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Abstract

Frontotemporal dementia (FTD) presents clinically with behavioral changes including disinhibition. Mutations in the tau-encoding MAPT gene identified in familial cases of FTD have been used to generate transgenic mouse models of the human condition. Here, we report behavioral changes in a recently developed P301S mutant tau transgenic mouse, including disinhibition-like behavior in the elevated plus maze and hyperactivity in the open field arena. Furthermore, histological analysis revealed the amygdala as a primary and early site of pathological tau deposition in these mice. Taken together, neuropathological and behavioral changes in P301S tau transgenic mice resemble features of human FTD.

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Disinhibition-like behavior in a P301S mutant tau transgenic mouse model of frontotemporal dementia

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Abstract

Frontotemporal dementia (FTD) presents clinically with behavioral changes including disinhibition. Mutations in the tau-encoding *MAPT* gene identified in familial cases of FTD have been used to generate transgenic mouse models of the human condition. Here, we report behavioral changes in a recently developed P301S mutant tau transgenic mouse, including disinhibition-like behavior in the elevated plus maze and hyperactivity in the open field arena. Furthermore, histological analysis revealed the amygdala as a primary and early site of pathological tau deposition in these mice. Taken together, neuropathological and behavioral changes in P301S tau transgenic mice resemble features of human FTD.

1. Introduction

Frontotemporal dementia (FTD) is a term collectively used to describe a clinically, pathologically and genetically diverse group of neurodegenerative disorders. Clinically, FTD patients may show changes in behavior, language, cognition and motor function. The most common clinical phenotype is the behavioral variant of FTD (bvFTD), characterized clinically by changes in behavior and personality, including apathy and disinhibition [19]. Early disinhibition in bvFTD may present as socially inappropriate behaviors, loss of manners, impulsive, rash and careless actions [17], with failure of inhibitory control [18]. Neuropathologically, FTD is characterized by the abnormal deposition of proteins in neurons and glia, including the microtubule associated binding protein tau, the transactive response DNA binding protein 43 (TDP-43), or less frequently, other proteins such as fused in sarcoma (FUS). Approximately one third of FTD cases are familial with the most frequent mutations found in the tau-encoding *MAPT* gene with tau pathology, and in *GRN* and *C9ORF72* associated with TDP-43 deposition [10]. Interestingly, behavioral disinhibition is more frequent amongst *MAPT*, than *GRN* and *C9ORF72* mutation carriers with familial FTD [21].

Tau is an unstructured multi-domain protein that binds to microtubules to regulate their dynamics and intracellular transport processes [2]. Tau is predominantly found in the axon of neurons, although small amounts localize to the post-synapse to regulate excitatory signaling [15]. Tau harbors over 80 potential phosphorylation sites, and in disease, it becomes aberrantly phosphorylated at many sites, which coined the term ‘hyperphosphorylated tau’ [11]. Hyperphosphorylation of tau compromises its binding to microtubules, resulting in accumulation of tau in the soma and dendrites of neurons [13]. Hyperphosphorylated tau is prone to oligomerize and form insoluble fibrillar aggregates that present as neurofibrillary tangles (NFTs), a common feature of FTD with tau pathology [5].

The identification of *MAPT* mutations in familial FTD has been instrumental in the generation of a significant number of transgenic mouse lines that develop functional deficits and NFT pathology (reviewed by [12]). We have recently reported TAU58/2 mice with neuronal expression of P301S mutant tau [24]. TAU58/2 mice present with motor deficits, and tau and neurofibrillar pathology reminiscent of human FTD with tau pathology. In the present study, we show that TAU58/2 mice develop early-onset disinhibition-like behavior and increased motor activity together with early NFT pathology in the amygdala, reminiscent of bvFTD.

2. Methods

2.1. Mice

TAU58/2 mice express the human 0N4R tau isoform with the P301S mutation under the control of the mouse Thy1.2 promoter, as previously described by us [24]. All animal experiments were approved by the Animal Ethics Committees of the University of New South Wales. All procedures complied with the statement on animal experimentation issued by the National Health and Medical Research Council of Australia.

2.2. Histology

Three, 6 and 12 month-old male TAU58/2 transgenic mice (n=4-9) and non-transgenic littermates (n=3-6) were used for histological analysis. At the desired age, mice were anesthetized and transcardially perfused with phosphate buffered saline (pH 7.4) to remove blood. Brains were removed and immersion fixed in 4% paraformaldehyde, processed in an Excelsior tissue processor (ThermoFisher, Waltham, MA, USA), embedded in paraffin and sectioned in the coronal plane at 3-8µm. One-2 Sections per mouse corresponding to approximately -2.54 mm relative to Bregma were stained with antibodies against tau phosphorylated at Ser214 (pS214, Abcam) and Ser422 (pS422, Abcam), and with Gallyas silver impregnation to reveal NFTs composed of insoluble tau aggregates, using previously published procedures [14]. Brain sections stained with pS422 and pS214 were scanned on a Scanscope Aperio FL (Leica Biosystems). One fluorescent channel Alexa Fluor 488 (Excitation 485/20-25, Emission 521/25) was imaged with an exposure time of 320 ms, which was kept consistent across all slide imaging. The number of pS422 and pS214-positive neurons were counted throughout the amygdala. Neurons with bright (high) staining signal for pS214 were counted separately of those neurons with less intensive (low) staining. Brightfield microscopy was performed with an Olympus BX51 (USA) microscope equipped with a DP70 color camera. The number of Gallyas silver positive NFTs, identified by black colour, and neuronal size and shape, were counted throughout the amygdala. Olympus CellSens software was used to delineate the regions of interest, and area measurements automatically calculated. All cell counts were converted to a density value (cells/mm²). For all quantitation, repeated measures on different days gave an inter- and intra-rater variability of <5%.

2.3. Behavioral testing

2.3.1. Elevated Plus Maze

Anxiety and disinhibition-like behavior were tested in 3, 6 and 10 month-old male TAU58/2 mice (n=10-18) and non-transgenic littermates (n=7-17) in an elevated plus maze (Ugo Basile), consisting of two open and two closed arms (each 35cm x 5.5cm), as well as a central platform (5.5cm x 5.5cm), arranged in a plus shape and elevated 60cm above

the ground. Mice were acclimatized to the room for 1 hour prior to testing, then placed on the central platform facing an open arm and recorded for 5 minutes. Recordings were done at 210-215 lx (open arm), 130-140 lx (closed arm). Videos were analyzed using the AnyMaze software (Stoelting) by a person blinded to the genotypes.

2.3.2. Open Field

Activity, anxiety and exploration pattern were tested in 3, 6 and 10 month-old male TAU58/2 mice (n=6-17) and non-transgenic littermates (n=6-13) in an open field arena. Mice were individually placed at the periphery of a box (40cm x 40cm) in an enclosed cupboard and their movement recorded for 10 minutes. Recordings were done at 200 lx. Videos were analyzed using the AnyMaze software by a person blinded to their genotypes. For analysis, the box was divided into an outer and inner zone, where the inner zone was represented by a 22.5cm x 22.5cm square in the center of the box.

2.4. Statistical analysis

All statistical analysis was done using the Graphpad Prism 6.0 software (GraphPad, La Jolla, CA, USA) using either Student's *t*-tests for comparison of two data sets, analysis of variance (ANOVA) for comparison of more than two data sets or two-way ANOVA for comparison across time. *P* values of below 0.05 were considered significant. All values are presented as mean $\pm$ standard error of the mean.

3. Results

3.1. Amygdala is an early site of tau pathology in TAU58/2 mice

TAU58/2 mice express P301S mutant human 0N4R tau under the control of the murine Thy1.2 promoter in CNS neurons, and we have previously reported motor deficits in this line when challenged in different test paradigms [24]. In the present study, we determined whether TAU58/2 mice recapitulate features of bvFTD, focusing on disinhibition and risk taking behavior.

Atrophy of the amygdala is observed in the early stages of FTD [16], and considerable tau pathology has been reported in the amygdala of patients with FTD and related neurodegenerative disorders [6, 26]. While we have previously assessed tau pathology in TAU58/2 mice [24], this analysis has not included the amygdala. Therefore, we determined tau pathology in the amygdala of young (3 months), adult (6 months) and aged (12 months) TAU58/2 mice, using both immunohistochemical staining for phosphorylated tau and Gallyas' silver staining of NFTs (**Figure 1**). PS214 is known to be a marker of early tau involvement, while pS422 is known to be affected later in disease course [8]. In line with this, abundant pS214-positive neurons were already seen in young TAU58/2 mice, with the number of intensely stained neurons significantly increasing in adult and aged transgenic mice (**Figure 1A and 1B**). In contrast,

only a few pS422-positive neurons were seen in the amygdala of young TAU58/2 mice, but their numbers significantly increased with age (**Figure 1C and 1D**). Similarly, NFTs were present in small numbers in young TAU58/2 mice, and significantly increased over time resulting in extensive pathology by 12 months of age (**Figure 1E and 1F**). Non-transgenic littermates were negative for phosphorylated tau and NFT pathology. Taken together, progressive hyperphosphorylated tau and NFT pathology manifests early in the amygdala of TAU58/2 mice.

3.2. Behavioral changes in TAU58/2 mice

The amygdala is an important area for behavior control [20]. To determine the impact of transgenic P301S mutant tau expression on the behavior in TAU58/2 mice, we subjected transgenic mice and non-transgenic littermates to elevated plus maze (EPM) and open field (OF) testing (**Figure 2 and 3**). Young (3 months), adult (6 months) and aged (10 months) TAU58/2 and non-transgenic control littermate mice were tested. EPM testing revealed that already young TAU58/2 mice spent significantly more time in the open arms than their non-transgenic littermates (**Figure 2A and 2B**). Similarly, both adult and aged TAU58/2 mice spent more time in the open arms than their respective non-transgenic littermates. When comparing TAU58/2 mice across ages, we found that aged spent significantly more time in the open arms than young and adult mice (**Figure 2B**). The time when mice emerged for the first time from the closed into the open arms was significantly reduced in TAU58/2 mice compared to non-transgenic littermates of all ages (**Figure 2C**). In all age groups, the time animals were mobile and distances travelled during testing were comparable in TAU58/2 and non-transgenic mice, showing motor competency (**Figure 2D**).

Next, we exposed young, adult and aged TAU58/2 mice, and the respective non-transgenic littermate controls, to a novel OF arena and recorded their exploration pattern and locomotion activity continuously over 10 minutes (**Figure 3**). Both young and adult TAU58/2 and their non-transgenic littermates travelled comparable distances during testing (**Figure 3A and 3B**). However, distance travelled and time mobile during testing were significantly higher in aged TAU58/2 mice compared to non-transgenic littermate controls, which presented reduced activity compared to younger mice (**Figure 3B and 3C**). The exploration paths in the OF arena were comparable between all age groups tested (**Figure 3A**), with similar frequent entries into the inner zone of the arena (**Figure 3D**). Taken together, TAU58/2 present with progressive early-onset deficits in the EPM, while changes in the OF are of late onset.

4. Discussion

In the present study, we showed that tau pathology in the amygdala of TAU58/2 mice is of early onset and progressive. EPM testing revealed disinhibition/reduced anxiety already in young TAU58/2 mice, while deficits in the exploration and hyperactivity in the OF test were of later onset.

Previous studies have not assessed tau pathology in the amygdala of TAU58/2 mice [23, 24]. While we found earlier that tau pathology presents in hippocampus, cortex and brain stem of TAU58/2 mice [24], the present study would suggest that the amygdala is a primary site of NFT pathology in this tau transgenic line. Accordingly, numbers of NFTs in the amygdala of aged TAU58/2 mice were approximately 4-fold those we reported earlier for the hippocampus and 2-fold higher compared to numbers in the brain stem [24]. Interestingly, significant atrophy of the amygdala has been found in the brains of FTD patients [3, 4]. Considering the importance of the amygdala in controlling behavior [20], early onset of pathology and behavioral changes in the EPM in TAU58/2 mice suggest a contributing role to the clinical presentation of FTD. However, other brain areas may contribute to the observed deficits including cortical regions [1], despite lower levels of tau pathology compared to the amygdala in TAU58/2 mice [24].

In parallel to the early tau pathology in the amygdala, we show here already in young TAU58/2 mice decreased anxiety behaviour consistent with disinhibition during EPM testing. Increased impulsivity/disinhibition-like behavior of TAU58/2 mice is furthermore supported by a reduced latency to leave the enclosed arms of the EPM. For comparison, abnormal and progressive behaviour in the EPM, with increased time spent in the open has been reported in other tau transgenic mouse models of FTD, some associated with widespread tau pathology (including in amygdala and cortex) [6, 7, 9, 22, 25]. Although the youngest group of TAU58/2 mice tested already showed marked EPM deficits, this further progressed as mice aged. In contrast to early EPM deficits in young TAU58/2 mice, exploration and activity in the OF were not altered at 3 and 6 months of age, but only became apparent in aged mice. TAU58/2 and non-transgenic mice similarly avoided the inner zone of the OF indicating similar anxiety levels, and further supporting that deficits in the EPM rather result from disinhibition than reduced anxiety. Similar behaviour in the OF has been reported for other tau transgenic lines [6]. Disinhibition and lack of emotional control with inappropriate social behaviour is a lead symptom of bvFTD [17, 18], resembled by TAU58/2 mice.

A very recent publication reported early increases in risk-taking behavior in young TAU58/2 when tested in the light/dark paradigm, but no changes to exploration and activity in the OF arena, including in aged mice [23]. Our study found similar behavior in young TAU58/2 mice using the EPM paradigm, as well as hyperactivity in the OF in aged mice, consistent with findings in other tau transgenic lines [6, 25]. The differences in OF behavior of TAU58/2 mice between studies may be due to alternative testing equipment and procedures, subtle differences in the genetic backgrounds or distinctive husbandry conditions.

5. Conclusion

Taken together, we found early-onset and progressive disinhibition-like behavior in TAU58/2 mice, together with early NFT pathology in the amygdala, resembling clinical presentations and neuropathology of bvFTD with tau pathology. We propose that EPM testing correlates with early tau pathology in the amygdala and is a reliable and quick

behavioral testing method to determine functional deficits in TAU58/2, which should be included in studies aiming at modifying disease progression, for example by crossing with other genetically modified mouse lines or by administering therapeutic compounds.

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Figure legends

Figure 1 Progressive tau pathology in the amygdala of TAU58/2 mice.

(A) Representative immunofluorescence (IF) staining of the amygdala of young, adult and aged TAU58/2 mice, using an antibody specific for tau phosphorylated at serine 214 (pS214). Arrows indicate neurons with 'high' staining intensity, while arrow heads indicate cells with 'low' staining intensity. No staining was observed in non-transgenic brain tissue. Scale bar, 50µm.

(B) Quantification of numbers of pS214-positive cells with low (pS214^{low}) and high (pS214^{high}) staining intensity per mm² (*, p<0.05; **, p<0.01; ***, p<0.001; n=4-9).

(C) Representative IF staining of the amygdala of young, adult and aged TAU58/2 mice, using an antibody specific for tau phosphorylated at serine 422 (pS422). No staining was observed in non-transgenic brain tissue. Scale bar, 50µm.

(D) Quantification of numbers of pS422-positive cells per mm² (*, p<0.05; ***, p<0.001; n=4-9).

(E) Representative Gallyas silver staining of NFTs (black) in the amygdala of young, adult and aged TAU58/2 mice. No staining was observed in non-transgenic brain tissue. Scale bar, 50µm.

(F) Quantification of numbers of NFTs per mm² (***, p<0.001; ****, p<0.0001; n=6-9).

Figure 2 Early-onset disinhibition-like behavior in TAU58/2 mice.

(A) Example traces of young, adult and aged TAU58/2 mice and non-transgenic littermate controls in the EPM, comprising two open and two closed (grey) arms.

(B) Quantification of relative time spent in the open arms, closed arms and center in the EPM (*, p<0.05; **, p<0.01; ***, p<0.001; ****, p<0.0001; n=10-18).

(C) Quantification of first time to emerge from the closed arms of the EPM into the open (*, p<0.05; **, p<0.01; n=10-18).

(D) Quantification of time mice were mobile and total distance travelled during EPM testing (n=10-18). No significant differences were found.

Figure 3 Increased activity in aged TAU58/2 mice.

(A) Heat map tracing of young, adult and aged TAU58/2 mice and non-transgenic littermate controls in the OF.

(B) Quantification of distance travelled in the OF over 10 min (**, p<0.01; n=6-10).

(C) Time aged mice were mobile each min in the OF over 10 min (*, p<0.05; n=6-10). SEM are depicted as shaded bars.

- 1 **(D)** Quantification of time spent in the inner zone in the OF over 10 min (n=6-10). No significant differences were
2 found.

Przybyla *et al.* **Figure 1**

Przybyla *et al.* Figure 3