in activity in rTg4510 compared to WT mice (Wes et al., 2014).

Memory and learning - A wide range of cognitive tests was used to compare cognitive performance between rTg4510 and WT mice. We identified 19 studies (83%) that assessed memory and learning. The most frequently used tests were Morris Water Maze, Novel Object Recognition, and different versions of T-Maze or Y-maze tests. Less frequently used were: Radial Arm Water Maze, Barnes Maze, and Fear Conditioning. Most of the tests were performed at or after 4 months of age. Y-Maze and T-Maze tests are commonly used to evaluate spatial memory, learning, and cognitive flexibility (Kraeuter et al., 2019; Schmitt et al., 2021). Across ages, there are inconsistencies in the results. Two studies indicated that rTg4510 mice seemed to have impaired memory compared to WT mice (Anglada-Huguet et al., 2023; Foster et al., 2019) at 4 and 6-7 months. Wes and colleagues (2014) also supported this evidence, although they only observed these differences when assessed at 2 and 4 months, and not at 6 months of age. On the other hand, three other studies were not able to demonstrate these differences (Fuller et al., 2024; Xolalpa-Cueva et al., 2022; Yanagisawa et al., 2018). Blackmore and

colleagues (2017) performed different versions of the Y-Maze and T-Maze tests. While the Rewarded T-Maze Alternation, Y-Maze Spatial Novelty Preference, and Aversive Y-Maze Spatial Reference Memory tests demonstrated cognitive impairments in rTg4510 mice compared to WT mice, the Rewarded Y-Maze Visual Discrimination and Spontaneous Y-Maze Continuous Alternation tests did not show the same results.

The Morris Water Maze was the **most commonly used** test to assess cognitive features such as spatial learning, reference memory, and working memory (Vorhees & Williams, 2006). Consistently, all studies reported in this review, except for one (Kubota & Kirino, 2021), showed that rTg4510 mice had cognitive deficits compared to WT mice between 2.5 and 5.5 months of age (Anglada-Huguet et al., 2023; Bailey et al., 2014; Jul et al., 2015; Polito et al., 2014; Rodriguez & Lippi, 2022; Schaler et al., 2021; Tondo et al., 2020; Yanagisawa et al., 2018). These deficits were evident through increased latency to reach the platform during the spatial acquisition phase and greater difficulty remembering the platform's location in the reference memory phase. These results are consistent with those observed in the Radial Arm Maze and Barnes Maze tests, which are also commonly used to quantify spatial learning and memory (Olton, 1987; Rodríguez Peris et al., 2024). The rTg4510 mice made more errors in both tests compared to the WT mice (Criado-Marrero et al., 2021; Fuller et al., 2024; Rodriguez Ospina et al., 2022).

The Fear Conditioning test, widely used to study associative learning and memory (Arakawa & Iguchi, 2018) showed decreased freezing behaviour in rTg4510 mice between 2 and 10 months of age when compared to WTs (Cook et al., 2014; Criado-Marrero et al., 2021).

Another common test is the Novel Object Recognition (NOR) test, which assesses recognition memory (Antunes & Biala, 2012). The results for this test were somewhat inconsistent between 2 and 10 months of age. Generally, from 4 months onward, rTg4510 mice showed a reduced ability to discriminate between objects (Crimins et al., 2011; Foster et al., 2019; Kubota & Kirino, 2021; Scullion et al., 2019; Wes et al., 2014). However, Scullion and colleagues (2019) did not find these differences when using a short-time protocol (15min) for presenting new objects. On the other hand, Kubota and Kirino (2021) did not find differences using a long-time protocol (24h) at 10 months of age, although at 6 months, the protocol differences did not seem to have an impact. **Of note: the results presented in this study were based on the DOX-off condition, although the authors also provided results for DOX-on condition in the same figure.**

Additionally, these authors did not find cognitive deficits at 4 months of age. Similarly, Wes and colleagues (2014) did not find differences at 2 months. Unexpectedly, Xolalpa-Cueva and colleagues (2022) found that at 1 month of age, rTg4510 mice had a higher recognition index than WT mice.

Balance and coordination - We identified only three studies (13%) that used the rotarod, a validated test for evaluating balance and coordination (Deacon, 2013). These studies found no differences between rTg4510 and WT mice at different ages: 2 months (Fuller et al., 2024), 5.5 months (Yanagisawa et al., 2018) and after 12 months (Blackmore et al., 2017).

Table 1 - Summary of studies of rTg4510 behaviour.

3.2.2. PS19 behavioural profile

For this strain, we decided to conduct a meta-analysis for the most representative behavioural tests. For the tests where we did not conduct a meta-analysis, we performed a systematic review, as was done for the rTg4510 mice. Out of 52 studies, 26 (50%) analysed data by grouping both males and females together, 17 (33%) included only males, six (12%) did not specify the sex used, and three (6%) included both females and males, analysed separately.

Anxiety-like behaviours – Eighteen articles (34%) were identified using various tests (Elevated Plus Maze, Open-Field and Dark-Light Test) to study anxiety-like behaviours). The results regarding anxiety behaviours appeared to be very inconsistent. Before 7 months of age, studies using the Elevated Plus Maze, Open-Field, and Dark-Light Test found both a decrease in anxiety phenotype in PS19 mice compared to WT mice (Apicco et al., 2018; Dumont et al., 2012; Elipenahli et al., 2012; Lyons et al., 2024; Takeuchi et al., 2011; Tapias et al., 2018; Tu et al., 2022) and no significant differences (Ahmad et al., 2021; Chalermpalanupap et al., 2018; Dumont et al., 2011; López-González et al., 2015; Takeuchi et al., 2011). After 7 months, although most studies using the Elevated Plus Maze indicated a decrease in anxiety in PS19 mice (López-González et al., 2015; Sebastián-Serrano et al., 2022; Stack et al., 2014; Tapias et al., 2018; Tu et al., 2022), one study did not find these differences (Hou et al., 2020). Ahmad and colleagues

(2021), showed that PS19 mice spend more time in the open arm at 12 months, but not at 8 months. Similarly, results from the Open-Field test were not clear. While some studies showed an increase in the time spent in the centre area (Dumont et al., 2012; Elipenahli et al., 2012), one study showed a reduction (Dutta et al., 2023), and another three did not find any significant differences (Chalermpalanupap et al., 2018; Ohia-Nwoko et al., 2014; Sandusky-Beltran et al., 2021). Interestingly, Serrano and colleagues (2022) showed that PS19 mice made more entries to the centre at 7 months but not at 9 months **compared** with WT. Dumont and colleagues (2011) results may suggest that these discrepancies might be related to sex differences.

Neurological dysfunction/ well-being – Only one article (2%) was identified in this category. Sun and colleagues (2020) reported that male PS19 mice exhibited impaired nest-building abilities during and after 9 months of age. No differences were found in females.

Depression-like behaviours – We found two articles (4%) that evaluated depression-like behaviours using the Forced Swim Test and Tail Suspension Test. Both assays measure dimensions of depression (Can et al., 2011; Yankelevitch-Yahav et al., 2015). Before 5 months of age, no differences were found in either test (López-González et al., 2015; Takeuchi et al., 2011). At 6 months authors found contradictory findings with the Tail Suspension Test (López-González et al., 2015; Takeuchi et al., 2011), where one study showed a decrease in immobility, while the other did not find any differences when comparing PS19 and WT mice. After 6 months, López-González and colleagues (2015) reported a reduction of immobility in PS19 mice compared to WT mice in the Tail Suspension Test.

Locomotion – Twenty-four studies (46%) that assessed locomotor behaviour were identified. Of these, 22 analysed the total distance in the Open-Field test comparing PS19 and WT mice. The two studies that did not report this measure opted to show: a) the distance travelled in the central area, where Sun and colleagues (2020) reported an increase in male PS19 mice at 11 months of age, and b) velocity, where Tu and colleagues (2022) did not find any differences. Additionally, 12 studies were excluded from the analysis because the animals performed in the Open-Field test for more than 15 minutes (attempting to control for variations in the protocols) or we did not obtain all the necessary statistical information. Seven studies did not find differences in locomotor behaviour (Eteläinen et al., 2023; Ferreira et al., 2021; McAvoy et al., 2019; Mikhail et al., 2015;

Ohia-Nwoko et al., 2014; Sebastián-Serrano et al., 2022; Wagner et al., 2015), but four showed an increase in locomotor behaviour in PS19 mice, across a range of different ages (Apicco et al., 2018; Elipenahli et al., 2012; Patel et al., 2022; Takeuchi et al., 2011).

In total, we were able to integrate 10 studies into this meta-analysis (Figure 2) (Ahmad et al., 2021; Ano et al., 2020, 2023; Dumont et al., 2011, 2012; Dutta et al., 2023; Jiang et al., 2016; Sandusky-Beltran et al., 2021; Stack et al., 2014; Wheeler et al., 2019). Of these 10 studies, five reported data for ages < 7 months and 10 reported data for ages ≥ 7 months. Compared to the control group, PS19 mice showed an increased distance in the Open-Field test for both age groups: < 7 months (*Hedges' g* = 0.54, 95% *CI* = 0.24 to 0.84, $p < 0.001$; *Q* statistics $p = 0.711$; $I^2 = 0\%$; $\beta 0 = -1.798$, $t = -1.077$, $p = 0.331$) and ≥ 7 months (*Hedges' g* = 0.73, 95% *CI* = 0.39 to 1.06, $p < 0.001$; *Q* statistics $p = 0.003$; $I^2 = 60.4\%$; $\beta 0 = -0.104$, $t = -0.118$, $p = 0.908$). The overall effect (without subgroup analysis) (*Hedges' g* = 0.66, 95% *CI* = 0.44 to 0.88, $p < 0.001$; *Q* statistics $p = 0.016$; $I^2 = 39.3\%$; $\beta 0 = -0.223$, $t = -0.330$, $p = 0.745$) indicated the same result. PS19 mice appeared to show a hyperactive profile even before the onset of the pathology. Regarding heterogeneity and publication bias, these analyses showed that: a) For ages < 7 months, the results were consistent, showing no significant heterogeneity or publication bias. b) For ages ≥ 7 months, there was moderate to substantial heterogeneity, but without publication bias. c) Overall, the combined studies demonstrated low to moderate heterogeneity, but no publication bias.

Figure 2 – Forest plot with subgroup analysis based on the age of the animals. Studies report distance in the Open-Field test (WT vs PS19 mice).

Memory and learning – Memory and learning were the most common assessments performed to assess differences between PS19 and WT mice, where we identified 47 studies (89%). The tests used to evaluate cognition included: Morris Water Maze, Novel Object Recognition, Barnes Maze, Eight-Arm Radial Maze and Fear Conditioning. Twelve studies using Y-Maze/T-maze tests were found: one study using the T-Maze showed no differences (Ferreira et al., 2021); two studies not using alternation behaviour showed that PS19 mice had a reduction in discrimination index (Jiang et al., 2016) and

novel arm time (M. Huang et al., 2023); and nine studies that met our criteria were used for meta-analysis (Figure 3) (Ahmad et al., 2021; Apicco et al., 2018; Fan et al., 2020; Giannopoulos et al., 2018; Jang et al., 2024; Patel et al., 2022; Sandusky-Beltran et al., 2021; Takeuchi et al., 2011; Vagnozzi et al., 2018). These studies reported alternation behaviour, three of which report data for ages < 7 months and seven report data for ages ≥ 7 months. As seen in Figure 3, PS19 mice show a decrease in alternation behaviour compared to the control group at < 7 months (*Hedges' g* = -0.88, 95% *CI* = -1.24 to -0.53, $p < 0.001$; *Q* statistics $p = 0.670$; $I^2 = 0\%$; $\beta 0 = 0.394$, $t = 0.357$, $p = 0.745$) and ≥ 7 months (*Hedges' g* = -1.03, 95% *CI* = -1.74 to -0.32, $p = 0.004$; *Q* statistics $p < 0.001$; $I^2 = 82.3\%$; $\beta 0 = 1.393$, $t = 1.099$, $p = 0.314$). The overall effect (without subgroup analysis) (*Hedges' g* = -0.97, 95% *CI* = -1.40 to -0.54, $p < 0.001$; *Q* statistics $p < 0.001$; $I^2 = 71.1\%$; $\beta 0 = 1.123$, $t = 1.466$, $p = 0.171$) also suggest that PS19 mice exhibit cognitive deficits relative to WT mice. There is substantial heterogeneity in the ≥ 7 months subgroup and overall, but no observed heterogeneity in the < 7 months subgroup. Generally, there is no significant evidence of publication bias.

Figure 3 – Forest plot with subgroup analysis based on the age of the animals. Studies report the alternation behaviour in the Y-Maze (WT vs PS19 mice).

The Morris Water Maze task for spatial learning also shows very inconsistent results. Twenty-one studies assessed spatial learning. Up to the age of 4 months, no differences between PS19 and WT mice were detected (Chalermpalanupap et al., 2018; Dumont et al., 2011; Sun et al., 2020; Zampar & Wirths, 2021). Between 5 and 10 months, results were balanced between those showing PS19 mice had more difficulty in learning the platform position (Chalermpalanupap et al., 2018; Dumont et al., 2011; Hou et al., 2020; Jiang et al., 2015, 2016; Takeuchi et al., 2011; Vagnozzi et al., 2018; Woo et al., 2022; Yao et al., 2023; Zhang et al., 2014; Zhu et al., 2022), although Dumont and colleagues (2011) found these differences only in males, and those without differences (Brody et al., 2022; Chalermpalanupap et al., 2018; Dave et al., 2021; Dumont et al., 2011; Giannopoulos et al., 2018; Harris et al., 2020; Lasagna-Reeves et al., 2016; Sun et al., 2020; Tang et al., 2020; Zampar & Wirths, 2021). Between 11 and 12 months, two studies indicate that PS19 mice show an increased latency to reach the quadrant/platform (Hou et al., 2020; Sun et al., 2020), however, these differences appear to be related to sex,

with one study showing differences in males and another study just on females. Twenty-two studies used Morris Water Maze to access reference memory. Fifteen studies analysed the time spent in the target quadrant in the Morris Water Maze (7 studies report data for ages < 7 months and 10 studies report data for ages ≥ 7 months) and were used in the meta-analysis (Figure 4) (Brody et al., 2022; Dumont et al., 2011; Harris et al., 2020; Hou et al., 2020; Izzy et al., 2021; Jiang et al., 2015, 2016; Lasagna-Reeves et al., 2016; Takeuchi et al., 2011; Tang et al., 2020; Woo et al., 2022; Yao et al., 2023; Zampar & Wirths, 2021; Zhang et al., 2014; Zhu et al., 2022). PS19 mice show a decrease of time spent in the target quadrant in the Morris Water Maze compared to the control group at < 7 months (*Hedges' g* = -1.14, 95% *CI* = -1.66 to -0.62, $p < 0.001$; *Q* statistics $p = 0.003$; $I^2 = 58.1\%$; $\beta 0 = 0.813$ $t = 1.337$, $p = 0.230$) and ≥ 7 months (*Hedges' g* = -1.73, 95% *CI* = -2.06 to -0.87, $p < 0.001$; *Q* statistics $p < 0.001$; $I^2 = 91.4\%$; $\beta 0 = 3.549$, $t = 4.110$, $p = 0.001$). The overall effect (without subgroup analysis) (*Hedges' g* = -1.58, 95% *CI* = -2.196 to -0.97, $p < 0.001$; *Q* statistics $p < 0.001$; $I^2 = 89.1\%$; $\beta 0 = 1.838$, $t = 3.298$, $p = 0.004$) also indicates that PS19 mice exhibit memory impairments relative to WT mice. There is moderate to substantial heterogeneity in the < 7 months subgroup and substantial heterogeneity in the ≥ 7 months subgroup and overall. There is no significant publication bias in the < 7 months subgroup. In the ≥ 7 months subgroup and overall, there is significant publication bias. There were seven studies that didn't measure the time spent in the target quadrant, but instead measured metrics related to the platform, such as time, crossings, and path length. Three studies didn't find any differences (Chalermpalanupap et al., 2018; Sun et al., 2020; Vagnozzi et al., 2018), while three studies showed a decrease in the efficiency (i.e., more time/frequency) of finding the platform (Dave et al., 2021; Giannopoulos et al., 2018; Tu et al., 2022). Ahmad and colleagues (2021) found that at 8 months, but not before, PS19 mice had to travel further to reach the place where the platform had been hidden.

Figure 4 – Forest plot with subgroup analysis based on the age of the animals. Studies report time spent in the target quadrant in the Morris Water Maze (WT vs PS19 mice).

The Barnes Maze (10 studies) and Eight-Arm Radial Maze (one study), PS19 mice show cognitive impairments within and after 7 months (Cao et al., 2023; Dutta et al., 2023; Eteläinen et al., 2023; Liu et al., 2019; Moreno-Gonzalez et al., 2021; Tu et al.,

2022; Wheeler et al., 2019). Before 7 months, the results are more inconsistent. While four studies didn't show differences between PS19 mice and WT (Eteläinen et al., 2023; Ferreira et al., 2021; Moreno-Gonzalez et al., 2021; Takeuchi et al., 2011), three studies showed a decrease in cognitive ability in PS19 mice (Brunden et al., 2010; Cao et al., 2023; Lyons et al., 2024).

Fifteen studies using the Novel Object Recognition test were found. Before 7 months, no differences were observed in most of the studies (Cao et al., 2023; Eteläinen et al., 2023; Ferreira et al., 2021; López-González et al., 2015; Zampar & Wirths, 2021). However, three studies show that PS19 mice had discrimination impairments (Apicco et al., 2018; Cao et al., 2023; Yao et al., 2023). Between 7 and 9 months, four studies show cognitive impairments (Fan et al., 2020; Tu et al., 2022; Wagner et al., 2015; Yao et al., 2023), although six studies did not show differences on this same period (Cao et al., 2023; Dutta et al., 2023; Eteläinen et al., 2023; Jang et al., 2024; López-González et al., 2015; Zampar & Wirths, 2021). The only three studies conducting this behaviour test at 10 months found cognitive impairments in PS19 mice (Guo et al., 2022; M. Huang et al., 2023; López-González et al., 2015). Additionally, in the version of the Novel Object Location (that access different cognitive domain), Sebastián-Serrano and colleagues (2022) also didn't find any impairments in PS19 mice at 7 and 9 months.

Fifteen studies were used to evaluate Context Fear Conditioning, out of these, 13 met our criteria and were included in the meta-analysis. In total five studies report data for ages < 7 months and 10 studies report data for ages ≥ 7 months (Figure 5) (Chalermpalanupap et al., 2018; Fan et al., 2020; Guo et al., 2022; Hou et al., 2020; Lasagna-Reeves et al., 2016; Litvinchuk et al., 2018; McAvoy et al., 2019; Mikhail et al., 2015; Patel et al., 2022; Stack et al., 2014; Takeuchi et al., 2011; Vagnozzi et al., 2018; Zhang et al., 2014). PS19 mice show a decrease of freezing compared to the control group at ≥ 7 months (*Hedges' g* = -0.83, 95% *CI* = -1.47 to -0.19, $p = 0.011$; *Q* statistics $p < 0.001$; $I^2 = 81.9\%$; $\beta 0 = 2.797$, $t = 1.386$, $p = 0.199$), however these differences were not found in early age: < 7 months (*Hedges' g* = -0.56, 95% *CI* = -1.12 to 0.01, $p = 0.054$; *Q* statistics $p = 0.026$; $I^2 = 60.4\%$; $\beta 0 = 2.160$, $t = 1.684$, $p = 0.153$). The overall effect (without subgroup analysis) (*Hedges' g* = -0.73, 95% *CI* = -1.17 to -0.29, $p = 0.001$; *Q* statistics $p < 0.001$; $I^2 = 76.3\%$; $\beta 0 = 2.377$, $t = 2.021$, $p = 0.060$) also indicates that PS19 mice have memory impairments in relation to WT. These analyses show that there is moderate to substantial and substantial heterogeneity across all groups. Generally, there

is no significant evidence of publication bias. The studies not included in the meta-analyses showed a decrease in freezing behaviour in the PS19 mice (Guo et al., 2022; Tapias et al., 2018)

Figure 5 – Forest plot with subgroup analysis based on the age of the animals. Studies report freezing behaviour in the Context Fear Conditioning (WT vs PS19 mice).

Balance and coordination – Twenty articles (38%) used behavioural tests for evaluation of motor assessment. Grip strength is commonly used to assess muscle strength (Lalonde et al., 2021). Before 7 months of age, published reports did not show any differences (Dumont et al., 2011; Sun et al., 2020; Takeuchi et al., 2011). After 7 months, results become more inconsistent. Up to 9 months of age, four studies showed a decrease in grip strength (Di et al., 2021; Dumont et al., 2011; Liu et al., 2019; Patel et al., 2022); however, Di and colleagues (2021) found differences only in females. Two studies, between 8 and 11 months didn't find any differences (Dumont et al., 2011; Sun et al., 2020). Conversely, Sun and colleagues (2020) showed a decrease in grip strength in male PS19 mice at 12 months of age. Another set of tests used to measure balance and coordination included Stride Length, Inverted Grid, Wire Hang, and Balance Beam. None of these tests were able to detect any differences in the motor function of PS19 mice compared to WT mice from an early age until 10 months of age (Brody et al., 2022; Dumont et al., 2011; Sun et al., 2020; Takeuchi et al., 2011; Zampar & Wirths, 2021). However, Sun and colleagues (2020), using Stride Length at 11-12 months of age, showed that differences could be related to the sex of the animals, as female PS19 mice showed impairments at 11 months, while male PS19 mice showed a decrease in performance at 12 months. The latency to fall in the Rotarod was used to assess motor differences in PS19 compared with WT mice (total of 17 studies). Five studies were not included in the meta-analysis because the data did not fit our criteria (Brunden et al., 2010; Dumont et al., 2011; Mikhail et al., 2015; Sebastián-Serrano et al., 2022; Sun et al., 2020). The five studies showed no differences between PS19 and WT mice, except for the study by Sun and colleagues (2020), where at 9 months, female PS19 mice spent more time on the rotarod and the study by Sebastián-Serrano and colleagues (2022) which also showed that PS19 mice (both sexes grouped) had less latency to fall. In total, 12 studies were used for

the meta-analysis: 6 report data for ages < 7 months and 10 studies report data for ages ≥ 7 months (Brody et al., 2022; Dutta et al., 2023; M. Huang et al., 2023; Izzy et al., 2021; López-González et al., 2015; Moreno-Gonzalez et al., 2021; Takeuchi et al., 2011; Tang et al., 2020; Vagnozzi et al., 2018; Wheeler et al., 2019; Zampar & Wirths, 2021) (Figure 6). PS19 mice show an increase of fall latency compared to the control group at < 7 months (*Hedges' g* = 0.38, 95% *CI* = 0.011 to 0.758, $p = 0.044$; *Q* statistics $p = 0.206$; $I^2 = 21.9\%$; $\beta 0 = 1.028$, $t = 1.129$, $p = 0.302$). However, no differences were found at ≥ 7 months (*Hedges' g* = 0.027, 95% *CI* = -0.496 to 0.550, $p = 0.920$; *Q* statistics $p < 0.001$; $I^2 = 78.4\%$; $\beta 0 = 1.572$, $t = 1.393$, $p = 0.191$) or in the overall effect (without subgroup analysis) (*Hedges' g* = 0.157, 95% *CI* = -0.196 to 0.511, $p = 0.383$; *Q* statistics $p < 0.001$; $I^2 = 69.2\%$; $\beta 0 = 1.207$, $t = 1.530$, $p = 0.142$), suggesting that PS19 mice do not exhibit motor deficits relative to WT mice. There is substantial heterogeneity in the ≥7 subgroup, moderate to substantial in the overall and low in the <7 subgroup. There is no significant evidence of publication bias in all groups.

Figure 6 – Forest plot with subgroup analysis based on the age of the animals. Studies report the latency to fall in the Rotarod (WT vs PS19 mice).

Table 2 - Summary of studies of PS19 behaviour.

4. Discussion

Tauopathy animal models are frequently used in research to gain a better understanding of neurodegenerative disorders. This review aimed to provide a behavioural characterization of the PS19 and rTg4510 tauopathy mouse models, revealing key insights into their phenotypic manifestations. We focused our analysis on anxiety, depressive-like behaviours; neurobiological dysfunction/well-being; locomotion; memory and learning; balance and coordination.

Cognitive decline is well-known and well-documented in **AD patients.** However, behavioural and psychological symptoms of dementia, such as anxiety and depression, have been less thoroughly studied (Hart et al., 2003). These symptoms have been reported

to appear in the early stages of dementia (Pentkowski et al., 2021). These behavioural alterations seem to be associated with the expression of plaques and tangles found in areas related to the limbic system (Pentkowski et al., 2021; Van Hoesen et al., 2000). To gain a broader understanding of this issue, we examined anxiety and depression-like behaviours reported in both rTg4510 and PS19 mouse strains, which could enhance our understanding of these symptoms.

In emotional behaviour assessments, it is valuable to explore how certain behavioural tests may be more suitable for specific evaluations than others. For example, the Elevated Plus Maze has been suggested to be a more effective test for assessing anxiety-like behaviour compared to the Open-Field test, as it is specifically designed to elicit a stronger anxiety response (Figueiredo Cerqueira et al., 2023). Another important consideration is the distinction between state and trait anxiety. Some studies propose that both the Elevated Plus Maze and the Open-Field tests measure state anxiety, not trait. Anxiety trait is expected to remain stable over time, but this is not observed when these studies are repeated. This is likely due to the apparatus losing its novelty, which often leads to inconsistent results (Andreatini & Bacellar, 2000). The free-exploratory paradigm has been proposed to assess trait anxiety. There are contradictions in the literature regarding whether individuals with high trait anxiety display a greater anxiety state compared to those with low trait anxiety (Andreatini & Bacellar, 2000; Goes et al., 2009).

At the onset of disease progression in PS19 mice, these animals appear to exhibit hyperactivity, disinhibition, and reduced anxiety. It would be beneficial to explore more ethological behaviours in the Elevated Plus Maze and Open-Field tests, focusing on risk assessment and exploratory behaviours such as head dips, stretched-attend postures, and rearing (Holmes & Rodgers, 1999; Macrì et al., 2002; Walf & Frye, 2007). This could help determine whether there is an association with risk-taking behaviour, as it has been suggested that Alzheimer's disease patients may display increased risk-taking tendencies (HA et al., 2012). This approach would provide a more comprehensive understanding of the behavioural profile of these mice. These deficits are often linked to dysfunction in the prefrontal cortex, a region crucial for decision-making and impulse control, underlying deficits in cognitive functions (Hiser & Koenigs, 2018; Xu et al., 2019). In neurodegenerative disease models such as rTg4510 and PS19 mice, this impairment in risk-behaviour may serve as an early indicator of broader cognitive decline, highlighting

a potential relationship between anxiety regulation, executive dysfunction, and memory deficits (Calcia et al., 2016; Kumar, 2018).

Memory and learning tests are the most used behavioural assays in research involving tauopathy mouse models. The rTg4510 and PS19 models are extensively utilized to investigate cognitive deficits because they closely resemble the pathological accumulation of tau protein observed in human neurodegenerative diseases, such as Alzheimer's disease and frontotemporal dementia (Alzforum, 2024; Ramsden et al., 2005; SantaCruz et al., 2005; Yoshiyama et al., 2007). Tau pathology is known to disrupt neuronal function, particularly in brain regions like the hippocampus and prefrontal cortex, which are critical for learning and memory (Rajmohan & Reddy, 2017). Cognitive tests such as the Morris Water Maze, Y-Maze, Novel Object Recognition, Contextual Fear Conditioning, and Barnes Maze are frequently used in these models to assess various aspects of cognition, including spatial learning, reference memory, working memory, and recognition memory (Antunes & Biala, 2012; Arakawa & Iguchi, 2018; Kraeuter et al., 2019; Olton, 1987; Rodríguez Peris et al., 2024; Vorhees & Williams, 2006). In this review, as expected, we found clear deficits in memory and learning that emerge after the disease onset in these strains—typically around 6-7 months of age in PS19 mice and around 3-4 months in rTg4510 mice. The meta-analysis on PS19 mice in the Morris Water Maze and Y-maze suggests that deficits may begin slightly earlier, around 5–6 months of age. In the Contextual Fear Conditioning test, deficits were observed just after 7 months. These tests help to quantify deficits that arise as tau pathology progresses, providing insights into how tau accumulation affects cognitive functions over time.

In summary, after disease onset, PS19 mice exhibit reduced anxiety-like behaviour, hyperactivity, impaired memory and learning, and no differences in balance and coordination. In contrast, rTg4510 mice show impaired neurological function and well-being, hyperactivity, and deficits in memory and learning (Table 3).

These findings highlight a general consistency in the behavioural changes seen across these models, while also emphasizing the need to thoroughly assess baseline performance in behavioural tests before planning studies which rely on behavioural deficits to demonstrate the effects of any pharmacological or genetic manipulation. Upon reviewing the compiled data, which was structured for maximum comparability, we noted that not all studies or tests produced consistent results. This variability can be attributed to several factors, including differences in experimental protocols, sample sizes,

husbandry conditions, mouse strain backgrounds, sex differences, the experimenter, handling procedures, and other variables (see more details here (Saré et al., 2021)). These factors can introduce heterogeneity into the data, affecting reproducibility and leading to inconsistencies between studies. In our analysis, we observed moderate to substantial heterogeneity in the behavioural tests used for the meta-analysis on PS19 mice. Additionally, we had to exclude some studies due to insufficient statistical information, and it is also important to be aware of studies that are not published due to the non-reporting of negative findings (Mlinarić et al., 2017). Therefore, while the meta-analysis provides valuable insights, it is important to interpret the results with caution. Understanding the sources of heterogeneity can help refine experimental designs and improve the reliability of future studies. It also underscores the need for standardized protocols and comprehensive reporting of experimental details to minimize variability and enhance the comparability of results across studies (Baker, 2016; Ioannidis, 2005). It is important to consider guidelines such as ARRIVE (Animal Research: Reporting of In Vivo Experiments) to continue improving the quality of publications (Percie du Sert et al., 2020).

Additionally, gaining a better understanding of the behavioural profiles of animal models could involve evaluating them through a series of tests designed to investigate various dimensions of a disease (Goes et al., 2009; Holter et al., 2015; Vautrin et al., 2005). For example, in humans, depression is associated with several characteristics, including anhedonia, anxiety, and despair (American Psychiatric Association, 2013). In mouse models, various tests are employed to assess these different dimensions, such as the sucrose preference test for anhedonia and the forced swim test for despair (Ménard et al., 2016). Given the complexity of human behaviour, it is crucial to consider how findings from these mouse models can be translated to human conditions. Advances in technology have enhanced our ability to translate behavioural findings more effectively.

In terms of cognitive assessments, touchscreen tests in mice have been revolutionary in this area. In humans, many cognitive tasks are traditionally conducted using "paper and pencil" methods, while in animals, cognitive assessments are often performed in mazes (Lee et al., 2021). Touchscreen-based tasks, applicable to both humans and mice, offer a more standardized approach, enhancing the potential for cross-species comparisons (Nithianantharajah & Grant, 2013; Sullivan et al., 2021). These tasks allow researchers to assess cognitive functions across multiple domains, such as attention, memory, and

executive function (Lee et al., 2021; Sullivan et al., 2021). Implementing touchscreen tests in PS19 and rTg4510 mice could increase the sensitivity and precision of behavioural assessments, leading to a better understanding of disease progression and the efficacy of potential treatments (Shepherd et al., 2021). Conversely, virtual reality technology is being used to place humans in more "maze-like" situations. Biedermann and colleagues (2017) were able to validate approach-avoidance behaviour in humans using the Elevated Plus Maze in a virtual reality environment. Technological improvements, such as those used in automated home-cage monitoring, have made it easier to assess rodent behaviour with less bias (Ho et al., 2023).

The study of tauopathies, particularly in the context of Alzheimer's disease, remains critically important for understanding the pathophysiology of these devastating conditions. Tau protein aggregation is a hallmark of Alzheimer's and related neurodegenerative diseases, and unravelling its role is key to developing effective therapeutic strategies. This comprehensive compilation of behavioural data from established tauopathy mouse models, such as PS19 and rTg4510, offers invaluable insights into the various cognitive and motor impairments associated with these diseases. By consolidating existing data on anxiety, depression, memory, and coordination, this review serves as an essential resource for researchers. It not only aids in understanding the current state of research but also provides a framework for designing future experiments that can more accurately assess the impact of genetic or pharmacological interventions on behavioural outcomes. Additionally, recognizing the heterogeneity of experiments is crucial. This synthesis will help new lines of inquiry and guide the development of more targeted, effective therapeutic approaches for tau-related disorders.

Table 3 - Summary of main results in both strains.

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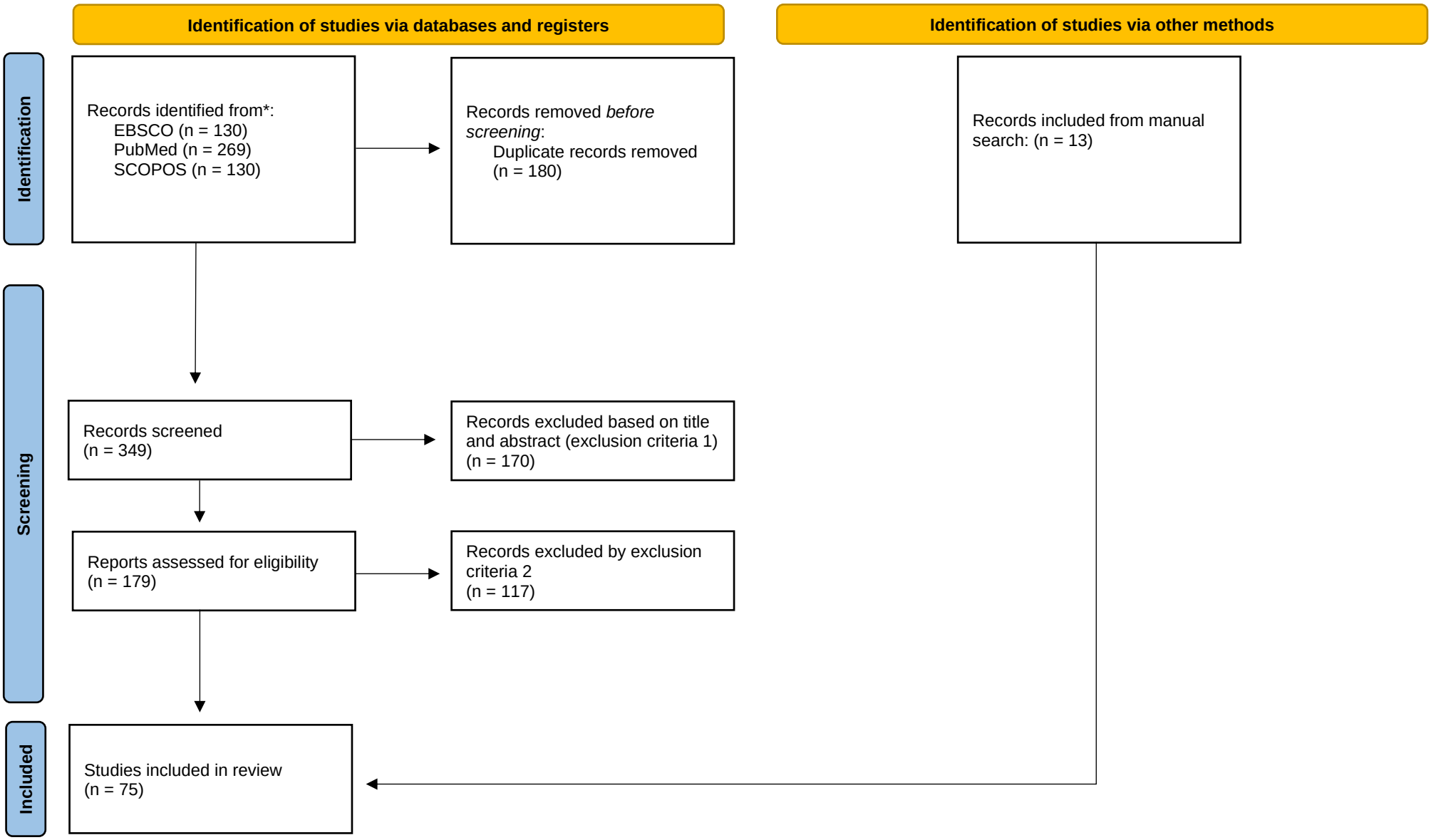
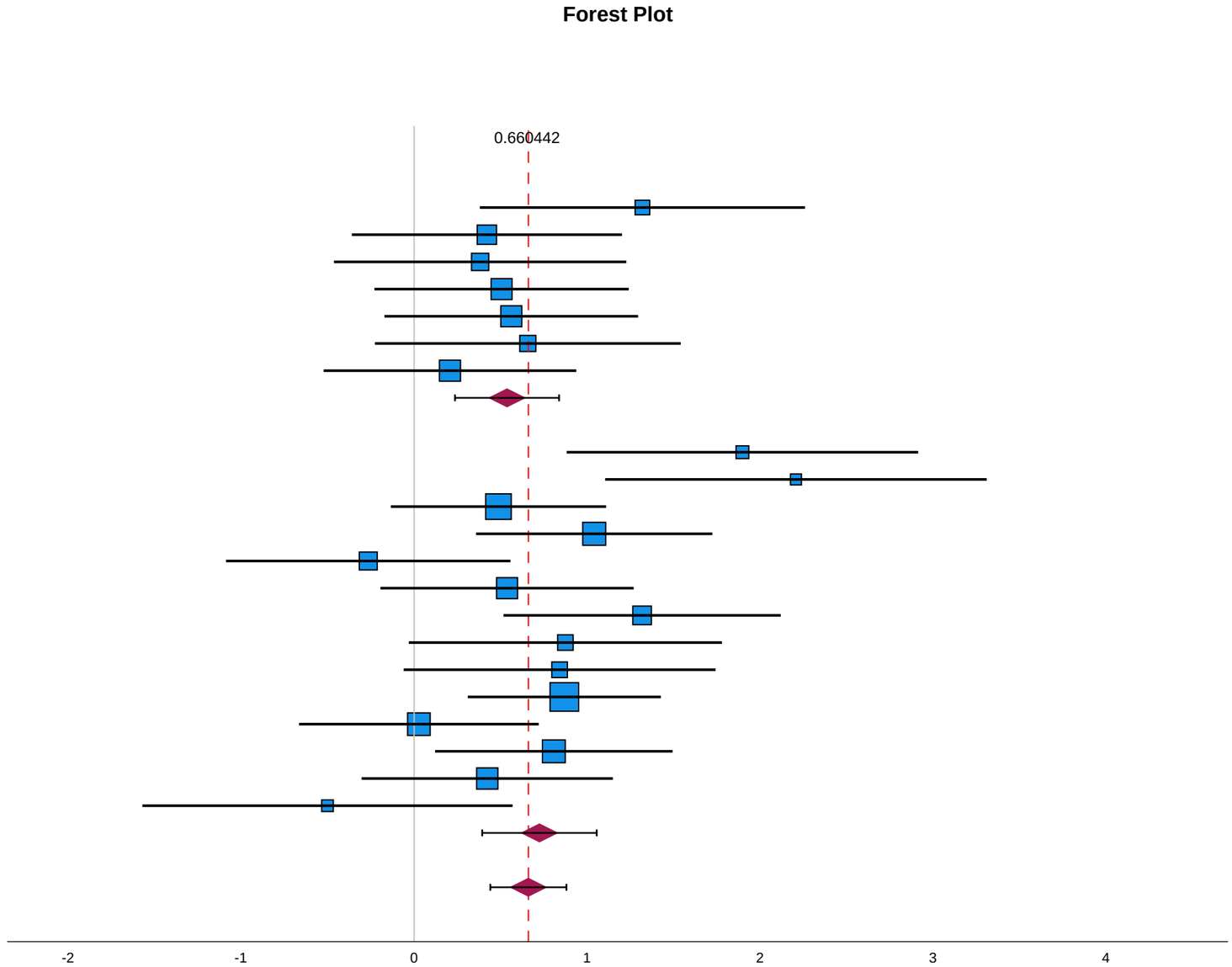

Identification of studies via databases and registers
Identification of studies via other methods
Identification
Screening
Included
Records identified from*:
EBSCO (n = 130)
PubMed (n = 269)
SCOPOS (n = 130)
Records removed *before screening*:
Duplicate records removed (n = 180)
Records included from manual search: (n = 13)
Records screened (n = 349)
Records excluded based on title and abstract (exclusion criteria 1) (n = 170)
Reports assessed for eligibility (n = 179)
Records excluded by exclusion criteria 2 (n = 117)
Studies included in review (n = 75)

Effect size of each study
Estimated overall effect size
No-effect value
Confidence interval of effect size
Overall effect size value
Estimated overall confidence interva

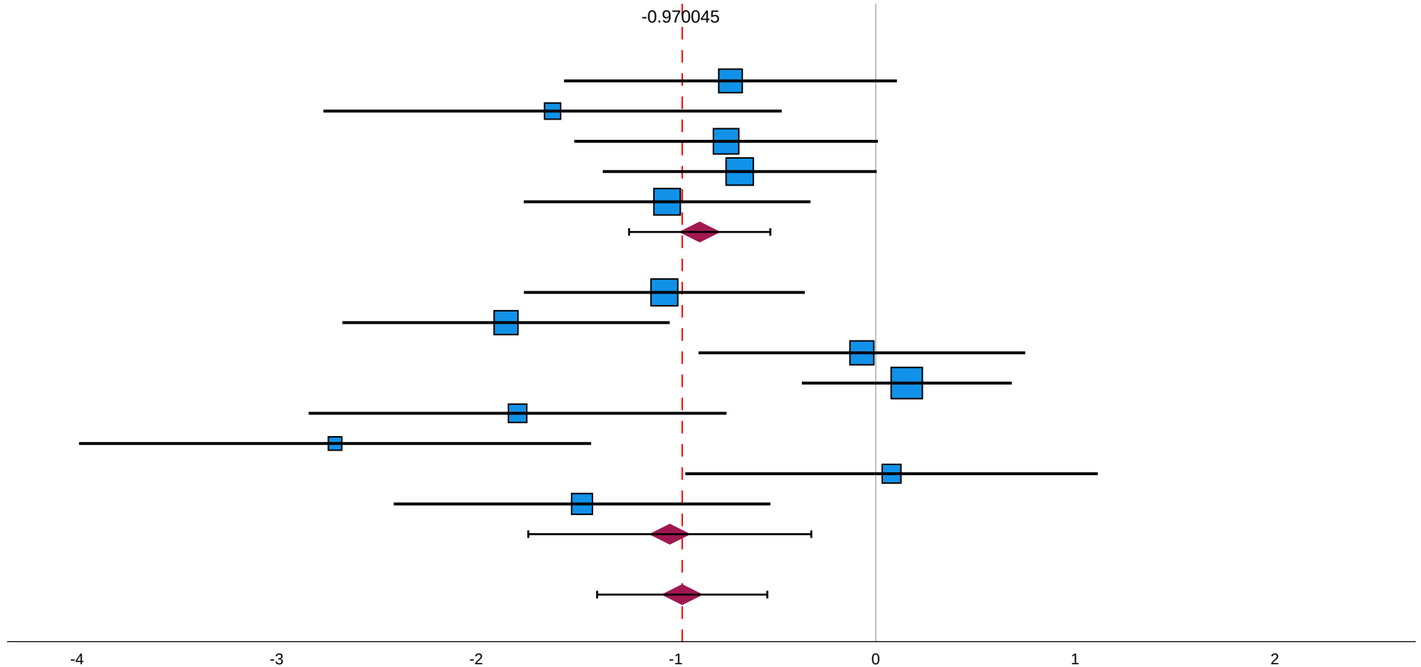
Age	ID	Study	Hedges' g	Lower	Upper	p-value	Weight	Weight (%)
< 7 months	Ano (2023)	Total distance (cm)	1.32	0.38	2.26	0.01	3.01	3.80
	Ahmad (2021)	Path length (m)	0.42	-0.36	1.20	0.29	3.84	4.84
	Ahmad (2021)	Path length (m)	0.38	-0.46	1.23	0.38	3.48	4.38
	Ahmad (2021)	Path length (m)	0.51	-0.23	1.24	0.18	4.13	5.20
	Dumont (2012)	Distance (cm)	0.56	-0.17	1.29	0.13	4.14	5.21
	Stack (2014)	Distance (cm)	0.66	-0.23	1.54	0.15	3.28	4.13
	Dumont (2011)	Distance (cm)	0.21	-0.52	0.94	0.58	4.16	5.23
		Subgroup Overall	0.54	0.24	0.84	0.00		
7 months	Ano (2020)	Total distance (cm)	1.90	0.88	2.91	0.00	2.70	3.40
	Ano (2023)	Total distance (cm)	2.21	1.10	3.31	0.00	2.39	3.01
	Ahmad (2021)	Path length (m)	0.49	-0.13	1.11	0.12	4.94	6.22
	Ahmad (2021)	Path length (m)	1.04	0.36	1.72	0.00	4.48	5.64
	S.Beltran (2021)	Total distance (m)	-0.27	-1.09	0.56	0.53	3.60	4.53
	Dumont (2012)	Distance (cm)	0.54	-0.19	1.27	0.15	4.15	5.22
	Dumont (2012)	Distance (cm)	1.32	0.52	2.12	0.00	3.72	4.68
	Stack (2014)	Distance (cm)	0.87	-0.03	1.78	0.06	3.17	4.00
	Stack (2014)	Distance (cm)	0.84	-0.06	1.74	0.07	3.19	4.02
	Wheeler (2019)	Distance (in)	0.87	0.31	1.43	0.00	5.47	6.89
	Jiang (2016)	Distance moved (m)	0.03	-0.67	0.72	0.94	4.41	5.56
	Dumont (2011)	Distance (cm)	0.81	0.12	1.49	0.02	4.46	5.61
	Dumont (2011)	Distance (cm)	0.42	-0.30	1.15	0.25	4.18	5.27
	Dutta (2023)	Distance (cm)	-0.50	-1.57	0.57	0.36	2.50	3.15
		Subgroup Overall	0.72	0.39	1.06	0.00		
Overall			0.66	0.44	0.88	0.00		



Model: Random-effects model
Heterogeneity: Tau-squared = 0.10, H-squared = 1.65, I-squared = 0.39
Test of overall effect size: z = 5.89, p-value = 0.00
Test of between-subgroup homogeneity: Q = 0.68, df = 1, p-value = 0.41

Effect size of each study
Estimated overall effect size
No-effect value
Confidence interval of effect size
Overall effect size value
Estimated overall confidence interva

Age	ID	Study	Hedges' g	Lower	Upper	p-value	Weight	Weight (%)
< 7 months	Ahmad (2021)	Alternation (%)	-0.73	-1.56	0.11	0.09	1.66	7.87
	Ahmad (2021)	Alternation (%)	-1.62	-2.77	-0.47	0.01	1.31	6.19
	Ahmad (2021)	Alternation (%)	-0.75	-1.51	0.01	0.05	1.75	8.28
	Takeuchi (2011)	% Alternation	-0.68	-1.37	0.00	0.05	1.84	8.71
	Apicco (2018)	% Correct alternations	-1.05	-1.76	-0.33	0.00	1.80	8.53
		Subgroup Overall	-0.88	-1.24	-0.53	0.00		
7 months	Ahmad (2021)	Alternation (%)	-1.06	-1.76	-0.36	0.00	1.82	8.61
	Ahmad (2021)	Alternation (%)	-1.85	-2.67	-1.03	0.00	1.68	7.94
	S.Beltran (2021)	% Alternation	-0.07	-0.89	0.75	0.87	1.68	7.95
	Patel (2022)	% Spontaneous alternation	0.16	-0.37	0.68	0.56	2.03	9.61
	Fan (2020)	Spontaneous alternatio...	-1.79	-2.84	-0.75	0.00	1.42	6.70
	Giannopoulos (2018)	% Alternation	-2.71	-3.99	-1.43	0.00	1.18	5.57
	Jang (2024)	% Alternation	0.08	-0.95	1.11	0.88	1.43	6.77
	Vagnozzi (2018)	% Alternation	-1.47	-2.42	-0.53	0.00	1.53	7.25
		Subgroup Overall	-1.03	-1.74	-0.32	0.00		
Overall			-0.97	-1.40	-0.54	0.00		

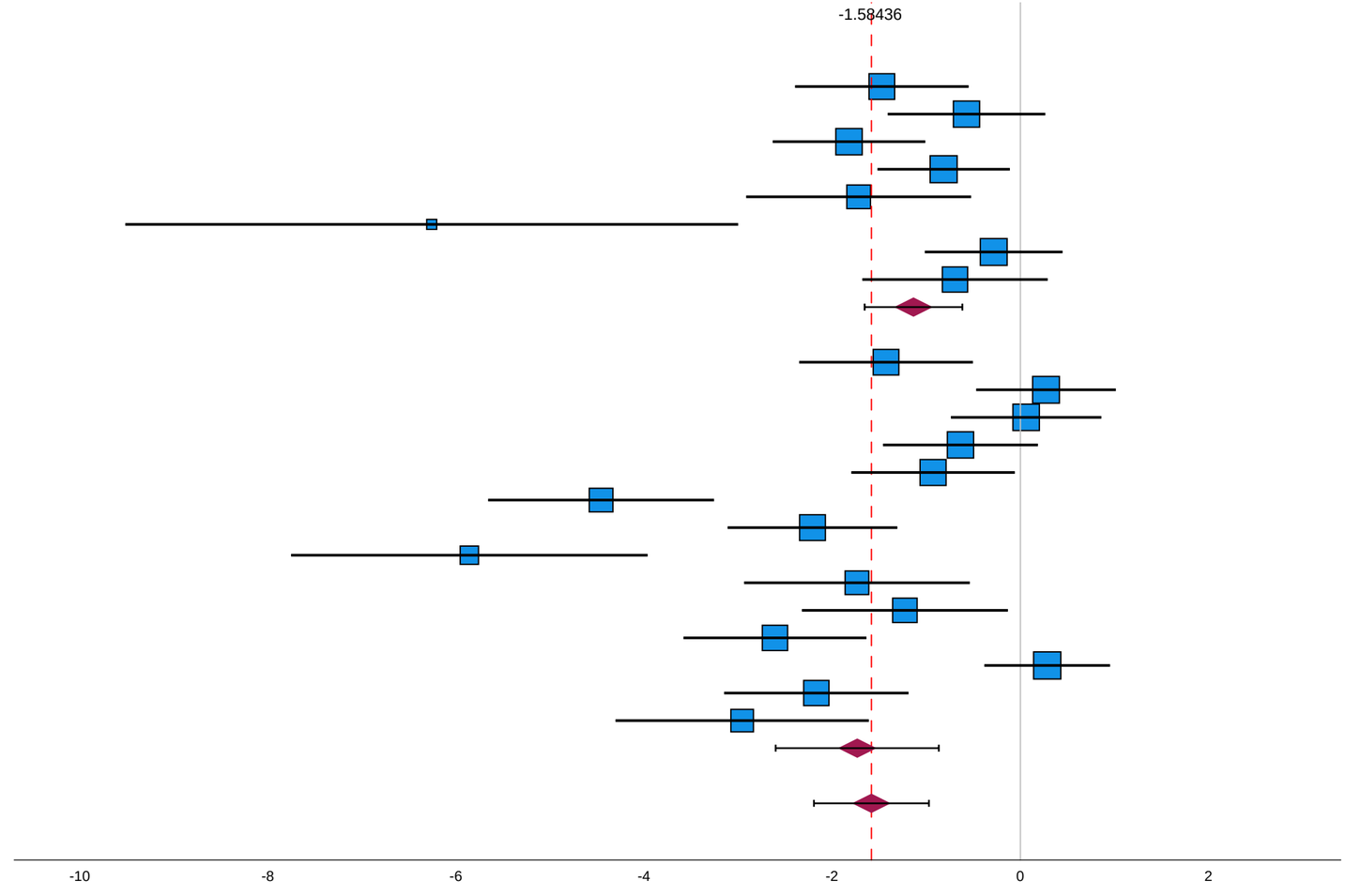


Model: Random-effects model
Heterogeneity: Tau-squared = 0.42, H-squared = 3.46, I-squared = 0.71
Homogeneity: Q = 41.84, df = 12, p-value = 0.00
Test of overall effect size: z = -4.46, p-value = 0.00
Test of between-subgroup homogeneity: Q = 0.14, df = 1, p-value = 0.71

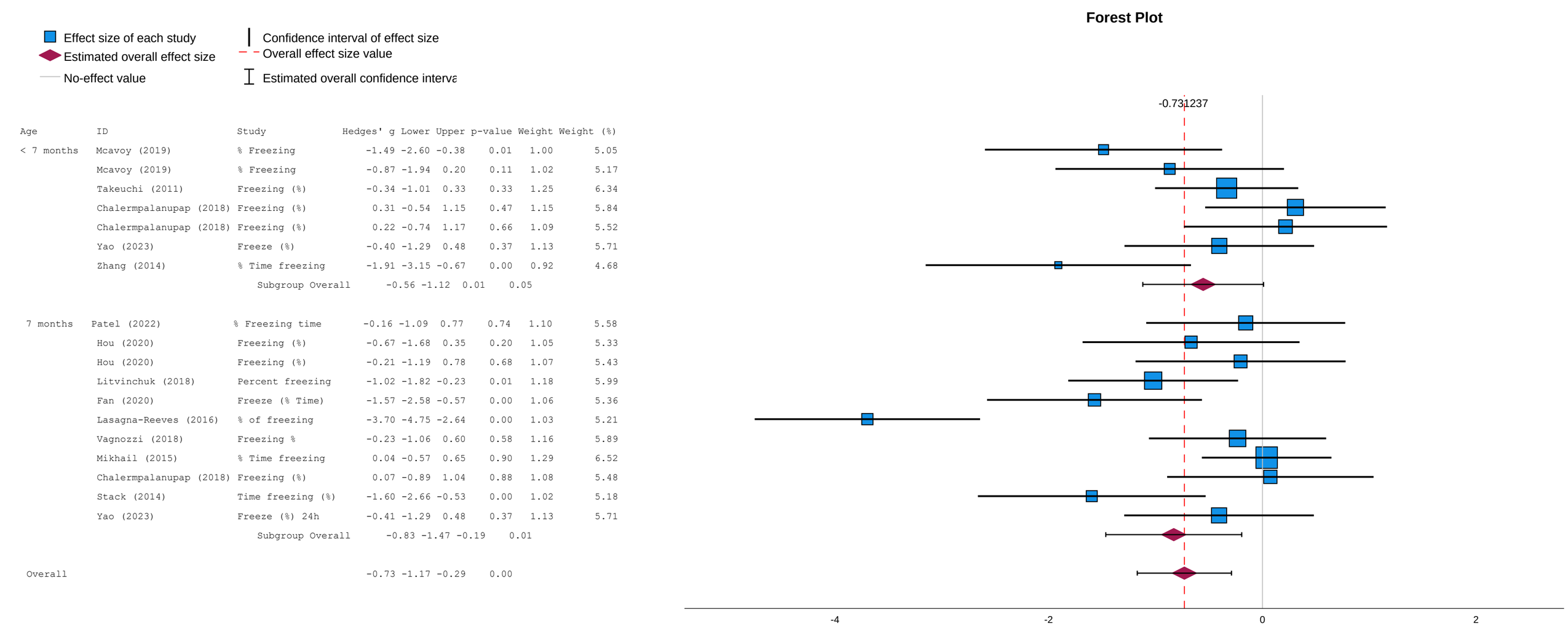
Forest Plot

Effect size of each study
Estimated overall effect size
No-effect value
Confidence interval of effect size
Overall effect size value
Estimated overall confidence interva

Age	ID	Study	Hedges' g	Lower	Upper	p-value	Weight	Weight (%)
< 7 months	Zampar (2021)	Time in target quadran...	-1.47	-2.40	-0.55	0.00	0.49	4.74
	Zampar (2021)	Time in target quadran...	-0.57	-1.41	0.26	0.18	0.50	4.84
	Takeuchi (2011)	% Time	-1.82	-2.63	-1.01	0.00	0.50	4.86
	Woo (2021)	Time in target quadran...	-0.82	-1.52	-0.11	0.02	0.51	4.97
	Zhang (2014)	Percentage of time spe...	-1.72	-2.92	-0.52	0.00	0.45	4.42
	Zhu (2022)	Time spent in quadrant...	-6.26	-9.52	-3.00	0.00	0.22	2.12
	Dumont (2011)	Time (%)	-0.28	-1.02	0.45	0.45	0.51	4.94
	Izzy (2021)	% Time in target quadrant	-0.70	-1.68	0.29	0.17	0.48	4.67
		Subgroup Overall	-1.14	-1.66	-0.62	0.00		
7 months	Zampar (2021)	Time in target quadran...	-1.43	-2.35	-0.50	0.00	0.49	4.74
	Brody (2022)	Percent time (%) (targ...	0.27	-0.47	1.02	0.47	0.51	4.93
	Harris (2020)	Percent time in target...	0.06	-0.74	0.86	0.88	0.50	4.87
	Harris (2020)	Percent time in target...	-0.64	-1.46	0.19	0.13	0.50	4.85
	Harris (2020)	Percent time in target...	-0.93	-1.80	-0.06	0.04	0.49	4.80
	Lasagna-Reeves (2016)	Percent of time spent ...	-4.46	-5.66	-3.26	0.00	0.45	4.41
	Jiang (2015)	Time spent in quadrant...	-2.21	-3.11	-1.31	0.00	0.49	4.77
	Tang (2020)	Time in target quadran...	-5.86	-7.76	-3.96	0.00	0.36	3.52
	Hou (2020)	Time %	-1.74	-2.94	-0.54	0.00	0.45	4.41
	Hou (2020)	Time %	-1.23	-2.32	-0.13	0.03	0.47	4.54
	Jiang (2016)	Time spent in quadrant...	-2.61	-3.58	-1.64	0.00	0.48	4.69
	Dumont (2011)	Time (%)	0.29	-0.38	0.95	0.40	0.51	5.00
	Dumont (2011)	Time (%)	-2.17	-3.15	-1.19	0.00	0.48	4.68
	Yao (2023)	Time in quadrant (%) q...	-2.96	-4.31	-1.61	0.00	0.43	4.23
		Subgroup Overall	-1.74	-2.60	-0.87	0.00		
Overall			-1.58	-2.20	-0.97	0.00		



Model: Random-effects model
Heterogeneity: Tau-squared = 1.83, H-squared = 9.15, I-squared = 0.89
Test of overall effect size: z = -5.08, p-value = 0.00
Test of between-subgroup homogeneity: Q = 1.34, df = 1, p-value = 0.25

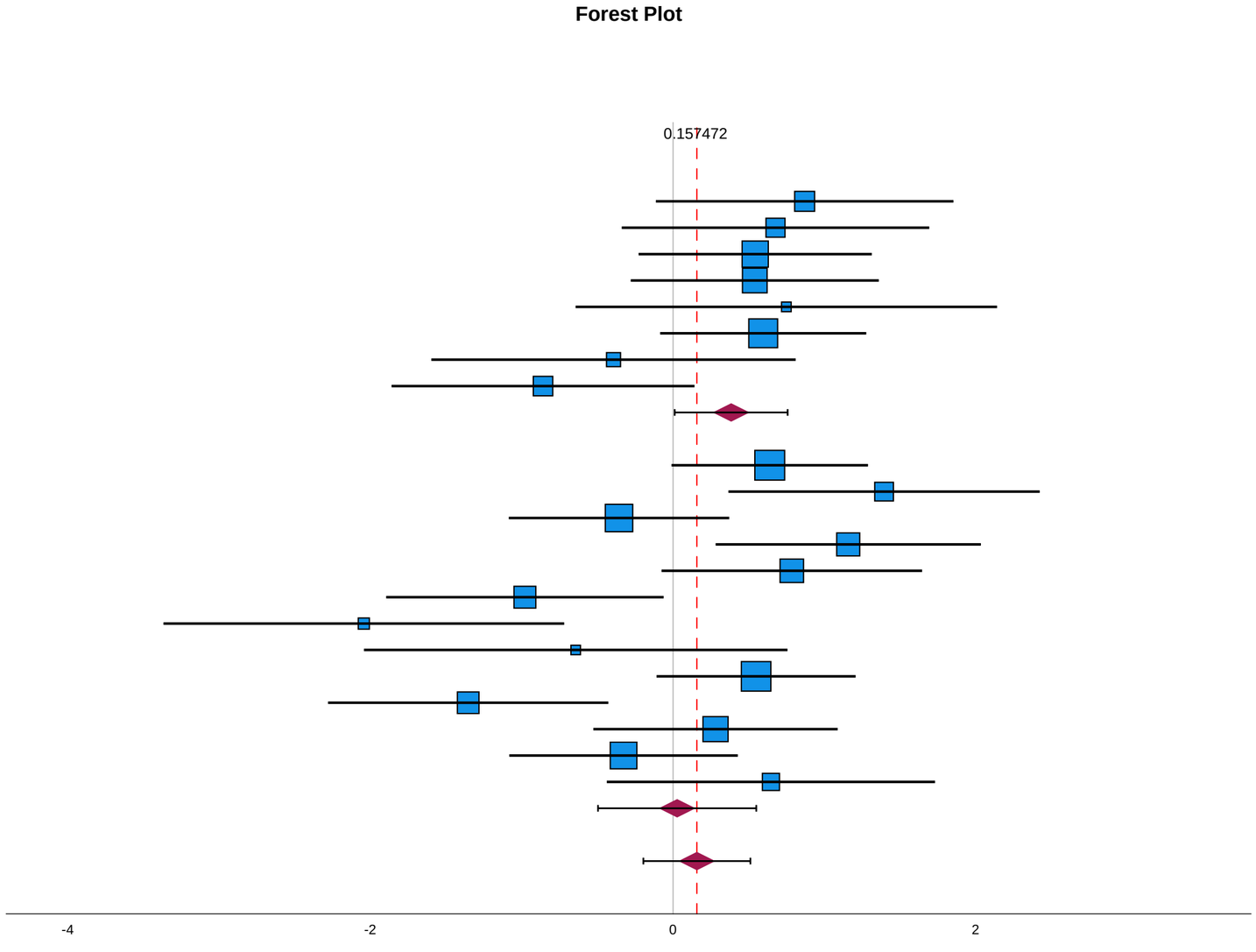


Age	ID	Study	Hedges' g	Lower	Upper	p-value	Weight	Weight (%)
< 7 months	Mcavoy (2019)	% Freezing	-1.49	-2.60	-0.38	0.01	1.00	5.05
	Mcavoy (2019)	% Freezing	-0.87	-1.94	0.20	0.11	1.02	5.17
	Takeuchi (2011)	Freezing (%)	-0.34	-1.01	0.33	0.33	1.25	6.34
	Chalermpalanupap (2018)	Freezing (%)	0.31	-0.54	1.15	0.47	1.15	5.84
	Chalermpalanupap (2018)	Freezing (%)	0.22	-0.74	1.17	0.66	1.09	5.52
	Yao (2023)	Freeze (%)	-0.40	-1.29	0.48	0.37	1.13	5.71
	Zhang (2014)	% Time freezing	-1.91	-3.15	-0.67	0.00	0.92	4.68
		Subgroup Overall	-0.56	-1.12	0.01	0.05		
7 months	Patel (2022)	% Freezing time	-0.16	-1.09	0.77	0.74	1.10	5.58
	Hou (2020)	Freezing (%)	-0.67	-1.68	0.35	0.20	1.05	5.33
	Hou (2020)	Freezing (%)	-0.21	-1.19	0.78	0.68	1.07	5.43
	Litvinchuk (2018)	Percent freezing	-1.02	-1.82	-0.23	0.01	1.18	5.99
	Fan (2020)	Freeze (% Time)	-1.57	-2.58	-0.57	0.00	1.06	5.36
	Lasagna-Reeves (2016)	% of freezing	-3.70	-4.75	-2.64	0.00	1.03	5.21
	Vagnozzi (2018)	Freezing %	-0.23	-1.06	0.60	0.58	1.16	5.89
	Mikhail (2015)	% Time freezing	0.04	-0.57	0.65	0.90	1.29	6.52
	Chalermpalanupap (2018)	Freezing (%)	0.07	-0.89	1.04	0.88	1.08	5.48
	Stack (2014)	Time freezing (%)	-1.60	-2.66	-0.53	0.00	1.02	5.18
	Yao (2023)	Freeze (%) 24h	-0.41	-1.29	0.48	0.37	1.13	5.71
		Subgroup Overall	-0.83	-1.47	-0.19	0.01		
Overall			-0.73	-1.17	-0.29	0.00		

Model: Random-effects model
Heterogeneity: Tau-squared = 0.68, H-squared = 4.22, I-squared = 0.76
Test of overall effect size: z = -3.25, p-value = 0.00
Test of between-subgroup homogeneity: Q = 0.40, df = 1, p-value = 0.53

Effect size of each study
Estimated overall effect size
No-effect value
Confidence interval of effect size
Overall effect size value
Estimated overall confidence interva

Age	ID	Study	Hedges' g	Lower	Upper	p-value	Weight	Weight (%)
< 7 months	López-González (2015)	Fall latency (sec)	0.87	-0.11	1.85	0.08	1.41	4.61
	López-González (2015)	Fall latency (sec)	0.68	-0.34	1.69	0.19	1.38	4.50
	Zampar (2021)	Latency to fall (s)	0.54	-0.23	1.31	0.17	1.64	5.34
	Zampar (2021)	Latency to fall (s)	0.54	-0.28	1.36	0.20	1.59	5.17
	Moreno-Gonzalez (2021)	Latency to fall (sec)	0.75	-0.64	2.14	0.29	1.04	3.39
	Takeuchi (2011)	Latency to fall (sec)	0.60	-0.09	1.28	0.09	1.73	5.65
	Etelainen (2023)	Latency to fall (sec)	-0.39	-1.60	0.81	0.52	1.20	3.91
	Izzy (2021)	Latency (s)	-0.86	-1.86	0.14	0.09	1.40	4.55
		Subgroup Overall	0.38	0.01	0.76	0.04		
7 months	López-González (2015)	Fall latency (sec)	0.64	-0.01	1.29	0.05	1.77	5.76
	López-González (2015)	Fall latency (sec)	1.40	0.37	2.42	0.01	1.37	4.46
	Brody (2022)	Best time (sec)	-0.36	-1.09	0.37	0.34	1.68	5.49
	Wheeler (2019)	Time in rotorod (sec)	1.16	0.28	2.03	0.01	1.53	4.97
	Zampar (2021)	Latency to fall (s)	0.79	-0.08	1.65	0.07	1.54	5.02
	Moreno-Gonzalez (2021)	Latency to fall (sec)	-0.98	-1.90	-0.06	0.04	1.48	4.83
	Moreno-Gonzalez (2021)	Latency to fall (sec)	-2.04	-3.37	-0.72	0.00	1.10	3.57
	Moreno-Gonzalez (2021)	Latency to fall (sec)	-0.64	-2.04	0.76	0.37	1.04	3.37
	Tang (2020)	Latency to fall (sec)	0.55	-0.11	1.21	0.10	1.76	5.73
	Vagnozzi (2018)	Latency to fall (sec)	-1.35	-2.28	-0.43	0.00	1.47	4.80
	Etelainen (2023)	Latency to fall (sec)	0.28	-0.53	1.09	0.50	1.60	5.21
	Huang (2023)	Latency to fall (s)	-0.33	-1.08	0.43	0.40	1.66	5.39
	Dutta (2023)	Latency to fall (s)	0.65	-0.44	1.73	0.24	1.31	4.28
		Subgroup Overall	0.03	-0.50	0.55	0.92		
Overall			0.16	-0.20	0.51	0.38		



Model: Random-effects model
Heterogeneity: Tau-squared = 0.46, H-squared = 3.25, I-squared = 0.69
Test of overall effect size: z = 0.87, p-value = 0.38
Test of between-subgroup homogeneity: Q = 1.19, df = 1, p-value = 0.28

Table 1 - Summary of studies of rTg4510 behaviour.

Assessment	Reference	Behavioural test		Month/Main results																	sex	*n*
				1	**2**	**2.5**	**3.5**	**4**	**4.5**	**5**	**5.5**	**6**	**7**	**8**	**8.5**	**9.5**	**10**	**12**	**13**	**14**	**15**		
Anxiety-like	Cook (2014)	EPM	Time in open arms (s)	-	ND	-	-	-	-	-	-	More	-	-	-	-	More	-	-	-	-	F+M	14-26
	Rodriguez (2022)	EZM	Percent (%)	-	-	-	-	-	ND	-	-	-	-	-	-	-	-	-	-	-	-	F+M	17
	Criado-Marrero (2021)	OF	Center time (s)	-	-	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	-	?	8-10
	Xolalpa-Cueva (2022)	OF	Time in center (s)	Less	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	10
	Ospina (2022)	OF	Time in center (s)	-	-	-	-	-	-	-	-	ND	-	-	-	-	-	-	-	-	-	F+M	10
	Rodriguez (2022)	OF	Percent time spent in the center	-	-	-	-	-	ND	-	-	-	-	-	-	-	-	-	-	-	-	F+M	17
	Anglada-Huguet (2023)	OF	% Time in the center	-	-	-	-	ND	-	-	-	-	-	-	-	-	-	-	-	-	-	?	7-16
	Cook (2014)	Dark-Light	Time in light (s)	-	ND	-	-	-	-	-	-	More	-	-	-	-	ND	-	-	-	-	F+M	14-26
Neurological dysfunction/ well-being	Hernandez (2019)	Marbles	Marbles buried (%)	-	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	-	-	F+M	6
	Rodriguez (2022)	Burrowing	Burrowed pea gravel (g)	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	-	-	-	F+M	17
	Anglada-Huguet (2023)	Burrowing	% of Burrowing	-	-	-	-	-	-	-	-	Less		-	-	-	-	-	-	-	-	?	9-14
	Hernandez (2019)	Nesting Test	Qualitative score	ND	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	-	-	F+M	12
	Barabas (2022)	Nest Scores	Predicted nest score	-		F:Less, M:ND			-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	?
	Rodriguez (2022)	Nesting	Nesting score	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	-	-	-	F+M	17
	Xolalpa-Cueva (2022)	Nesting	Nesting rating	ND	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	10
	Anglada-Huguet (2023)	Nesting	Nesting score	-	-	-	-	-	-	-	-	Less		-	-	-	-	-	-	-	-	?	9-14
Locomotion	Cook (2014)	OF	Total distance (m)	-	ND	-	-	-	-	-	-	More	-	-	-	-	More	-	-	-	-	F+M	14-26
	Wes (2014)	Spontaneous LMA	Total distance (m)	-	More	-	-	ND	-	-	-	More	-	-	-	-	-	-	-	-	-	F	7-15
	Blackmore (2017)	LMA	Distance move (m)	-	-	-	-	More	-	-	-	More	-	More	-	-	More	More	-	-	-	M	9-93
			Distance move (m)	-	-	-	-	-	-	-	-	-	-	-	-	-	-		More			M	9
	Wang (2018)	Spontaneous LMA	LMA distance (cm)	-	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	-	-	?	20-27
	Foster (2019)	OF	Distance (cm)	-	-	-	-	More	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	10-13
	Criado-Marrero (2021)	OF	Distance (m)	-	-	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	-	?	8-10
	Xolalpa-Cueva (2022)	OF	Distance travelled (cm)	ND	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	10
	Ospina (2022)	OF	Total distance (m)	-	-	-	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	F+M	10
	Anglada-Huguet (2023)	OF	Distance covered (cm)	-	-	-	-	-	-	-	-	ND		-	-	-	-	-	-	-	-	?	9-14
	Fuller (2024)	LMA	A.U.C LMA distance binned (a.u.)	-	ND	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	M	6-11
	Rostgaard (2023)	LMA	Total activity counts	-	-	-	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	?	36
	Jul (2015)	LA in 3h Test	Total activity counts	-	-	-	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	F+M	55-57
Memory + learning	Blackmore (2017)	AYSRM	Correct choices (%)	-	-	-	-	Less	-	-	-	-	-	Less	-	-	-	Less	-	-	-	M	10-18

		Correct choices (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		Less			M	9
Blackmore (2017)	RYVD	Correct choices (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		ND			M	9
Blackmore (2017)	SYCA	Alternation (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		ND			M	9
Blackmore (2017)	YSNP	Novelty discrimination (ratio)	-	-	-	-	Less	-	-	-	-	-	ND	-	-	-	Less		-	-	-	M	10-18
		Novelty discrimination (ratio)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		Less			M	9
Wes (2014)	STSWM	Alternation (%)	-	Less	-	-	Less	-	-	-	ND	-	-	-	-	-	-	-	-	-	-	F	10-12
Foster (2019)	Y-Maze	Alternation (%)	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	10-13
Yanagisawa (2018)	Y-Maze	% Alteration	-	-	-	-	-	-	-	ND	-	-	-	-	-	-	-	-	-	-	-	M	8
Fuller (2024)	Y-Maze	Spontaneous alternations (%)	-	ND	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	M	6-11
Anglada-Huguet (2023)	Y-Maze	Novel arm preference (%)	-	-	-	-	-	-	-	-	Less		-	-	-	-	-	-	-	-	-	?	9-14
Blackmore (2017)	RTA	Correct choices (%)	-	-	-	-	Less	-	-	-	Less	-	Less	-	-	Less	Less	-	-	-	-	M	9-93
		Correct choices (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		Less			M	9
Xolalpa-Cueva (2022)	T-Maze	Alternation (%)	ND	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	10
Bailey (2014)	MWM (SL)	Escape latency (s)	-	-	More	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	5
Polito (2014)	MWM (SL)	Latency (s)	-	-	-	-	More	-	-	-	-	-	-	-	-	-	-	-	-	-	-	M	10-14
Jul (2015)	MWM (SL)	Latency to platform (s)	-	-	-	-	More	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	17-21
Yanagisawa (2018)	MWM (SL)	Escape latency (s)	-	-	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	-	-	M	8
Tondo (2020)	MWM (SL)	Latency (s)	-	-	-	-	More	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	16-20
Kubota (2021)	MWM (SL)	Escape latency (s)	-	-	-	-	ND	-	-	-		-	-	-	-	-	-	-	-	-	-	F+M	?
Schaler (2021)	MWM (SL)	Escape latency (s)	-	-	-	-	More	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	10-22
Rodriguez (2022)	MWM (SL)	Latency (s)	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	17
Anglada-Huguet (2023)	MWM (SL)	Latency to escape (s)	-	-	-	-	More	-	-	-	-	-	-	-	-	-	-	-	-	-	-	?	7-16
Bailey (2014)	MWM (RM)	Path in TQ (%)	-	-	Less	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	5
Polito (2014)	MWM (RM)	No of platform crossing	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	-	-	-	-	-	M	10-14
Jul (2015)	MWM (RM)	% Time spent in quadrants (target)	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	17-21
Yanagisawa (2018)	MWM (RM)	Time in target quadrant (s)	-	-	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	-	-	M	8
Tondo (2020)	MWM (RM)	Path in target quadrant (%)	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	16-20
Kubota (2021)	MWM (RM)	Time spent in each quadrant (%)	-	-	-	-	ND	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	?
Rodriguez (2022)	MWM (RM)	Percent (%)	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	17
Anglada-Huguet (2023)	MWM (RM)	Time in target quadrant (%)	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	-	-	-	-	-	?	7-16
Criado-Marrero (2021)	RAWM	Errors	-	-	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	-	-	?	8-10
Ospina (2022)	RAWMR	Errors	-	-	-	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	-	F+M	10
Wes (2014)	NOR	% Time spent exploring objects	-	ND	-	-	Less	-	-	-	Less	-	-	-	-	-	-	-	-	-	-	F	12-15

	Foster (2019)	NOR	Discrimination Index	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	10-13
	Scullion (2019)	NOR	Discrimination ratio 15min	-	-	-	-	-	-	-	-	-	-	ND		-	-	-	-	-	-	M	15
			Discrimination ratio 24h	-	-	-	-	-	-	-	-	-	-	Less		-	-	-	-	-	-	M	15
	Kubota (2021)	NOR	Exploratory ratio (%) 2h	-	-	-	-	ND	-	-	-	Less	-	-	-	-	Less	-	-	-	-	F+M	?
			Exploratory ratio (%) 24h	-	-	-	-	ND	-	-	-	Less	-	-	-	-	ND	-	-	-	-	F+M	?
	Criminis (2011)	ORT	Mean discrimination ratio (%)	-	-	-	-	-	-	-	-	-	-	-	Less		-	-	-	-	-	?	5-6
	Xolalpa-Cueva (2022)	NOR	Recognition Index	More	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F+M	8-10
	Fuller (2024)	BM	Errors to hole	-	-	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	-	M	6-11
	Cook (2014)	CFC	Time freezing (%) (Context)	-	Less	-	-	-	-	-	-	Less		-	-		Less	-	-	-	-	F+M	14-26
	Criado-Marrero (2021)	FCE	% Freezing (Recall of Extinction)	-	-	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	-	?	8-10
Balance + Coordination	Blackmore (2017)	RR	Fall latency (s)	-	-	-	-	-	-	-	-	-	-	-	-	-	-		ND			M	9
	Yanagisawa (2018)	RR	Latency fall (s)	-	-	-	-	-	-	-	ND	-	-	-	-	-	-	-	-	-	-	M	8
	Fuller (2024)	RR	Time on rotarod (s)	-	ND	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	M	6-11

Note: More=refers to an increased deviation from the control (PS19 mice vs. WT). Less=indicates a decreased deviation from the control (PS19 mice vs. WT). ND=No differences. OF=Open Field. NOR=Novel Object Recognition. RR=Rotarod. MWM=Morris Water Maze. SL=Spatial learning. RM=Reference memory. ORT=Object Recognition Test. CFC=Context Fear Conditioning. FCE=Fear Conditioning and Extinction. RAWM=Radial Arm Water Maze. RAWMR=Radial Arm Water Maze Reversal. RTA=Rewarded T-Maze Alternation. LMA=Locomotor Activity. AYSRM=Aversive Y-Maze Spatial Reference Memory. RYVD=Rewarded Y-Maze Visual Discrimination. SYCA=Spontaneous Y-Maze Continuous Alternation. YSNP=Y-Maze Spatial Novelty Preference. STSWM=Short Term Spatial Working Memory. EPM=Elevated Plus Maze. EZM=Elevated Zero Maze. BM=Barnes maze. F=Female. M=Male.

Table 2 - Summary of studies of PS19 behaviour.

Assessment	Reference	Behavioural test		Month/Main results															sex	*n*
				2	**3**	**3.5**	**4**	**5**	**6**	**7**	**7.5**	**8**	**8.5**	**9**	**9.5**	**10**	**11**	**12**		
Anxiety-like	Stack (2014)	EPM	Time spent in open arms (s)	-	-	-	-	-	-	More	-	-	-	More	-	-	-	-	F+M	9-10
	López-González (2015)	EPM	Time open arm (s)	-	ND	-	-	-	ND	-	-	-	-	More	-	More	-	-	M	16-40
	Ahmad (2021)	EPM	Open arms (s)	ND	-	-	ND	-	ND	-	-	ND	-	-	-	-	-	More	M	11-15
	Lyons (2024)	EPM	Time in open arms (s)	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	M	4-17
	Dumont (2011)	EPM	Time open arms (%)	ND	-	-	-	-	-	F:More M:ND	-	-	-	-	-	F:ND M:More	-	-	F+M	14-20
	Takeuchi (2011)	EPM	Time on open arms (%)	-	-	More		-	-	-	-	-	-	-	-	-	-	-	M	15-16
	Izzy (2021)	EPM	% Time (open arm)	-	?	-	-	-	-	-	-	-	-	-	-	-	-	-	M	6-14
	Tapias (2018)	EPM	Time in open arms (%)	-	-	-	-	More	-	More	-	-	-	More	-	-	-	-	F+M	6
	Hou (2020)	EPM	Open arm redistance time (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	ND	-	M	8
		EPM	Open arm redistance time (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	ND	-	M	8
	Sebastián-Serrano (2022)	EPM	Open arms vs closed arms (time)	-	-	-	-	-	-	More	-	-	-	More	-	-	-	-	F+M	5-7
	Tu (2022)	EPM	Number of entries (closed arms)	-	-	-	-	-	Less	-	-	-	-	Less	-	-	Less	-	M	10-22
	Takeuchi (2011)	OF	Center time (s)	-		More		-	-	-	-	-	-	-	-	-	-	-	M	16-19
	Dumont (2012)	OF	Time spent in center (s)	-	-	-	-	More	-	More	-	-	-	More	-	-	-	-	?	14-16
	Elipenahli (2012)	OF	Time in center (s)	-	-	-	-	More	-	More	-	-	-	-	-	-	-	-	?	12-20
	Sandusky-Beltran (2021)	OF	Time in center zone (s)	-	-	-	-	-	-	-	-	ND	-	-	-	-	-	-	F+M	11-12
	Ohia-Nwoko (2014)	OF	% of Time spent in center	-	-	-	-	-	-	-	-	-	-	-	-	ND	-	-	F+M	6-10
	Apicco (2018)	OF	% Time in center zone	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	F+M	6-7
	Chalermpalanupap (2018)	OF	Time Spent in center (%)	-	-	-	ND	-	ND	-	-	-	-	-	-	ND	-	-	F+M	9-12

	Sebastián-Serrano (2022)	OF	Entries center	-	-	-	-	-	-	More	-	-	-	ND	-	-	-	-	F+M	5-8
	Dutta (2023)	OF	Center frequency	-	-	-	-	-	-	-	-	Less	-	-	-	-	-	-	?	7
	Takeuchi (2011)	Dark-Light	Stay time in light (s)	-		ND	-	-	-	-	-	-	-	-	-	-	-	-	M	16-19
Neurological dysfunction/ well-being	Sun (2020)	Nesting	Score detected at 24th	-	-	ND	-	-	ND	-	-	-	-	F:ND M:Less	-	-	-	F:ND M:Less	F+M	?
	Takeuchi (2011)	PFS	Immobilty (%)	-	-	ND		-	-	-	-	-	-	-	-	-	-	-	M	16-19
Depressive-like	Takeuchi (2011)	TS	Immobilty (%)	-	-	-	-	-	ND	-	-	-	-	-	-	-	-	-	M	16-18
	López-González (2015)	TS	Immobility time (s)	-	ND	-	-	-	Less	-	-	-	-	Less	-	Less	-	-	M	8-24
Locomotion	Dumont (2011)	OF	Distance (cm)	ND	-	-	-	-	-	F:More M:ND	-	-	-	-	-	ND	-	-	F+M	14-20
	Takeuchi (2011)	OF	Total distance (cm)	-		More		-	-	-	-	-	-	-	-	-	-	-	M	16-19
	Dumont (2012)	OF	Distance (cm)	-	-	-	-	More	-	More	-	-	-	More	-	-	-	-	?	14-16
	Elipenahli (2012)	OF	Distance (cm)	-	-	-	-	More	-	More	-	-	-	-	-	-	-	-	?	12-20
	Ohia-Nwoko (2014)	OF	Total distance traveled (cm)	-	-	-	-	-	-	-	-	-	-	-	-	ND	-	-	F+M	6-10
	Stack (2014)	OF	Distance (cm)	-	-	-	-	More	-	More	-	-	-	More	-	-	-	-	F+M	10-11
	Izzy (2021)	OF	Distance (cm)	-	?	-	-	-	-	-	-	-	-	-	-	-	-	-	M	6-10
	Mikhail (2015)	OF	Distance traveled (cm)	-	-	-	-	-	ND	ND	-	ND	-	ND	-	-	-	-	?	?
	Ferreira (2021)	OF	Total distance (cm)	ND	ND	-	-	-	ND	-	-	-	-	-	-	-	-	-	F+M	9-24
	Ano (2020)	OF	Total distance (cm)	-	-	-	-	-	-	-	-	-	-	More	-	-	-	-	M	11-12
	Ano (2023)	OF	Total distance (cm)	-	-	-	-	More	-	More	-	-	-	-	-	-	-	-	M	11
	Eteläinen (2023)	OF	cm	-	ND	-	-	ND	-	ND	-	-	-	-	-	-	-	-	F+M	6-42
	Dutta (2023)	OF	Distance (cm)	-	-	-	-	-	-	-	-	ND	-	-	-	-	-	-	?	7
	Wagner (2015)	OF	Total distance (m)	-	-	-	-	-	-	-	-	-	-	ND	-	-	-	-	F+M	19-24
	Jiang (2016)	OF	Distance moved (m)	-	-	-	-	-	-	ND	-	-	-	-	-	-	-	-	M	16
	Apicco (2018)	OF	Distance (m)	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	F+M	7-8
	Ahmad (2021)	OF	Path length (m)	ND	-	-	ND	-	ND	-	-	ND	-	-	-	-	-	More	M	11-15
	Sandusky-Beltran (2021)	OF	Total distance (m)	-	-	-	-	-	-	-	-	ND	-	-	-	-	-	-	F+M	11-12

	Patel (2022)	OF	Distance (m)	-	-	-	-	-	-	-	-	-	-	More	-	-	-	-	F+M	26-30
	Mcavoy (2019)	OF	Total distance (mm)	-	-	-	-	ND	ND	-	-	-	-	-	-	-	-	-	F+M	10-24
	Sebastián-Serrano (2022)	OF	Travel distance	-	-	-	-	-	-	ND	-	-	-	-	-	-	-	-	F+M	5-8
	Wheeler (2019)	OF	Distance (in)	-	-	-	-	-	-	-	-	More	-	-	-	-	-	-	F+M	19-45
	Sun (2020)	OF	Distance traveled in central area (mm)	-	-	-	F:More M:ND	-	-	ND	-	-	-	-	-	-	F:ND M:More	-	F+M	17-20
	Tu (2022)	OF	Velocity (mm/s)	-	-	-	-	-	ND	-	-	-	-	ND	-	-	-	-	M	9-10
Memory + Learning	Takeuchi (2011)	Y-Maze	% Alternation	-	-		Less		-	-	-	-	-	-	-	-	-	-	M	16-19
	Apicco (2018)	Y-Maze	% Correct alternations	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	F+M	15-20
	Giannopoulos (2018)	Y-Maze	% Alternation	-	-	-	-	-	-	-	-	-	-	-	-	Less	-	-	F+M	10
	Vagnozzi (2018)	Y-Maze	% Alternation	-	-	-	-	-	-	-	-	-	-	Less	-	-	-	-	F+M	9-15
	Fan (2020)	Y-Maze	Spontaneous alternation (%)	-	-	-	-	-	-	-	-	Less	-	-	-	-	-	-	F+M	10-11
	Ahmad (2021)	Y-Maze	Alternation (%)	ND	-	-	ND	-	ND	-	-	ND	-	-	-	-	-	Less	M	7-19
	Sandusky-Beltran (2021)	Y-Maze	% Alternation	-	-	-	-	-	-	-	-	ND	-	-	-	-	-	-	F+M	11-12
	Patel (2022)	Y-Maze	% Spontaneous alternation	-	-	-	-	-	-	-	-	-	-	ND	-	-	-	-	F+M	26-30
	Jang (2024)	Y-Maze	% Alternation	-	-	-	-	-	-	-	-	-	-	ND	-	-	-	-	M	6-9
	Jiang (2016)	Y-Maze	Discrimination index (%)	-	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	M	16
	Huang (2023)	Y-Maze	Novel arm time (%)	-	-	-	-	-	-	-	-	-	-	-	-	Less	-	-	F+M	11-18
	Ferreira (2021)	T-Maze	Error (%)	ND	ND	-	-	-	ND	-	-	-	-	-	-	-	-	-	F+M	9-24
	Dumont (2011)	MWM (SL)	Latency (s)	ND	-	-	-	-	-	ND	-	-	-	-	-	F:ND M:More	-	-	F+M	14-19
	Takeuchi (2011)	MWM (SL)	Latency (s)	-	-	-	-	More		-	-	-	-	-	-	-	-	-	F	11-29
	Lasagna-Reeves (2016)	MWM (SL)	Latency (s)	-	-	-	-	-	-	-	ND	-	-	-	-	-	-	-	F+M	20
	Chalermpalanupap (2018)	MWM (SL)	Latency (s)	-	-	-	ND	-	ND	-	-	-	-	-	-	More	-	-	F+M	9-12

Giannopoulos (2018)	MWM (SL)	Latency to platform (s)	-	-	-	-	-	-	-	-	-	-	-	-	ND	-	-	F+M	10
Vagnozzi (2018)	MWM (SL)	Test duration (s)	-	-	-	-	-	-	-	-	-	-	More	-	-	-	-	F+M	9-15
Hou (2020)	MWM (SL)	Latency (s)	-	-	-	-	-	-	-	-	-	-	-	-	-	More	-	M	8
	MWM (SL)	Latency (s)	-	-	-	-	-	-	-	-	-	-	-	-	-	More	-	M	8
	MWM (SL)	Time to find platform (s) (hidden platform)	-	-	-	-	-	-	-	-	-	-	-	F:ND M:ND	-	-	-	F+M	24
Harris (2020)	MWM (SL)	Time to find platform (s) (hidden platform)	-	-	-	-	-	-	-	-	-	ND	-	-	-	-	-	F	11-12
Sun (2020)	MWM (SL)	Latency (s)	-	ND	-	-	-	ND	-	-	-	-	ND	-	-	-	F:More M:ND	F+M	?
Tang (2020)	MWM (SL)	Latency (s)	-	-	-	-	-	-	-	-	ND	-	-	-	-	-	-	F+M	11-15
Dave (2021)	MWM (SL)	Latency to platform (s)	-	-	-	-	-	-	ND	-	-	-	-	-	-	-	-	F+M	9-10
Izzy (2021)	MWM (SL)	Latency (s)	-	?	-	-	-	-	-	-	-	-	-	-	-	-	-	M	6-14
Woo (2022)	MWM (SL)	Escape latency (s)	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	?	16-18
Zampar (2021)	MWM (SL)	Average escape latency (s)	-	ND	-	-	ND	-	-	-	-	-	ND	-	-	-	-	F+M	10-14
Brody (2022)	MWM (SL)	Latency to platform (s)	-	-	-	-	-	-	-	-	-	-		ND		-	-	F+M	12-17
Tu (2022)	MWM (SL)	Latency to plataform (s)	-	-	-	-	-	?	-	-	-	-	?	-	-	-	-	M	10-13
Yao (2023)	MWM (SL)	Latency (s)	-	-	-	-	-	More	-	-	-	-	More					M	10
Zhu (2022)	MWM (SL)	Escape latency (s)	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	M	6
Zhang (2014)	MWM (SL)	Distance to platform (mm)	-	-	-	-	-	More	-	-	-	-	-	-	-	-	-	M	8
Jiang (2015)	MWM (SL)	Path length (m)	-	-	-	-	-	-	More	-	-	-	-	-	-	-	-	M	16
Jiang (2016)	MWM (SL)	Path length (m)	-	-	-	-	-	-	More	-	-	-	-	-	-	-	-	M	16
Dumont (2011)	MWM (RM)	Time (%)	ND	-	-	-	-	-	ND	-	-	-	-	-	ND	-	-	F+M	13-19
Takeuchi (2011)	MWM (RM)	% Time	-	-	-	-		Less	-	-	-	-	-	-	-	-	-	F	11-29
Zhang (2014)	MWM (RM)	Percentage of time spent in target quadrant	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	M	8
Jiang (2015)	MWM (RM)	Time spent in quadrant (%)	-	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	M	16

Lasagna-Reeves (2016)	MWM (RM)	Percent of time spent in the target quadrant	-	-	-	-	-	-	-	Less	-	-	-	-	-	-	-	F+M	20
Jiang (2016)	MWM (RM)	Time spent in quadrant (%)	-	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	M	16
Hou (2020)	MWM (RM)	Time %	-	-	-	-	-	-	-	-	-	-	-	-	-	Less	-	M	8
	MWM (RM)	Time %	-	-	-	-	-	-	-	-	-	-	-	-	-	Less	-	M	8
Harris (2020)	MWM (RM)	Percent time in target quadrant	-	-	-	-	-	-	-	-	-	-	-	F:ND M:ND	-	-	-	F+M	24
	MWM (RM)	Percent time in target quadrant	-	-	-	-	-	-	-	-	-	Less	-	-	-	-	-	F	11-12
Tang (2020)	MWM (RM)	Time in target quadrant (%)	-	-	-	-	-	-	-	-	Less	-	-	-	-	-	-	F+M	11-15
Izzy (2021)	MWM (RM)	% Time in target quadrant	-	?	-	-	-	-	-	-	-	-	-	-	-	-	-	M	6-14
Brody (2022)	MWM (RM)	Percent time (%) (target quadrant)	-	-	-	-	-	-	-	-	-	-		ND		-	-	F+M	12-17
Zhu (2022)	MWM (RM)	Time spent in quadrant (%)	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	M	6
Yao (2023)	MWM (RM)	Time in quadrant (%) quadran	-	-	-	-	-	-	-	-	-	-	Less	-	-	-	-	M	10
Woo (2022)	MWM (RM)	Time in target quadrant (s)	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	?	16-18
Zampar (2021)	MWM (RM)	Time in target quadrant (s)	-	Less	-	-	ND	-	-	-	-	-	Less	-	-	-	-	F+M	10-14
Tu (2022)	MWM (RM)	% of time spent in plataform quadrant	-	-	-	-	-	Less	-	-	-	-	Less	-	-	-	-	M	10-14
Vagnozzi (2018)	MWM (RM)	Time spent in platform zone (s)	-	-	-	-	-	-	-	-	-	-	ND	-	-	-	-	F+M	9-15
Chalermpalanupap (2018)	MWM (RM)	Time in platform quadrant (%)	-	-	-	ND	-	ND	-	-	-	-	-	-	ND	-	-	F+M	9-12
Dave (2021)	MWM (RM)	Platform quadrant duration (s)	-	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	F+M	9-10
Giannopoulos (2018)	MWM (RM)	Platform crossings	-	-	-	-	-	-	-	-	-	-	-	-	Less	-	-	F+M	10
Sun (2020)	MWM (RM)	Number of target plataform crossing	-	ND	-	-	-	ND	-	-	-	-	ND	-	-	-	ND	F+M	15-20

Ahmad (2021)	MWM (WM)	Path length (m) (hidden platform)	ND	-	-	ND	-	ND	-	-	More	-	-	-	-	-	-	M	11-15
Ferreira (2021)	NOR	Novel object time (%)	ND	ND	-	-	-	ND	-	-	-	-	-	-	-	-	-	F+M	9-23
Fan (2020)	NOR	% of total time spent	-	-	-	-	-	-	-	-	Less	-	-	-	-	-	-	F+M	10-11
Dutta (2023)	NOR	Novel object time spent (s)	-	-	-	-	-	-	-	-	ND	-	-	-	-	-	-	?	6
Tu (2022)	NOR	Novel object idex (NOI) %	-	-	-	-	-	-	-	-	-	-	Less	-	-	-	-	M	9-18
Yao (2023)	NOR	Interaction ratio (novel/familiar)	-	-	-	-	-	Less	-	-	-	-	Less	-	-	-	-	M	10
Apicco (2018)	NOR	Preference index (%)	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	F+M	11-15
Eteläinen (2023)	NOR	Preference index	-	-	-	-	ND	-	ND	-	-	-	-	-	-	-	-	F+M	4-13
Wagner (2015)	NOR	Discriminatio n ratio	-	-	-	-	-	-	-	-	-	-	Less	-	-	-	-	F+M	19-24
Zampar (2021)	NOR	Discrimiation index	-	ND	-	-	ND	-	-	-	-	-	ND	-	-	-	-	F+M	10-14
Guo (2022)	NOR	Discriminatio n index (%)	-	-	-	-	-	-	-	-	-	-	-	-	Less	-	-	M	9-10
Cao (2023)	NOR	Discriminatio n index	ND		ND		Less		-	-	-	-	ND	-	-	-	-	F+M	9-21
Huang (2023)	NOR	Discriminatio n index	-	-	-	-	-	-	-	-	-	-	-	-	Less	-	-	F+M	11-18
Jang (2024)	NOR	Discriminatio n index	-	-	-	-	-	-	-	-	-	-	ND	-	-	-	-	M	6-8
López-González (2015)	NOR	Recognition index	-	ND	-	-	-	ND	-	-	-	-	ND	-	Less	-	-	M	8-24
Sebastián-Serrano (2022)	NOL	Recognition index	-	-	-	-	-	-	ND	-	-	-	ND	-	-	-	-	F+M	5-6
Brunden (2010)	BM	% Success	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	M	10-12
Eteläinen (2023)	BM	Latency to target zone entry (Probe trial 2)	-	-	-	-	ND	-	More	-	-	-	-	-	-	-	-	F+M	5-10
Wheeler (2019)	BM	Time to locate escape hole (s)	-	-	-	-	-	-	-	-	More	-	-	-	-	-	-	F+M	32-33
Moreno-Gonzalez (2021)	BM	Latency to escape (s)	-	-	-	-	-	ND	-	-	More	-	-	-	-	-	-	?	?
Dutta (2023)	BM	Latency to goal box (s)	-	-	-	-	-	-	-	-	More	-	-	-	-	-	-	?	7
Liu (2019)	BM	Latency to target hole (s)	-	-	-	-	-	-	-	-	More	-	-	-	-	-	-	F+M	8-10
Takeuchi (2011)	BM	Time spent around each hole (s)	-	-	-	-		ND		-	-	-	-	-	-	-	-	M	16-19

	Lyons (2024)	BM	Time in goal zone/avg time in other zones	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	M	4-11
	Ferreira (2021)	BM	Time in target zone (%)	ND	ND	-	-	-	ND	-	-	-	-	-	-	-	-	-	F+M	9-24
	Cao (2023)	BM	Spatial memory index	ND		Less		Less		-	-	-	-	Less	-	-	-	-	F+M	10-21
	Tu (2022)	EARM	Error ratio (%)	-	-	-	-	-	-	-	-	-	-	More	-	-	-	-	M	21-22
	Takeuchi (2011)	CFC	Freezing (%)	-	-	-	-	-	ND	-	-	-	-	-	-	-	-	-	M	16-19
	Stack (2014)	CFC	Time freezing (%)	-	-	-	-	-	-	-	-	-	-	Less	-	-	-	-	F+M	9-10
	Zhang (2014)	CFC	% Time freezing	-	-	-	-	-	Less	-	-	-	-	-	-	-	-	-	M	8
	Mikhail (2015)	CFC	% Time freezing	-	-	-	-	-	-	-	-	-	-	ND	-	-	-	-	?	16-30
	Lasagna-Reeves (2016)	CFC	% of Freezing	-	-	-	-	-	-	-	Less	-	-	-	-	-	-	-	F+M	20
	Chalermpalanupap (2018)	CFC	Freezing (%)	-	-	-	ND	-	ND	-	-	-	-	-	-	ND	-	-	F+M	9-12
	Litvinchuk (2018)	CFC	Percent freezing	-	-	-	-	-	-	-	-	Less	-	-	-	-	-	-	F+M	14
	Tapias (2018)	CFC	Freezing (%)	-	-	-	-	-	-	-	-	-	-	Less	-	-	-	-	F+M	6
	Vagnozzi (2018)	CFC	Freezing %	-	-	-	-	-	-	-	-	-	-	ND	-	-	-	-	F+M	9-15
	Hou (2020)	CFC	Freezing (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	Less	-	M	8
		CFC	Freezing (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	Less	-	M	8
	Mcavoy (2019)	CFC	% Freezing	-	-	-	-	-	ND	-	-	-	-	-	-	-	-	-	F+M	14-19
	Fan (2020)	CFC	Freeze (% Time)	-	-	-	-	-	-	-	-	Less	-	-	-	-	-	-	F+M	10-11
	Guo (2002)	CFC	% Freezing	-	-	-	-	-	-	-	-	-	-	-	-	Less	-	-	M	13-14
	Patel (2022)	CFC	% Freezing time	-	-	-	-	-	-	-	-	-	-	ND	-	-	-	-	F+M	8-10
	Yao (2023)	CFC	Freeze (%) 24h	-	-	-	-	-	ND	-	-	-	-	ND	-	-	-	-	M	10
Balance + Coordination	Dumont (2011)	GS	Time (s)	ND	-	-	-	-	-	Less	-	-	-	-	-	ND	-	-	F+M	14-19
	Takeuchi (2011)	GS	Grip strenght (N)	-		ND	-	-	-	-	-	-	-	-	-	-	-	-	M	16-19
	Liu (2019)	GS	Grip strenght (g)	-	-	-	-	-	-	-	-	Less	-	-	-	-	-	-	F+M	7-8
	Sun (2020)	GS	Grip strenght (g)	-	-	ND	-	ND	ND	-	-	ND	-	ND	-	F:ND M:More	ND	F:ND M:Less	F+M	?
	Patel (2022)	GS	Grip strenght (g)	-	-	-	-	-	-	-	-	-	-	Less	-	-	-	-	F+M	26-30
	Di (2021)	GS	Latency to fall (s)	-	-	-	-	-	-	F:Less M:ND	-	-	-	-	-	-	-	-	F+M	16-17

Brunden (2010)	RR	Latency to fall (s)	-	-	-	-	-	ND	-	-	-	-	-	-	-	-	-	M	6-11
Dumont (2011)	RR	Fall latency (s)	ND	-	-	-	-	-	ND	-	-	-	-	-	ND	-	-	F+M	12-19
Takeuchi (2011)	RR	Latency to fall (s)	-	-	ND		-	-	-	-	-	-	-	-	-	-	-	M	16-19
López-González (2015)	RR	Fall latency (s)	-	ND	-	-	-	ND	-	-	-	-	More	-	More	-	-	M	8-24
Mikhail (2015)	RR	Time on rod (s)	-	-	-	-	-	ND	ND	-	ND	-	ND	-	-	-	-	?	?
Vagnozzi (2018)	RR	Latency to fall (s)	-	-	-	-	-	-	-	-	-	-	Less	-	-	-	-	F+M	9-15
Wheeler (2019)	RR	Time on rotorod (s)	-	-	-	-	-	-	-	-	More	-	-	-	-	-	-	F+M	12
Sun (2020)	RR	Rotating test latency (s)	-	-	ND	-	ND	ND	ND	-	ND	-	F:More M:ND	-	ND	ND	ND	F+M	?
Tang (2020)	RR	Rotarod time (s)	-	-	-	-	-	-	-	-	ND	-	-	-	-	-	-	F+M	18-19
Izzy (2021)	RR	Latency (s)	-	?	-	-	-	-	-	-	-	-	-	-	-	-	-	M	6-14
Moreno-Gonzalez (2021)	RR	Latency to fall (s)	-	-	-	-	-	ND	-	-	Less	-	-	-	Less	-	Less	?	?
Zampar (2021)	RR	Latency to fall (s)	-	ND	-	-	ND	-	-	-	-	-	ND	-	-	-	-	F+M	10-14
Brody (2022)	RR	Best time (s)	-	-	-	-	-	-	-	-	-	-		ND		-	-	F+M	13-17
Eteläinen (2023)	RR	Latency to fall (s)	-	-	-	-	ND	-	ND	-	-	-	-	-	-	-	-	F+M	5-13
Dutta (2023)	RR	Latency to fall (s)	-	-	-	-	-	-	-	-	ND	-	-	-	-	-	-	?	7
Huang (2023)	RR	Latency to fall (s)	-	-	-	-	-	-	-	-	-	-	-	-	ND	-	-	F+M	11-18
Sebastián-Serrano (2022)	RR	Latency to fall (r.p.m.)	-	-	-	-	-	-	ND	-	-	-	Less	-	-	-	-	F+M	6-9
Sun (2020)	SL	Stride lenght (cm)	-	-	ND	-	ND	ND	ND	-	ND	-	ND	-	ND	F:More M:ND	F:ND M:Less	F+M	?
Zampar (2021)	IG	Latency to fall (s)	-	ND	-	-	ND	-	-	-	-	-	ND	-	-	-	-	F+M	10-14
Takeuchi (2011)	WH	Wire hang (s)	-		ND	-	-	-	-	-	-	-	-	-	-	-	-	M	16-19
Brody (2022)	WH	Mean latency (s)	-	-	-	-	-	-	-	-	-	-		ND		-	-	F+M	13-17
Dumont (2011)	BB	Fall latency (s)	ND		-	-	-	-	ND	-	-	-	-	-	ND	-	-	F+M	14-19
Zampar (2021)	BB	Latency to fall (s)	-	ND	-	-	ND	-	-	-	-	-	ND	-	-	-	-	F+M	10-14

Note: More=refers to an increased deviation from the control (PS19 mice vs. WT). Less=indicates a decreased deviation from the control (PS19 mice vs. WT). ND=No differences. OF=Open Field. NOR=Novel Object Recognition. RR=Rotarod. MWM=Morris Water Maze. SL=Spatial Learning. RM=Reference Memory. CFC=Context Fear Conditioning. EPM=Elevated Plus Maze. BM=Barnes Maze. PFS=Forced Swim Test. TS=Tail Suspension. NOL=Novel Object Location. EARM=Eight-Arm Radial Maze. GS=Grip Strength. SL=Stride Length. IG=Inverted Grid. WH=Wire Hang. BB=Balance Beam. F=Female. M=Male.

Table 3 - Summary of main results in both strains.

	rTg4510		PS19 mice	
Anxiety-like behaviours	< 4 months	Inconclusive	< 7 months	Inconclusive
	≥ 4 months	Inconclusive	≥ 7 months	Low
Depressive-like behaviour	< 4 months	----------	< 7 months	Inconclusive
	≥ 4 months	----------	≥ 7 months	Inconclusive
Neurological dysfunction/well-being	< 4 months	Inconclusive	< 7 months	Inconclusive
	≥ 4 months	Impaired	≥ 7 months	Inconclusive
Locomotion	< 4 months	Inconclusive	< 7 months	Hyperactivity*/Inconclusive
	≥ 4 months	Hyperactivity	≥ 7 months	Hyperactivity
Memory and learning	< 4 months	Inconclusive	< 7 months	No differences
	≥ 4 months	Impaired	≥ 7 months	Impaired
Balance and coordination	< 4 months	Inconclusive	< 7 months	No differences
	≥ 4 months	Inconclusive	≥ 7 months	No differences

Note: *Result just based in the meta-analysis. Inconclusive=Few studies/mixed results.