**Supplementary data**

**Table S1: Number of animals used for histological and behavioral evaluation**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Model* | **Tau58/2** | | | | | | | | **Tau58/4** | | | | | | | |
| *Age* | 3M | | 6M | | 9M | | 12M | | 3M | | 6M | | 9M | | 12M | |
| *Genotype* | WT | HET | WT | HET | WT | HET | WT | HET | WT | HET | WT | HET | WT | HET | WT | HET |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Histology and EM | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| SHIRPA, neuromotor tests, EPM, OFT and PA | 10 | 10 | 15 | 21 | 13 | 12 | 7 | 15 | 9 | 10 | 11 | 11 | 11 | 12 | 15 | 16 |
| MWM | 9 | 10 | 13 | 11 | 10 | 10 | 10 | 10 | 13 | 11 | 10 | 13 | 10 | 10 | 12 | 11 |
| Activity recordings | 8 | 8 | 8 | 8 | 8 | 8 | 10 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

WT=wild-type; HET=heterozygous; EM=electron microscopy; SHIRPA=SmithKline Beecham, Harwell, Imperial College, Royal London Hospital, phenotype assessment; EPM=elevated plus maze; OFT=open field test; PA=passive avoidance test; MWM=Morris water maze test

**Table S2: Overview of histopathology stains conducted in both mouse models**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Staining** | | | | | |
| **Line** | **Age** | **Genotype** | **AT8** | **AT100** | **AT270** | **Gallyas** | **HT7** | **SMI** |
| 58/2 | 3 | WT | - | NA | - | NA | - | NA |
|  | HET | (+) | NA | +(+) | NA | +++ | NA |
| 6 | WT | - | NA | - | - | - | - |
|  | HET | ++ | NA | ++ | - | ++ | ++ |
| 9 | WT | - | NA | - | NA | - | NA |
|  | HET | ++ | NA | ++ | NA | ++ | NA |
| 12 | WT | - | - | - | NA | +/- | - |
|  | HET | +++ | +++ | ++ | NA | ++ | ++ |
| 15 | WT | - | - | - | NA | +/- | - |
|  | HET | +++ | +++ | +++ | NA | +++ | +++ |
| 18 | WT | - | NA | - | - | +/- | - |
|  | HET | +++ | NA | +++ | +++ | +++ | +++ |
| 58/4 | 3 | WT | - | NA | +/- | NA | - | NA |
|  | HET | (+) | NA | + | NA | +++ | NA |
| 6 | WT | - | NA | - | - | - | - |
|  | HET | +(+) | NA | + | - | ++ | ++ |
| 9 | WT | - | NA | - | NA | - | NA |
|  | HET | ++ | NA | + | NA | ++ | NA |
| 12 | WT | - | - | - | NA | - | - |
|  | HET | ++ | ++ | + | NA | ++ | ++ |
| 15 | WT | - | - | - | NA | +/- | - |
|  | HET | +++ | ++(+) | ++ | NA | ++ | ++ |
| 18 | WT | - | NA | - | - | +/- | - |
|  | HET | +++ | NA | + | +++ | ++ | ++ |

+++ pathology observed in brainstem, midbrain and frontal cortex

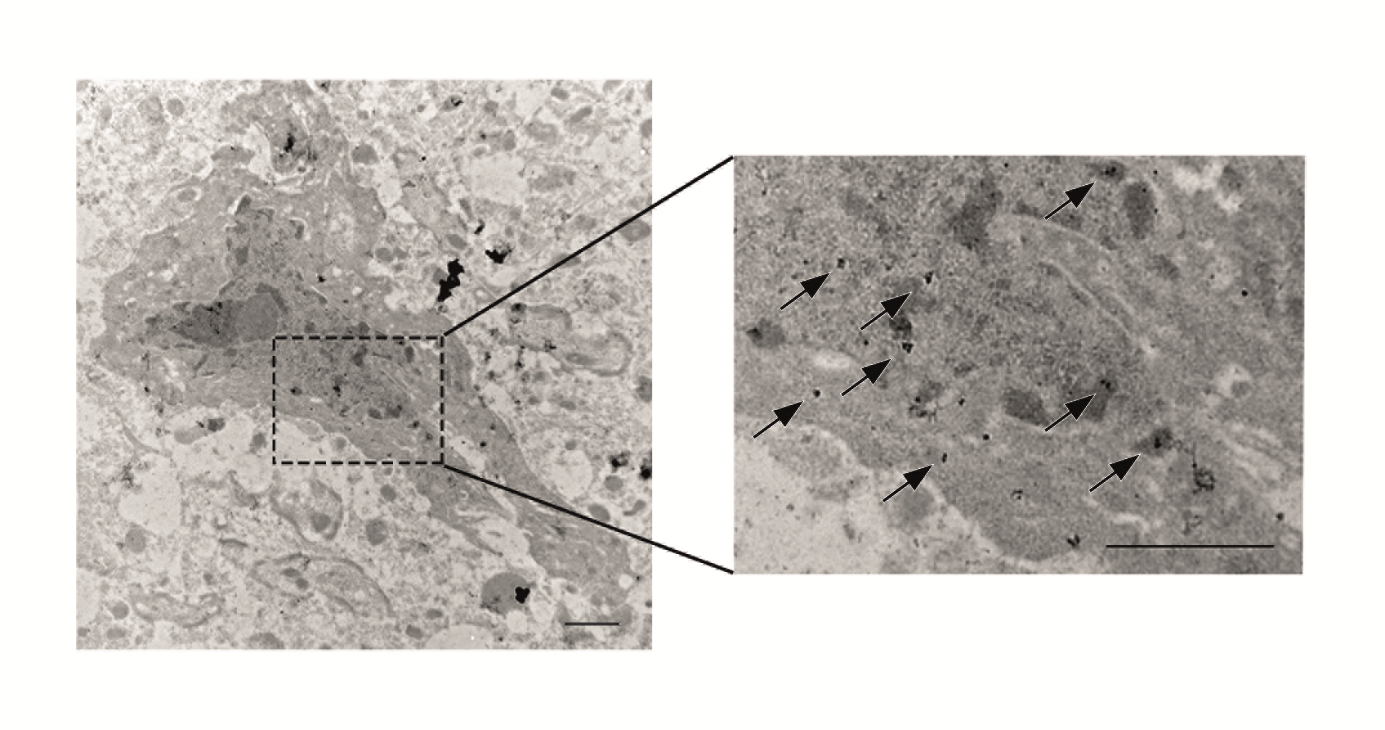
++ pathology observed in brainstem, minor frontal cortex staining

+ pathology observed in brainstem

+/- some pathology observed in brainstem and spinal cord; no pathology in brain

- no pathology observed

NA = not available; WT = wild-type; HET = heterozygous; AT8 = phosphorylated tau antibody (Ser202, Thr205); AT100 = phosphorylated tau antibody (Thr212, Ser 214); AT270 = phosphorylated tau antibody (Thr181); Gallyas = antibody to argyrophilic structures, including neurofibrillary tangles; HT7 = antibody to human tau, amino acid sequence PPGQK; SMI = antibody to neurofilament.



**Figure S1: AT8 immuno-EM staining for phosphorylated tau** (phosphorylation sites: serine 202 and threonine 205) with 10-nm gold particles in a pyramidal neuron located in the frontal cortex of a 12-month-old Tau58/2 mouse. Inset: arrows denote the intraneuronal gold particles, indicative of the presence of phosphorylated tau. Scale bar indicates 1 µm.



**Figure S2:Semi-quantification of tau immunoreactivity in frontal cortex.** The number of DAB-positive pixels versus the total number of pixels based on HT7, AT8 and AT270 immunostaining in the frontal cortex of Tau58/2 and Tau58/4 mice was determined using ImageJ combined with the IHC plugin. **A**. HT7 staining in WT and 58/2 mice. **B**. HT7 staining in WT and 58/4 mice. **C**. AT8 staining in WT and 58/2 mice. **D**. AT8 staining in WT and 58/4 mice. **C**. AT270 staining in WT and 58/2 mice. **D**. AT270 staining in WT and 58/4 mice. DAB = 3, 3′-Diaminobenzidine, HET = heterozygous, WT = wild-type.



**Figure S3: 47-h cage activity recordings in the Tau58/2 mouse line**. **A**. Activity profile of WT mice (black bars) aged 12 months. **B**. Recordings of HET mice (white bars) aged 12 months. Activity profiles of HET and WT mice look similar, though the difference in the active (i.e., dark) and inactive phase in HET mice looks less pronounced. Total number of counts did not differ between both genotypes. Activity during the active (light) phase of day two (16:00-20:00h and 08:00-15:00h) is significantly higher in HET animals compared with WT controls (two-tailed Student’s t-test, t18=-2.334, p=0.031). Each data point represents mean (± S.E.M.) across all measured time points (30 min bins). HET = heterozygous, WT = wild-type.



**Figure S4: 47-h cage activity recordings in the Tau58/4 mouse line**. **A**. Activity profile of WT mice (black bars) aged 12 months. **B**. Recordings of HET mice (white bars) aged 12 months. HET mice are more active during the second half of the first night (two-tailed Student’s t-test, t18=-3.060, p=0.007). This (hyper)activity corresponds with the increased distance observed in the open field test (Table 3; Figure 5).

References

1. Frank S, Clavaguera F, Tolnay M. Tauopathy models and human neuropathology: Similarities and differences. Acta *Neuropathol* **2008**, 115, 39–53. DOI: 10.1007/s00401-007-0291-9
2. Spillantini MG, Goedert M. Tau pathology and neurodegeneration. Lancet Neurol 2013, 12, 609–622. DOI: 10.1016/S1474-4422(13)70090-5
3. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol* **1991**, 82, 239–259. DOI: 10.1007/BF00308809
4. Robinson JL, Geser F, Corrada MM, Berlau DJ, Arnold SE, Lee VMY, Kawas CH, Trojanowski JQ. Neocortical and hippocampal amyloid-B and tau measures associate with dementia in the oldest-old. *Brain* **2011**, 134, 3708–3715. DOI: 10.1093/brain/awr308
5. Nelson PT, Braak H, Markesbery WR. Neuropathology and Cognitive Impairment in Alzheimer Disease: A Complex but Coherent Relationship. *J Neuropathol Exp Neurol* **2009**, 68, 1–14. DOI: 10.1097/NEN.0b013e3181919a48
6. Hong M. Mutation-Specific Functional Impairments in Distinct Tau Isoforms of Hereditary FTDP-17. *Science* **1998**, 282, 1914–1917. DOI: 10.1126/science.282.5395.1914.
7. Hutton M, Heutink P, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, Pickering-Brown S, Chakraverty S, Isaacs A, Grover A, Hackett J, Adamson J, Lincoln S, Dickson D, Davies P, Petersen RC, Stevens M, de Graaff E, Wauters E, van Baren J, Hillebrand M, Joosse M, Kwon JM, Nowotny P, Che LK, Norton J, Morris JC, Reed LA, Trojanowski J, Basun H, Lannfelt L, Neystat M, Fahn S, Dark F, Tannenberg T, Dodd PR, Hayward N, Kwok JB, Schofield PR, Andreadis A, Snowden J, Craufurd D, Neary D, Owen F, Oostra BA, Hardy J, Goate A, van Swieten J, Mann D, Lynch T, Heutink P. Association of missense and 5’-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* **1998**, 393, 702–705. DOI: 10.1038/31508.
8. MAPT mutations. Alzforum. Retrieved December 8, 2022 from <https://www.alzforum.org/mutations/mapt>.
9. Williams DR. Tauopathies: classification and clinical update on neurodegenerative diseases associated with microtubule-associated protein tau. *Intern Med J* **2006**, 36, 652–660. DOI: 10.1111/j.1445-5994.2006.01153.x
10. Hutton M, Lewis J, Dickson D, Yen SH, McGowan E. Analysis of tauopathies with transgenic mice. *Trends Mol Med* **2001**, 7, 467–470. DOI: 10.1016/s1471-4914(01)02123-2
11. Duff K, Suleman F. Transgenic mouse models of Alzheimer’s disease: how useful have they been for therapeutic development? *Brief Funct Genomic Proteomic* **2004**, 3, 47–59. DOI: 10.1093/bfgp/3.1.47
12. Lee VMY, Kenyon TK, Trojanowski JQ. Transgenic animal models of tauopathies. *Biochim Biophys Acta - Mol Basis Dis* **2005**, 1739, 251–259. DOI: 10.1016/j.bbadis.2004.06.014
13. Götz J, Ittner LM. Animal models of Alzheimer’s disease and frontotemporal dementia*. Nat Rev Neurosci* **2008**, 9, 532–544. DOI: 10.1038/nrn2420
14. Denk F, Wade-Martins R. Knock-out and transgenic mouse models of tauopathies. *Neurobiol Aging* **2009**, 30, 1–13. DOI: 10.1016/j.neurobiolaging.2007.05.010
15. Götz JJ, Götz J. Experimental Models of Tauopathy - From Mechanisms to Therapies. *Adv Exp Med Biol* **2019**, 1184, 381-391. DOI: 10.1007/978-981-32-9358-8\_28.
16. Gotz J. Formation of Neurofibrillary Tangles in P301L Tau Transgenic Mice Induced by Abeta 42 Fibrils. *Science* **2001**, 293, 1491–1495. DOI: 10.1126/science.1062097
17. Lewis J, McGowan E, Rockwood J, Melrose H, Nacharaju P, Van Slegtenhorst M, Gwinn-Hardy K, Paul Murphy M, Baker M, Yu X, Duff K, Hardy J, Corral A, Lin WL, Yen SH, Dickson DW, Davies P, Hutton M. Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein. *Nat Genet* **2000**, 25, 402–405. DOI: 10.1038/78078
18. Bugiani O, Murrell JR, Giaccone G, Hasegawa M, Ghigo G, Tabaton M, Morbin M, Primavera A, Carella F, Solaro C, Grisoli M, Savoiardo M, Spillantini MG, Tagliavini F, Goedert M, Ghetti B. Frontotemporal Dementia and Corticobasal Degeneration in a Family with a P301S Mutation in Tau. *J Neuropathol Exp Neurol* **1999**, 58, 667–677. DOI: 10.1097/00005072-199906000-00011
19. Sperfeld AD, Collatz MB, Baier H, Palmbach M, Storch A, Schwarz J, Tatsch K, Reske S, Joosse M, Heutink P, Ludolph AC. FTDP-17: An early-onset phenotype with parkinsonism and epileptic seizures caused by a novel mutation. *Ann Neurol* **1999**, 46, 708–715. DOI: 10.1002/1531-8249(199911)46:5<708::aid-ana5>3.0.co;2-k.
20. Yasuda M, Yokoyama K, Nakayasu T, Nishimura Y, Matsui M, Yokoyama T, Miyoshi K, Tanaka C. A Japanese patient with frontotemporal dementia and parkinsonism by a tau P301S mutation. *Neurol* **2000**, 55, 1224–1227. DOI: 10.1212/wnl.55.8.1224.
21. Lossos A, Reches A, Gal A, Newman JP, Soffer D, Gomori JM, Boher M, Ekstein D, Biran I, Meiner Z, Abramsky O, Rosenmann H. Frontotemporal dementia and parkinsonism with the P301S tau gene mutation in a Jewish family. *J Neurol* **2003**, 250, 733-740. DOI: 10.1007/s00415-003-1074-4.
22. Werber E, Klein C, Grünfeld J, Rabey JM. Phenotypic presentation of frontotemporal dementia with Parkinsonism-chromosome 17 type P301S in a patient of Jewish-Algerian origin. *Mov Disord* **2003**, 18, 595-8. DOI: 10.1002/mds.10401.
23. Baba Y, Baker MC, Le Ber I, Brice A, Maeck L, Kohlhase J, Yasuda M, Stoppe G, Bugiani O, Sperfeld AD, Tsuboi Y, Uitti RJ, Farrer MJ, Ghetti B, Hutton ML, Wszolek ZK. Clinical and genetic features of families with frontotemporal dementia and parkinsonism linked to chromosome 17 with a P301S tau mutation. *J Neural Transm* **2007**, 114, 947–950. DOI: 10.1007/s00702-007-0632-9
24. van Eersel J, Stevens CH, Przybyla M, Gladbach A, Stefanoska K, Chan CK, Ong WY, Hodges JR, Sutherland GT, Kril JJ, Abramowski D, Staufenbiel M, Halliday GM, Ittner LM. Early-onset axonal pathology in a novel P301S-Tau transgenic mouse model of frontotemporal lobar degeneration. *Neuropathol Appl Neurobiol* **2015**, 41, 906-25. DOI: 10.1111/nan.12233.
25. Przybyla M, Stevens CH, van der Hoven J, Harasta A, Bi M, Ittner A, van Hummel A, Hodges JR, Piguet O, Karl T, Kassiou M, Housley GD, Ke YD, Ittner LM, van Eersel J. Disinhibition-like behavior in a P301S mutant tau transgenic mouse model of frontotemporal dementia. *Neurosci Lett* **2016**, 631, 24-29. DOI: 10.1016/j.neulet.2016.08.007.
26. Van der Jeugd A, Vermaercke B, Halliday GM, Staufenbiel M, Götz J. Impulsivity, decreased social exploration, and executive dysfunction in a mouse model of frontotemporal dementia. *Neurobiol Learn Mem* **2016**, 130, 34-43. DOI: 10.1016/j.nlm.2016.01.007.
27. Yin Z, Valkenburg F, Hornix BE, Mantingh-Otter I, Zhou X, Mari M, Reggiori F, Van Dam D, Eggen BJL, De Deyn PP, Boddeke E. Progressive Motor Deficit is Mediated by the Denervation of Neuromuscular Junctions and Axonal Degeneration in Transgenic Mice Expressing Mutant (P301S) Tau Protein. *J Alzheimers Dis* **2017**, 60, S41-S57. DOI: 10.3233/JAD-161206.
28. Gomes LA, Hipp SA, Rijal Upadhaya A, Balakrishnan K, Ospitalieri S, Koper MJ, Largo-Barrientos P, Uytterhoeven V, Reichwald J, Rabe S, Vandenberghe R, von Arnim CAF, Tousseyn T, Feederle R, Giudici C, Willem M, Staufenbiel M, Thal DR. Aβ-induced acceleration of Alzheimer-related τ-pathology spreading and its association with prion protein. *Acta Neuropathol* **2019**, 138, 913-941. DOI: 10.1007/s00401-019-02053-5.
29. Ke YD, Chan G, Stefanoska K, Au C, Bi M, Müller J, Przybyla M, Feiten A, Prikas E, Halliday GM, Piguet O, Kiernan MC, Kassiou M, Hodges JR, Loy CT, Mattick JS, Ittner A, Kril JJ, Sutherland GT, Ittner LM. CNS cell type-specific gene profiling of P301S tau transgenic mice identifies genes dysregulated by progressive tau accumulation. *J Biol Chem* **2019**, 294, 14149-14162. DOI: 10.1074/jbc.RA118.005263.
30. Cheng H, Deaton LM, Qiu M, Ha S, Pacoma R, Lao J, Tolley V, Moran R, Keeton A, Lamb JR, Fathman J, Walker JR, Schumacher AM. Tau overexpression exacerbates neuropathology after repeated mild head impacts in male mice. *Neurobiol Dis* **2020**, 134, 104683. DOI: 10.1016/j.nbd.2019.104683.
31. Przybyla M, van Eersel J, van Hummel A, van der Hoven J, Sabale M, Harasta A, Müller J, Gajwani M, Prikas E, Mueller T, Stevens CH, Power J, Housley GD, Karl T, Kassiou M, Ke YD, Ittner A, Ittner LM. Onset of hippocampal network aberration and memory deficits in P301S tau mice are associated with an early gene signature. *Brain* **2020**, 143, 1889-1904. DOI: 10.1093/brain/awaa133.
32. van der Hoven J, van Hummel A, Przybyla M, Asih PR, Gajwani M, Feiten AF, Ke YD, Ittner A, van Eersel J, Ittner LM. Contribution of endogenous antibodies to learning deficits and astrocytosis in human P301S mutant tau transgenic mice. *Sci Rep* **2020,** 10, 13845. DOI: 10.1038/s41598-020-70845-x.
33. Van Erum J, Valkenburg F, Van Dam D, De Deyn PP. Pentylenetetrazole-induced Seizure Susceptibility in the Tau58/4 Transgenic Mouse Model of Tauopathy. *Neuroscience* **2020**, 425, 112-122. DOI: 10.1016/j.neuroscience.2019.11.007.
34. Watt G, Chesworth R, Przybyla M, Ittner A, Garner B, Ittner LM, Karl T. Chronic cannabidiol (CBD) treatment did not exhibit beneficial effects in 4-month-old male TAU58/2 transgenic mice. *Pharmacol Biochem Behav* **2020**, 196, 172970. DOI: 10.1016/j.pbb.2020.172970.
35. Watt G, Przybyla M, Zak V, van Eersel J, Ittner A, Ittner LM, Karl T. Novel Behavioural Characteristics of Male Human P301S Mutant Tau Transgenic Mice – A Model for Tauopathy. *Neuroscience* **2020**, 431, 166-175. DOI: 10.1016/j.neuroscience.2020.01.047.
36. Kreilaus F, Masanetz R, Watt G, Przybyla M, Ittner A, Ittner L, Karl T. The behavioural phenotype of 14-month-old female TAU58/2 transgenic mice. *Behav Brain Res* **2021**, 397, 112943. DOI: 10.1016/j.bbr.2020.112943.
37. Kreilaus F, Przybyla M, Ittner L, Karl T. Cannabidiol (CBD) treatment improves spatial memory in 14-month-old female TAU58/2 transgenic mice. *Behav Brain Res* **2022**, 425, 113812. DOI: 10.1016/j.bbr.2022.113812.
38. Andrä K, Abramowski D, Duke M, Probst A, Wiederhold KH, Bürki K, Goedert M, Sommer B, Staufenbiel M. Expression of APP in transgenic mice: A comparison of neuron-specific promoters. *Neurobiol Aging* **1996**, 17, 183-190. DOI: 10.1016/0197-4580(95)02066-7
39. Yin Z, Valkenburg F, Hornix BE, Mantingh-Otter I, Zhou X, Mari M, Reggiori F, Van Dam D, Eggen BJL, De Deyn PP, Boddeke E. Progressive Motor Deficit is Mediated by the Denervation of Neuromuscular Junctions and Axonal Degeneration in Transgenic Mice Expressing Mutant (P301S) Tau Protein. *J Alzheimers Dis.* **2017**; 60, S41-S57. DOI: 10.3233/JAD-161206.
40. Varghese F, Bukhari AB, Malhotra R, De A. IHC Profiler: an open source plugin for the quantitative evaluation and automated scoring of immunohistochemistry images of human tissue samples. *PLoS One* **2014**; 9, e96801. DOI: 10.1371/journal.pone.0096801.
41. Vandermeeren M, Borgers M, Van Kolen K, Theunis C, Vasconcelos B, Bottelbeergs A, Wintmolders C, Daneels G, Willems R, Dockx K, Delbroek L, Marreiro A, Ver Donck L, Sousa C, Nanjunda R, Lacy E, Van De Casteele T, Van Dam D, De Deyn PP, Kemp JA, Malia TJ, Mercken MH. Anti-Tau Monoclonal Antibodies Derived from Soluble and Filamentous Tau Show Diverse Functional Properties in vitro and in vivo. *J Alzheimers Dis* **2018**, 65, 265-281. DOI: 10.3233/JAD-180404
42. Rafael JA, Nitta Y, Peters J, Davies KE. Testing of SHIRPA, a mouse phenotypic assessment protocol, on Dmd(mdx) and Dmd(mdx3cv) dystrophin-deficient mice. *Mamm Genome* **2000**, 11, 725-728. DOI: 10.1007/s003350010149
43. Rogers DC, Fisher EMC, Brown SDM, Peters J, Hunter AJ, Martin JE. Behavioral and functional analysis of mouse phenotype: SHIRPA, a proposed protocol for comprehensive phenotype assessment. *Mamm Genome* **1997, 8,** 711–713. DOI: 10.1007/s003359900551.
44. Van Dam D, Errijgers V, Kooy RF, Willemsen R, Mientjes E, Oostra BA, De Deyn PP. Cognitive decline, neuromotor and behavioural disturbances in a mouse model for fragile-X-associated tremor/ataxia syndrome (FXTAS). *Behav Brain Res* **2005**, 162, 233-9. DOI: 10.1016/j.bbr.2005.03.007.
45. Roth L, Van Dam D, Van der Donckt C, Schrijvers DM, Lemmens K, Van Brussel I, De Deyn PP, Martinet W, De Meyer GR. Impaired gait pattern as a sensitive tool to assess hypoxic brain damage in a novel mouse model of atherosclerotic plaque rupture. *Physiol Behav* **2015**, 139, 397-402. DOI: 10.1016/j.physbeh.2014.11.047.
46. Van Dam D, D'Hooge R, Staufenbiel M, Van Ginneken C, Van Meir F, De Deyn PP. Age-dependent cognitive decline in the APP23 model precedes amyloid deposition. *Eur J Neurosci* **2003**, 17, 388-396. DOI: 10.1046/j.1460-9568.2003.02444.x.
47. Van Erum J, Van Dam D, Sheorajpanday R, De Deyn PP. Sleep architecture changes in the APP23 mouse model manifest at onset of cognitive deficits. *Behav Brain Res* **2019**, 373, 112089. DOI: 10.1016/j.bbr.2019.112089.
48. Vloeberghs E, Van Dam D, Engelborghs S, Nagels G, Staufenbiel M, De Deyn PP. Altered circadian locomotor activity in APP23 mice: a model for BPSD disturbances. *Eur J Neurosci* **2004**, 20, 757-66. DOI: 10.1111/j.1460-9568.2004.03755.x.
49. Vloeberghs E, Van Dam D, Franck F, Staufenbiel M, De Deyn PP. Mood and male sexual behaviour in the APP23 model of Alzheimer's disease. *Behav Brain Res* **2007**, 180, 146-51. DOI: 10.1016/j.bbr.2007.03.002.
50. Kurien T, Gross T, Scofield RH. Barbering in mice: a model for trichotillomania. *Br Med J* **2005**, 331, 1503–1505. DOI: 10.1136/bmj.331.7531.1503.
51. Mendez MF, Bagert BA, Edwards-lee T. Self-injurious behavior in frontotemporal dementia. Neurocase 1997;3:231–236.
52. Viskontas IV, Possin KL, Miller BL. Symptoms of frontotemporal dementia provide insights into orbitofrontal cortex function and social behavior. *Ann N Y Acad Sci* **2007**, 1121, 528-45. DOI: 10.1196/annals.1401.025.
53. Murray R, Neumann M, Forman MS, Farmer J, Massimo L, Rice A, Miller BL, Johnson JK, Clark CM, Hurtig HI, Gorno-Tempini ML, Lee V M-L, Trojanowski JQ, Grossman M. Cognitive and motor assessment in autopsy-proven corticobasal degeneration. *Neurol* **2007**, 68, 1274–1283. DOI: 10.1212/01.wnl.0000259519.78480.c3.
54. Brooks SP, Dunnett SB. Tests to assess motor phenotype in mice: a user's guide. *Nat Rev Neurosci* **2009**, 10, 519-29. DOI: 10.1038/nrn2652. Epub 2009 Jun 10.
55. Allen B, Ingram E, Takao M, Smith MJ, Jakes R, Virdee K, Yoshida H, Holzer M; Craxton M, Emson PC, Atzori C, Migheli A, Crowther RA, Ghetti B, Spillantini MG, Goedert M. Abundant tau filaments and nonapoptotic neurodegeneration in transgenic mice expressing human P301S tau protein. *J Neurosci* **2002**, 22, 9340–9351. DOI: 10.1523/JNEUROSCI.22-21-09340.2002.
56. Lalonde R, Strazielle C. Brain regions and genes affecting limb-clasping responses. *Brain Res Rev* **2011**, 67, 252-9. DOI: 10.1016/j.brainresrev.2011.02.005.
57. Leroy K, Bretteville A, Schindowski K, Gilissen E, Authelet M, De Decker R, Yilmaz Z, Buée L, Brion J-P. Early axonopathy preceding neurofibrillary tangles in mutant tau transgenic mice. *Am J Pathol* **2007**, 171, 976–992. DOI: 10.2353/ajpath.2007.070345.
58. Terwel D, Lasrado R, Snauwaert J, Vandeweert E, Van Haesendonck C, Borghgraef P, Van Leuven F. Changed conformation of mutant tau-P301L underlies the moribund tauopathy, absent in progressive, nonlethal axonopathy of tau-4R/2N transgenic mice. *J Biol Chem* **2005**, 280, 3963–3973. DOI: 10.1074/jbc.M409876200.
59. Denk F, Wade-Martins R. Knock-out and transgenic mouse models of tauopathies. *Neurobiol Aging*, **2009**, 30, 1-13. DOI: 10.1016/j.neurobiolaging.2007.05.010.
60. Probst A, Götz J, Wiederhold KH, Tolnay M, Mistl C, Jaton AL, Hong M, Ishihara T, Lee VM, Trojanowski JQ, Jakes R, Crowther RA, Spillantini MG, Bürki K, Goedert M. Axonopathy and amyotrophy in mice transgenic for human four-repeat tau protein. *Acta Neuropathol* **2000**, 99, 469–481. DOI: 10.1007/s004010051148.
61. Aiello M, Silani V, Rumiati RI. You stole my food! Eating alterations in frontotemporal dementia. *Neurocase* **2016**, 22, 400-9. DOI: 10.1080/13554794.2016.1197952.
62. Piguet O, Petersén A, Yin Ka Lam B, Gabery S, Murphy K, Hodges JR, Halliday GM. Eating and hypothalamus changes in behavioral-variant frontotemporal dementia. Ann Neurol **2011**, 69, 312-319. DOI: 10.1002/ana.22244. Epub 2010 Nov 12.
63. Ahmed RM, Latheef S, Bartley L, Irish M, Halliday GM, Kiernan MC, Hodges JR, Piguet O. Eating behavior in frontotemporal dementia: Peripheral hormones vs hypothalamic pathology. *Neurology* **2015**, 85, 1310-1317. DOI: 10.1212/WNL.0000000000002018.
64. Buccarello L, Grignaschi G, Di Giancamillo A, Domeneghini C, Melcangi RC, Borsello T. Neuroprotective effects of low fat-protein diet in the P301L mouse model of tauopathy. *Neuroscience* **2017**, 23, 208-220. DOI: 10.1016/j.neuroscience.2017.04.027.
65. Brownlow ML, Joly-Amado A, Azam S, Elza M, Selenica ML, Pappas C, Small B, Engelman R, Gordon MN, Morgan D. Partial rescue of memory deficits induced by calorie restriction in a mouse model of tau deposition. *Behav Brain Res* **2014**, 271, 79-88. DOI: 10.1016/j.bbr.2014.06.001.
66. Joly-Amado A, Serraneau KS, Brownlow M, Marín de Evsikova C, Speakman JR, Gordon MN, Morgan D. Metabolic changes over the course of aging in a mouse model of tau deposition. *Neurobiol Aging* **2016**, 44, 62-73. DOI: 10.1016/j.neurobiolaging.2016.04.013.
67. Brooks SP, Dunnett SB. Tests to assess motor phenotype in mice: a user’s guide. *Nat Rev Neurosci* **2009**; 10, 519–529. DOI: 10.1038/nrn2652.
68. Bott NT, Radke A, Stephens ML, Kramer JH. Frontotemporal dementia: diagnosis, deficits and management. *Neurodegener Dis Manag* **2014**, 4, 439-54. DOI: 10.2217/nmt.14.34.
69. Turri MG, Datta SR, DeFries J, Henderson ND, Flint J. QTL analysis identifies multiple behavioral dimensions in ethological tests of anxiety in laboratory mice. *Curr Biol* **2001**, 11, 725-34. DOI: 10.1016/s0960-9822(01)00206-8.
70. Crawley JN. Emotional behaviors: Animal models of psychiatric diseases. In What’s wrong with my mouse? Behavioral phenotyping of transgenic and knockout mice, 1st ed.; Wiley-Liss, New York, USA, 2000; pp. 179-208.
71. Lister RG. The use of a plus-maze to measure anxiety in the mouse. *Psychopharmacology (Berl)* **1987**, 92, 180-5. DOI: 10.1007/BF00177912.
72. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EG, Onyike CU, Hillis AE, Josephs KA, Boeve BF, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini ML, Rosen H, Prioleau-Latham CE, Lee A, Kipps CM, Lillo P, Piguet O, Rohrer JD, Rossor MN, Warren JD, Fox NC, Galasko D, Salmon DP, Black SE, Mesulam M, Weintraub S, Dickerson BC, Diehl-Schmid J, Pasquier F, Deramecourt V, Lebert F, Pijnenburg Y, Chow TW, Manes F, Grafman J, Cappa SF, Freedman M, Grossman M, Miller BL. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* **2011**, 134, 2456-77. DOI: 10.1093/brain/awr179.
73. Magrath Guimet N, Miller BL, Allegri RF, Rankin KP. What Do We Mean by Behavioral Disinhibition in Frontotemporal Dementia? *Front Neurol* **2021**, 12, 707799. DOI: 10.3389/fneur.2021.707799.
74. Tanguy D, Rametti-Lacroux A, Bouzigues A, Saracino D, Le Ber I, Godefroy V, Morandi X, Jannin P, Levy R, Batrancourt B, Migliaccio R; ECOCAPTURE Study Group. Behavioural disinhibition in frontotemporal dementia investigated within an ecological framework. *Cortex* **2023**, 160, 152-166. DOI: 10.1016/j.cortex.2022.11.013.
75. Silverman AP. Motor activity. In Animal behaviour in the laboratory. 1st ed.; Chapman and Hall, London, UK, 1978 ; pp. 79-92.
76. Vloeberghs E, Van Dam D, Engelborghs S, Nagels G, Staufenbiel M, De Deyn PP. Altered circadian locomotor activity in APP23 mice: a model for BPSD disturbances. *Eur J Neurosci* **2004**, 20, 2757-66. DOI: 10.1111/j.1460-9568.2004.03755.x.
77. Anderson KN, Hatfield C, Kipps C, Hastings M, Hodges JR. Disrupted sleep and circadian patterns in frontotemporal dementia. *Eur J Neurol* **2009**, 16, 317-23. DOI: 10.1111/j.1468-1331.2008.02414.x.
78. Bonakis A, Economou N-T, Paparrigopoulos T, Bonanni E, Maestri M, Carnicelli L, Di Coscio E, Ktonas P, Vagiakis E, Theodoropoulos P, Papageorgiou SG. Sleep in frontotemporal dementia is equally or possibly more disrupted, and at an earlier stage, when compared to sleep in Alzheimer’s disease. *J Alzheimers Dis* **2014**, 38, 85–91. DOI: 10.3233/JAD-122014.
79. Holton CM, Hanley N, Shanks E, Oxley P, McCarthy A, Eastwood BJ, Murray TK, Nickerson A, Wafford KA. Longitudinal changes in EEG power, sleep cycles and behaviour in a tau model of neurodegeneration. *Alzheimers Res Ther* **2020,** 12, 84. DOI: 10.1186/s13195-020-00651-0.
80. Ögren SO, Stiedl O. Passive avoidance. In Encyclopedia of Psychopharmacology. Stolerman IP, Ed; Springer, Berlin, Heidelberg, Germany, 2010. DOI: 10.1007/978-3-540-68706-1\_160.
81. D’Hooge R, De Deyn PP. Applications of the Morris water maze in the study of learning and memory. *Brain Res Rev* **2001**, 36, 60–90. DOI: 10.1016/s0165-0173(01)00067-4.

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