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Impulsivity, decreased social exploration, and executive dysfunction in a mouse model of frontotemporal dementia

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ABSTRACT

Frontotemporal lobar degeneration (FTLD) is a neurodegenerative disorder, a major subset of which is characterized by the accumulation of abnormal forms of the protein tau, leading to impairments in motor functions as well as language and behavioral alterations. Tau58-2/B mice express human tau with the P301S mutation found in familial forms of FTLD in neurons. By assessing three age cohorts of Tau58-2/B mice in a comprehensive behavioral test battery, we found that the tauopathy animals showed age-dependent signs of impulsivity, decreased social exploration and executive dysfunction. The deficit in executive function was first limited to decreased spatial working memory, but with aging this was extended to impaired instrumental short-term memory. Tau pathology was prominent in brain regions underlying these behaviors. Thus, Tau-58-2/B mice recapitulate neurological deficits of the behavioral variant of frontotemporal dementia (bvFTD), presenting them as a suitable model to test therapeutic interventions for the amelioration of this variant.

1. Introduction

Frontotemporal lobar degeneration (FTLD) is characterized by atrophy of the frontal and temporal lobes and deposition of abnormal protein aggregates in these areas (Galimberti & Scarpini, 2010; Rademakers, Neumann, & Mackenzie, 2012; Sieben et al., 2012). Common proteinopathies involve the accumulation of tau, a protein that under physiological conditions, is mainly localized to the axon of mature neurons where it binds to and stabilizes microtubules; however, tau has also been found in the dendritic compartment where the protein has a role in targeting the kinase Fyn to the dendritic spines (Ittner et al., 2010). Under pathological conditions such as FTLD, tau becomes hyperphosphorylated and forms filaments that eventually form microscopic lesions known as neurofibrillary tangles (NFTs) (Ittner et al., 2015).

FTLD has been difficult to diagnose due to the heterogeneity of the associated symptoms, which affect behavior, language and cognition (Bigio, 2013; Mendez, 2004; Seltman & Matthews, 2012). Clinically, the three syndromes associated with FTLD are jointly classified as frontotemporal dementia (FTD) and include behavioral variant frontotemporal dementia (bvFTD) that affects social skills, emotions, personal conduct, and self-awareness, and two language variants, primary progressive aphasia (PPA) and semantic dementia (SD) (Hodges et al., 2004). More specifically, bvFTD presents with changes in social behavior and conduct, such as loss of social awareness and social withdrawal, restlessness and poor impulse control leading to compulsive behaviors including stereotyped hair-pulling and skin picking (Eslinger, Moore, Anderson, & Grossman, 2011; Lindau et al., 2000; Mendez & Perryman, 2002; Pressman & Miller, 2014; Snowden et al., 2001, 2003). At later stages, patients develop deficits in executive function: they have problems planning, coordinating and executing simple tasks (Harciarek & Cosentino, 2013; Huey et al., 2009; Johns et al., 2009; Moy et al., 2004; Stopford, Thompson, Neary, Richardson, & Snowden, 2012). The clinical features can be complicated by motor neuron signs, parkinsonism, and gait disturbances, with some patients developing motor problems resulting from motor neuron pathology (Devenney, Vucic, Hodges, & Kiernan, 2015; Merrilees, Klapper, Murphy, Lomen-Hoerth, & Miller, 2010). FTD is the second most common type of presenile dementia and the fourth most common type of senile dementia, although it is among the more costly due to its symptom characteristics (Neary, Snowden, & Mann, 2005; Seltman & Matthews, 2012).

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To elucidate the contribution of hyperphosphorylated tau pathology to the behavioral manifestations and cognitive deficits observed in FTD, we analyzed the tau expression pattern and studied the effects of tau overexpression by subjecting P301S tau transgenic Tau58-2/B (Tg) mice to a behavioral test battery probing for signs and symptoms relevant for FTD. We analyzed Tau58-2/B mice of three age groups to investigate whether with progressive tau accumulation this would be associated with more pronounced behavioral changes. We found that this murine model is histologically characterized by progressive deposition of hyperphosphorylated forms of tau in neurons. In addition, we found deficits in behaviors modeling the symptoms of bvFTD, including increased impulsivity and risk-taking behaviors, decreased social interest, and executive dysfunction. The distinctive behavioral phenotype was augmented with advanced age, reflecting the age-dependent tauopathy that characterizes the Tau58-2/B mice. Together, this set of FTD-like phenotypic traits and a distinct brain pathology renders the Tau58-2/B strain a suitable model for bvFTD, with the prospect of determining whether therapeutic interventions also ameliorate the phenotype that characterizes the behavioral variant of FTD.

2. Materials and methods

2.1. Mouse models

Tau58-2/B mice (Tg) express the human 0N4R tau isoform together with the P301S mutation under control of a murine Thy1.2 promoter on a C75Bl/6 background (Tau58, Novartis Institutes for Biomedical Research, Basel, Switzerland). Mice from the Novartis colony were separately shipped to Australia to establish independent colonies. One colony was mainly analyzed histologically (Van Eersel et al., 2015). We established a separate colony by continued breeding of Tau58 onto a C57BL/6 background, generating Tau58-2/B mice. Non-transgenic littermates (wild-type, Wt) were included as controls.

2.2. Experimental design

For behavior, mice were divided into the following age groups: 2–3 months, 6–7 months, and 10–11 months. Animals were housed in groups of 2–5 animals per cage. They were kept on a 12 h light/dark cycle (light on at 8:00AM, with testing during the light period) with free access to food and water unless otherwise stated. For behavioral experiments, the Tau58-2/B mice were directly compared with Wt littermates (5 males and 5 females per genotype per age-group), and tested cross-sectionally using the following experimental sequence: SHIRPA screen, open field, social exploration, light/dark box, Y-maze, and puzzle-box (Supplementary Tables 1 and 2). Testing of any mouse did not exceed 2 h a day, starting with the least stressful tests from merely observational and explorative to more challenging and demanding. For histological studies ($n = 3$ per age group), the 6–7 month group was used after the behavioral data had been obtained (by then 7–8 months old) and the 10–11 month group after the behavioral data had been obtained (by then 11–12 months old). A separate batch of 16 months old Tau58-2/B mice was included for histology. All animal experiments were approved by the Animal Ethics Committees of the University of Queensland and all procedures complied with the statement on animal experimentation issued by the National Health and Medical Research Council of Australia.

2.3. Histology

Animals were anesthetized, perfused, and brains removed and post-fixed in 4% paraformaldehyde at 4 °C overnight, dehydrated, and then embedded in paraffin. Seven μm-thick brain sections were cut with a microtome in the frontal or sagittal plane and mounted on silane-coated slides. Brains of 7–8, 11–12, and 16 month-old Tau58-2/B mice were analyzed for the presence of pathological tau species (Xia, Li, & Götz, 2015) (Fig 1). The following anti-tau antibodies were used: pSer235 (1:500, Thermo Scientific), pSer422 (1:500, Thermo Scientific), AT8 (pSer202/pThr205 Tau, 1:500, Thermo Scientific), AT100 (pThr212/pSer214 Tau, 1:500, Thermo Scientific), AT180 (pThr231/pThr235 Tau, 1:500, Thermo Scientific), and HT7 (pan Tau, 1:500, Thermo Scientific), which recognizes total tau. Bielschowsky silver staining was employed to reveal NFTs (Ke, Delerue, Gladbach, Götz, & Ittner, 2009).

2.4. Murine neurobehavioral screen and motor abilities

A comprehensive modified SHIRPA screen (Rafael, Nitta, Peters, & Davies, 2000; Rogers et al., 1997) was performed. Using this test battery, physical characteristics, sensory reactions and reflexes, as well as motor abilities were investigated (for a complete checklist and photos of the setups used see Supplementary Data). The collected physical characteristics included the body weight and general appearance. Next, mouse behavior was observed which included transfer behavior, spontaneous activity, and the occurrence of tremors, palpebral closure and gait (Supplementary Fig. 1). Subsequently, reactions to simple stimuli such as touch escape, trunk curl, and the reaching reflex, Preyer reflex, and the toe pinch reflex were assessed. Finally, basic motor abilities were measured using the grip strength, wire hanging and accelerating Rotarod tests.

2.5. Exploratory behavior, sociability and anxiety

General exploration and social exploration (Callaerts-Vegh, Leo, Vermaercke, Meert, & D'Hooge, 2012; Crawley, 1985) were examined using a 30×30 cm^2 square arena of Plexiglas. Animals were placed in the experimental room 30 min before the test started. They were then placed individually in the arena (600 lux) for 10 min, where their movement was recorded using EthoVision video tracking equipment and software (Noldus, Wageningen, The Netherlands). Total distance traveled and velocity were included as measures of locomotor activity. Time spent exploring the center (within an imaginary inner square of 20×20 cm) and the corners, and the number of visits to the center and corners were recorded as a measure of anxiety-like behaviors. In addition, heat maps were generated using a custom-made program to examine anxiety and thigmotaxis (wall-hugging behavior) (Van der Jeugd, Blum, et al., 2013; Van Der Jeugd, Vermaercke, et al., 2013).

For the assessment of sociability, the open field arena contained a cage with a diameter of 10 cm and a height of 20 cm holding an unfamiliar mouse of the same gender. Again, total distance traveled and velocity were included as measures of locomotor activity. The time exploring the stranger mouse (within an imaginary annulus of 5 cm around the cage containing the mouse), and the number of visits to the center of the arena was recorded as a measure of social exploration.

2.6. Anxiety, impulsivity and risk-taking behaviors

The light/dark box arena consisted of a Plexiglas box divided by a small underpass into two compartments: a larger brightly lit zone (58 cm long, 28 cm wide, 750 lux) and a smaller covered dark zone (15 cm long, 28 cm wide) (Crawley, 1985; Tasan et al., 2009). Prior to the test, animals were habituated to the dark for 30 min. They were then placed in the dark chamber of the apparatus facing away from the door and tracked for 5 min using EthoVision software (Noldus). The latency to the first entry into the light, the time

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