Accepted Manuscript

Title: Mouse models of frontotemporal dementia: A comparison of phenotypes with clinical symptomatology

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Please cite this article as: Ahmed, Rebekah M, Irish, Muireann, Eersel, Janet van, Ittner, Arne, Ke, Yazi D, Volkerling, Alexander, Hoven, Julia van der, Tanaka, Kimi, Karl, Tim, Kassiou, Michael, Kril, Jillian J, Piguet, Olivier, Götz, Jürgen, Kiernan, Matthew C, Halliday, Glenda M, Hodges, John R, Ittner, Lars M, Mouse models of frontotemporal dementia: A comparison of phenotypes with clinical symptomatology.Neuroscience and Biobehavioral Reviews http://dx.doi.org/10.1016/j.neubiorev.2017.01.004

Highlights

- Frontotemporal dementia is the second most common form of young onset dementia.
- There is much clinical, pathological and genetic heterogeneity within FTD.
- Mouse models focusing predominantly on recapitulating neuropathological and molecular changes of disease have been developed, with most transgenic lines expressing a single specific protein or genetic mutation.
- Together with the species-typical presentation of functional deficits, this makes generalized conclusions drawn from these models that are directly translatable to humans difficult.
- Understanding the phenotypical presentations in mice and how they may relate to clinical symptomology in humans is essential for advancing translation in FTD.

Mouse models of frontotemporal dementia: a comparison of phenotypes with clinical symptomatology

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Key words: Frontotemporal dementia, transgenic, mouse, Amyotrophic lateral sclerosis,

behavioural neurology

Conflicts of interest
No author reports a conflict of interest

Abstract

Frontotemporal dementia (FTD) is the second most common cause of young onset dementia. It is increasingly recognized that there is a clinical continuum between FTD and amyotrophic lateral sclerosis (ALS). At a clinical, pathological and genetic level there is much heterogeneity in FTD, meaning that our understanding of this condition, pathophysiology and development of treatments has been limited. A number of mouse models focusing predominantly on recapitulating neuropathological and molecular changes of disease have been developed, with most transgenic lines expressing a single specific protein or genetic mutation. Together with the species-typical presentation of functional deficits, this makes the direct translation of results from these models to humans difficult. However, understanding the phenotypical presentations in mice and how they relate to clinical symptomology in humans is essential for advancing translation. Here we review current mouse models in FTD and compare their phenotype to the clinical presentation in patients.

Introduction

The term frontotemporal dementia (FTD) refers to a group of neurodegenerative disorders characterized by atrophy of the frontal and anterior temporal lobes of the brain. Prevalence studies suggest that FTD is the second most common cause of young onset dementia (Ratnavalli et al., 2002; Rosso et al., 2003). Two main clinical syndromes of FTD exist, based on the predominant clinical features at presentation: behavioural variant FTD (bvFTD), where there is deterioration in social function and personality; and primary progressive aphasia (PPA), with an insidious decline in language skills. PPA is further subdivided based on the nature of language breakdown into semantic variant primary progressive aphasia (sv-PPA), and non-fluent or agrammatic aphasia (progressive non-fluent aphasia: PNFA) (Gorno-Tempini et al., 2011; Hodges and Patterson, 2007). FTD overlaps with ALS at a clinical, genetic and pathological level (Mitsuyama and Inoue, 2009), a position confirmed with the discovery of the *C9ORF72* repeat expansion in FTD, FTD-ALS and ALS cases (Hodges, 2012).

Each of the FTD syndromes presents with distinct clinical symptoms, neuroimaging, and pathological profiles (Table 1). Considerable overlap and heterogeneity exist within and between the syndromes, with limited correlations between clinical phenotype, underlying pathology and genotype. Given this complexity, the development of animal models of FTD has proven difficult. Currently available mouse models focus on the genetic causes and pathological changes and these only imperfectly correlate with clinical phenotypes. Here, we review current transgenic mouse models and compare their phenotypes to clinical features and functional deficits in FTD, which may guide the development of disease-modifying therapies.

Pathology of FTD

Both sporadic and autosomal dominant FTD are associated with a range of underlying pathologies, classified according to the protein predominantly accumulating in patients' brains. These proteins include the microtubule-associated protein tau, with different tau isoforms being affected in FTD subtypes such as 4-repeat tau (progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) or globular glial tauopathy (GGT) that is characterized neuropathologically by widespread globular oligodendroglial and astrocytic tau inclusions (Ahmed et al., 2013), 3-repeat tau (Pick's disease), and mixed 3- and 4-repeat tau forms;TAR-DNA binding protein (TDP)-43 (type A to D; for details see (Mackenzie et al., 2011)); and fused in sarcoma (FUS). In bvFTD, any of these pathological variants can be found, with tau or TDP-43 positive cases found at similar frequencies (Josephs et al., 2011; Seelaar et al., 2011). In sv-PPA the predominant pathology is TDP type C (Josephs et al., 2011; Rohrer et al., 2010). The pathology of the other language variants is more variable and includes tauopathies, and TDP-43 proteinopathies. The co-occurrence of FTD and ALS is strongly suggestive of an underlying TDP-43 pathology (typically type B) (Seelaar et al., 2011). Recent research has suggested that FTD and ALS may potentially result from a contiguous (almost 'prion-like') spread (Braak et al., 2013; Ludolph and Brettschneider, 2015; Tan et al., 2015). This occurs in a recognised centrifugal pattern with 4 stages of spread

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in ALS beginning in the motor neocortex, progressing to the spinal cord and brainstem, with involvement of fronto-parietal regions and finally the temporal lobes (Brettschneider et al., 2013). Such a pattern of spread may explain the development of cognitive symptoms in ALS and the spectrum of ALS and FTD. In behavioural variant FTD (bvFTD) pathological spread has been suggested to develop with a fronto-occipital gradient involving initially the frontal regions, and then pre-motor, primary motor, parietal and occipital cortex (Brettschneider et al., 2014).

Genetic causes of FTD

About 25-33% of FTD patients have a family history with an autosomal dominant pattern of inheritance (Rohrer et al., 2009; Rohrer and Warren, 2011; Rohrer et al., 2015a; Rohrer et al., 2015b), most commonly associated with bvFTD (Seelaar et al., 2008). The three most common genes involved in FTD are *C9ORF72*, microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*). Mutations in other, much less frequent, gene loci include *VCP*, *CHMP2B*, *FUS*, *TARBP*, *DCTN1* and *SQSTM1*. The frequency of each mutation varies according to the geographical location. In a USA-based cohort (DeJesus-Hernandez et al., 2011) *C9ORF72* was the most common mutation, whereas in a Dutch cohort (Simon-Sanchez et al., 2012) *MAPT* mutations were more common, and in a UK-based cohort *C9ORF72* expansions and *MAPT* mutations occurred with equal frequency (Mahoney et al., 2012). Clinical phenotypes vary across the different genetic syndromes, but certain phenotypes are more commonly associated with specific mutations. For *GRN* mutations, the most common phenotypes are bvFTD, followed by PNFA and corticobasal syndrome (Chen-Plotkin et al., 2011; Yu et al., 2010). *MAPT* mutations are also most frequently associated with bvFTD, but language presentations including semantic impairment have also been described (Seelaar et al., 2008). For both *MAPT* and *GRN* mutations, patients can present with parkinsonian motor symptoms (Rohrer and Warren, 2011). Therefore, extrapolating from the clinical presentation to the underlying pathology or genetic abnormality remains inaccurate.

Rationale to model FTD in mice

Given the heterogeneity of FTD, a wide range of transgenic mouse models have been designed, predominantly aiming at recapitulating neuropathological and molecular changes of disease. Mice, as the most commonly used model organism, have a neuronal network similar to humans and allow for molecular and functional studies at the gene and protein level (Roberson, 2012). As model systems, however, most transgenic lines focus on a specific protein or genetic mutation. Together with the species-typical presentation of functional deficits, this limits the extent to which we can generalize from findings from these models to humans. Therefore, understanding the phenotypical presentations in mice and how they relate to clinical symptomology and functional deficits in humans is essential for advancing translation.

Importantly, mouse models of FTD offer the potential to help understand the pathological mechanisms that underlie the clinical features of the disease *in vivo*. A major advantage of these models is that they allow for the monitoring of early pathological changes, which is difficult to achieve in humans with the current diagnostic standards. A plethora of *in vivo* and *ex vivo* techniques enable studying pathological changes in mouse models up to the molecular level. Animal models also offer the potential to establish proof-of-principle evidence for targeting specific pathomechanisms, for example by using genetic tools such as knockout mice, or to trial treatments and examine their effects on underlying pathological processes at different (early) disease stages. For example in Alzheimer's disease, a number of treatments have shown promise at the mouse model level, yet extrapolating these findings to humans has been troublesome.

In FTD, which predominantly involves emotional behavioral and language changes – cognitive domains that might lack clear equivalents in other species – finding animal models that reflect these changes and functional deficits has proven difficult. On the other hand, recently pervasive changes in physiology and metabolism in FTD have been suggested, which may be easier and more valid to study in mouse models, including their impact on behavioural and cognitive changes (Ahmed et al., 2016c; Fletcher et al., 2015). Although this

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review focuses on mouse models of FTD and their potential contribution to understanding disease, other species – both of lower (e.g. *C. elegans* or *Drosophila*) or higher order (e.g. primates) – are likely to contribute within their own realms. Accordingly, no single species will likely be sufficient to capture the marked heterogeneity of FTD presentations and combinations across mice, and other species may be required.

A new approach: examining clinical features/functional impairment in FTD and transgenic mouse models

Transgenic mouse models, alone or in combination, have been key to understanding fundamental molecular pathomechanisms in FTD and other neurodegenerative conditions (Boxer et al., 2013; Roberson, 2012) [For a list and description of currently available mouse models see http://www.alzforum.org/research-models/search]. There is little doubt that this will continue to be the case and that these models will provide in-depth understanding of underlying pathomechanisms. However, given the complexity of FTD genetics and pathology and the heterogeneous phenotypes across mouse models in terms of pathology and functional impairments, it is important to assess existing and novel transgenic mouse models by taking the clinical symptoms and functional deficits of human FTD into account. This may establish confidence in mouse model-based therapeutic developments. A holistic approach where multiple models are examined based on functional impairments in relation to clinical presentations and functional deficits in humans may facilitate conclusions that will aid understanding of brain networks involved. This will in turn aid earlier diagnoses and targeting of treatments. Therefore, we review FTD mouse models in the context of the functional impairments seen in human FTD including behavioral, socioemotional, memory, language, eating and metabolism, and motor. Figure 1 shows the specific phenotypes reported in a selection of current transgenic mouse models of FTD, and proposed future directions.

Behavioural changes in FTD

Behavioral changes in humans

Assessment of behavioral changes represents a cornerstone of the investigation of bvFTD, forming the basis of the current diagnostic criteria (Rascovsky et al., 2011). Patients with bvFTD typically present with changes in behavior ranging from apathy, reduced motivation, inertia, and a lack of interest in previous hobbies(Piguet et al., 2011), to disinhibition with impulsive and often socially inappropriate actions, such as overspending, gambling, or sexually inappropriate remarks (Rascovsky et al., 2011). Mental rigidity and stereotypical behavior are also widely reported by caregivers, leading to alterations in food preferences and eating behavior (see below). Interestingly, recent studies have elucidated commonalities in the neural substrates of behavioral changes in FTD. For example, both disinhibited (Hornberger et al., 2011) and apathetic (Go et al., 2012) behaviors relate to atrophy in the orbitofrontal cortex, one of the core sites of early pathology (Seeley, 2008).

Behavioral changes in mouse models

Concerted efforts have been directed at modeling behavioral changes and socioemotional dysfunction in transgenic mouse models of FTD (Roberson, 2012). Behavioural changes including disinhibition and apathy have been reported in mutant tau transgenic mouse lines. These specific behavioral changes display in mice as hyperactivity assessed in the open field arena (with increased locomotor activity and altered exploration patterns of the novel environment), or reduced anxiety in the elevated plus maze, light/dark chamber, and cued fear-conditioning paradigms (Cook et al., 2014; Pennanen et al., 2006; Przybyla et al., 2016; Van der Jeugd et al., 2016). The contribution of fear-associated memory deficits, however, remains unclear. These types of behavioral alterations in tau transgenic mice are thought to result mainly from pathology in the amygdala, although detailed investigations of the orbitofrontal cortex integrity are lacking, despite the use of pan-neuronal promoters that drive expression throughout the forebrain. This may be partly due to studies focusing in their behavioral analysis on well-defined anatomical structures, such as the hippocampus and amygdala (Pennanen et al., 2004). Interestingly, young tau transgenic mice display impaired nest-building behavior, suggesting apathy (another common symptom observed in FTD

patients) (Warmus et al., 2014), or decreased attention. Recently a forebrain-specific (CaMKII α promoter), human mutated Tau (hTauP301L+R406W) knock-in mouse was generated which showed heightened anxiety and depressive/ apathetic behavior (Koss et al., 2016). Similar to tau transgenic mice, *GRN* knockout mice display impaired fear conditioning (Filiano et al., 2013) and remain immobile for longer periods in the forced swim test (Yin et al., 2010), which may relate to a depressive-like state. This suggests a complex alteration to emotional behavior in *GRN* knockout lines. A recent adeno-associated virus (AAV)-based model expressing human *C9ORF72* poly-GC-repeats similarly presented with hyperactivity and anxiety-like exploration in the open field arena (Chew et al., 2015). While two transgenic mouse lines expressing bacterial artificial chromosomes (BACs) containing the full human C9ORF72 gene and ~500 or ~1,000 poly-GC repeats resulted in disease-like neuropathological changes (RNA foci and RAN dipeptides) without behavioral deficits or neurodegeneration (O'Rourke et al., 2015; Peters et al., 2015), a recent C9ORF72 BAC mouse line with ~500 poly-GC repeats presented with both neuropathological changes, paralysis, reduced survival, and also anxiety (Liu et al., 2016). The introduction of these C9ORF72 BAC models will provide the basis for function in-depth studies of associated pathomechanisms *in vivo*.

In a number of mouse models, anxiety paradigms are used, such as the elevated plus maze or open field arena. However, locational memory dysfunction may significantly contribute to the displayed behavior, which needs to be taken into consideration when interpreting this data (Dvorkin et al., 2008). Reduced levels of anxiety in mice could be interpreted as excessive risk-taking behavior and/or disinhibition or even emotional dysfunction, which are often observed in FTD patients (Przybyla et al., 2016). These findings illustrate the importance of objective evaluations of emotional behavior in mice along with a comprehensive analysis (including considering test confounders and false positive results), rather than a blunt matching to human symptoms to suggest translation.

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Other clinically relevant behavioral changes in FTD may have correlates in FTD mouse models. Repetitive behavior is a clinical feature in FTD patients (Rascovsky et al., 2011), and may be represented in mice by abnormal repetitive grooming. For example, repetitive grooming has been reported in aged mutant tau-transgenic mice where it increases with age, and is hypothesized to reflect ventral striatum dysfunction (Warmus et al., 2014). Interestingly, this dysfunction correlates with the severity of repetitive behaviors in FTD patients (Josephs et al., 2008). Treatment of tau transgenic mice with the NMDA receptor co-agonist cycloserine to increase NMDA receptor functioning significantly decreased grooming, as well as improved nest building and elevated plus maze performance in these mice, and was thought to mediate its effects through improving synaptic deficits in the striatum (Warmus et al., 2014). Over-grooming has also been observed in transgenic mice with forebrain-specific expression of FTD mutant *CHMP2B*.(Gascon et al., 2014)

Socioemotional changes in FTD

Socioemotional changes in humans

Social dysfunction represents one of the hallmark features of FTD, with caregivers reporting prominent changes in social comportment, appropriateness, as well as reduced social interest leading to social withdrawal (Piguet et al., 2011). Altered emotion processing is widely documented in FTD patients, with recognition of negative emotions such as anger, fear, and disgust, predominantly affected (Kumfor et al., 2013; Werner et al., 2007). These difficulties extend beyond the recognition of facial emotional expressions and lead to a marked inability to empathize or to share the emotional experience of others (Dermody et al., 2016; Rankin et al., 2005). Recently clinical research in FTD has focused on the link between emotion processing and physiological changes in terms of autonomic function in FTD (Fletcher et al., 2015; Guo et al., 2016). In addition, FTD patients have difficulty inferring the thoughts and beliefs of others (i.e., theory of mind) (Adenzato et al., 2010), resulting in an apparent lack of regard for the thoughts and feelings of others (Hsieh et al., 2013; Lough et al., 2006).

Mounting evidence suggests that these deficits map to medial prefrontal and right anterior temporal lobe pathology (Irish et al., 2014a; Rankin et al., 2006).

Socioemotional changes in mouse models

Reduced social engagement and aggression has been demonstrated in a number of *GRN* knockout mice (Filiano et al., 2013; Ghoshal et al., 2012; Petkau et al., 2012; Yin et al., 2010), which may align with the social dysfunction observed in FTD. Interestingly, social and emotional dysfunction were attributed to impaired neuronal activation in the amygdala (Filiano et al., 2013). Mutant tau expressing mice have been reported to display impairments in the Crawley's social interaction test (a test examining sociability and social novelty (Crawley, 2004)) , suggestive of reduced sociability and/or impaired recognition memory (Takeuchi et al., 2011). Furthermore, mice expressing non-functional TDP-43 (lacking the nuclear localization sequence) in forebrain neurons displayed reduced sniffing behavior in the social interaction test (Alfieri et al., 2014). Reduced performance in the social interaction test has also been reported for mice expressing 66 G_4C_2 repeats to mimic C9*ORF*72 repeat expansion (Chew et al., 2015). Mice with forebrain-specific expression of mutant CHMP2B displayed reduced sociability as measured by the Crawley's social interaction test (Gascon et al., 2014). Together, these studies suggest that social dysfunction is a common phenotype across various FTD mouse models, unifying the different types of pathogenic transgenes expressed. Future research in this area could examine the applicability of physiological measures e.g., heart rate, skin conductance, pupillary response and autonomic function previously used in humans to examine social and emotional dysfunction, to mouse models.

Memory dysfunction in FTD

Memory dysfunction in humans

Perhaps the most commonly studied cognitive function in dementia is episodic memory, which refers to the ability to consciously encode, store, and retrieve information regarding previously experienced events. Episodic memory dysfunction represents the hallmark feature

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of Alzheimer's disease (AD), with marked deficits evident on standard neuropsychological tests of visual and verbal recall (de Toledo-Morrell et al., 2000; Irish et al., 2016) and the recall of personally relevant autobiographical memories (Irish et al., 2011b).

Not surprisingly, mouse models of AD rely heavily on behavioral paradigms of hippocampal-dependent learning and memory, with typical tasks such as the Morris water maze, radial arm maze, and novel object recognition tests (Gotz and Ittner, 2008). While crucial to functionally validate disease mechanisms, these behavioral paradigms have not been widely applied to FTD mouse models. This lack of research reflects a long-held, but erroneous, assumption that hippocampal functioning, and therefore episodic memory, is relatively spared in humans with FTD as reflected in the current diagnostic criteria for bvFTD (Rascovsky et al., 2011). Mounting evidence from neuroimaging and neuropsychological studies in humans, however, converge to reveal clear-cut episodic memory deficits in FTD (Hornberger and Piguet, 2012). Patients display memory impairment equivalent to that of matched AD cases across standardized tests of verbal and visual, immediate and delayed, recall (Hornberger et al., 2010; Irish et al., 2014c; Pennington et al., 2011), and retrieval of autobiographical events from the past (Irish et al., 2011a; Irish et al., 2014b). These deficits extend to the domain of source memory, with bvFTD patients being unable to correctly retrieve the spatial or temporal context of previously presented items (Irish et al., 2012a; Söderlund et al., 2008). Recently it has been suggested that verbal impairments in FTD may confound memory function (Baldock et al., 2016), however verbal deficits tend to occur late in the bvFTD disease course. Further, while initially it was assumed that episodic memory impairments in bvFTD stemmed from the degeneration of prefrontal cortical regions (Pennington et al., 2011; Simons et al., 2002), it is becoming increasingly clear that the hippocampus and anterior and medial temporal regions are also involved (Frisch et al., 2013; Irish et al., 2014c). As such, we propose that the long-standing view that behavioral paradigms of hippocampal-dependent learning in FTD mouse models are not relevant to clinical FTD warrants revision

Memory dysfunction in mouse models

Classic episodic memory based tests such as the Morris water maze have, in fact, demonstrated memory impairments in several FTD mouse models, such as for mutant tau (Santacruz et al., 2005; Tatebayashi et al., 2002), TDP-43 (Swarup et al., 2011) and VCP transgenic (Custer et al., 2010; Rodriguez-Ortiz et al., 2013), and *GRN* knockout mice (Ghoshal et al., 2012; Wils et al., 2012; Yin et al., 2010). A new and increasingly popular method of assessing cognitive function in mice is through the use of automated touchscreen operant chambers, which involve training animals to use touchscreen platforms to respond to various stimuli presented on a screen to receive a food reward (Horner et al., 2013; Mar et al., 2013; Oomen et al., 2013). In many cases, these tasks are similar to those used in human cognitive testing (e.g., Cambridge neuropsychological test automated battery) and can be used to assess a range of neuropsychological functions, such as learning, memory, attention and cognitive flexibility. A further benefit of this technique is the low stress levels involved, due to appetitive (positive) rather than aversive reinforcement. Although the technique may have high translational potential (Horner et al., 2013; Mar et al., 2013; Oomen et al., 2013), it is labor- and cost-intensive, and trials often take many weeks of continual testing. Therefore, other paradigms, such as the radial arm maze, T-maze and Barne's maze that cause significantly less stress than, for example, the Morris water maze, remain valid alternatives. Nevertheless, automated and standardized memory testing may overcome the limited comparability of other non-standardized tests, allowing cross-comparison between the various tasks and FTD mouse models. To date, automated touchscreen operant chambers have not been used in FTD mouse models. Testing well-defined human FTD cohorts and corresponding transgenic mouse models of FTD in parallel using similar touchscreen test protocols may therefore serve to increase our understanding of the cognitive deficits in humans with FTD and the underlying molecular mechanisms in mice.

Language impairment in FTD

Language impairment in humans

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Language impairment in FTD is complex with 2 distinct clinical presentations: svPPA associated with progressive breakdown of the semantic memory (the memory system that stores knowledge about objects and words) and PNFA by a progressive breakdown in speech output with effortful, non-fluent speech, characterized by agrammatism, and/or problems with motor-based speech planning, termed apraxia of speech, characterized by groping, segmentation and loss of prosody (Ash et al., 2009; Josephs et al., 2006a). Mutations in FOXP2 have been associated with severe language deficits (Lai et al., 2003). Interestingly, FOXP2 polymorphisms, although not constituting a genetic risk for FTD, when present, reduce language performance and impact on perfusion of language-associated brain areas in overt FTD (Padovani et al., 2010; Premi et al., 2012). Both FOXP2 protein and mRNA were found to be reduced in the frontal cortex in a small cohort of FTD with tau pathology and language impairment (Lopez-Gonzalez et al., 2016).

Language impairment in mouse models

Examining language in mouse models is complex. An interesting example of a clinical symptom-driven approach was provided by Menuet *et al*, who examined whether language anomalies in FTD patients have a correlate in tau transgenic mouse models (Menuet et al., 2011). The study found impaired ultrasonic vocalizations in aged mutant tau mice, which correlated with tau pathology in midbrain and brainstem nuclei controlling vocalization and respiration (Menuet et al., 2011). This may partially resemble the language disorders observed in FTD patients, and awaits confirmation in other lines. It would also be interesting to determine how altered vocalization in tau transgenic mice is affected by tau-targeted therapeutic intervention. The degree to which muscle anomalies of the larynx contribute to impaired vocalization remains unclear, especially as wasting of large muscles has been reported in several tau transgenic lines (Ittner et al., 2008; Lewis et al., 2000; Probst et al., 2000). Showing parallels to FTD in humans, both FOXP2 protein and mRNA levels were reduced in mutant tau transgenic mice (Lopez-Gonzalez et al., 2016). Furthermore, heterozygous depletion of FOXP2 or mutant FOXP2 knockin in mice resulted in altered

ultrasonic vocalization, while learning and memory appeared normal (Fujita et al., 2008; Shu et al., 2005). These findings suggest that ultrasonic vocalization in mice, although not resembling the complexity of human language, may be an according readout in mice to study molecular mechanisms underlying language changes in FTD, for example by crossing mutant FOXP2 mice with FTD models. Yet, the ability to examine semantic deficits in mouse models remains limited, and other approaches examining behavioral responses to vocalisations and learned "rules" and "syntax" may prove fruitful. Recent models have attempted to examine semantic knowledge using food preference studies (Koss et al., 2016), however this approach is problematic given the changes in food preference that are seen in both bvFTD and svPPA. The origins of such changes are inherently complex, attributable to neural atrophy in orbitofrontal cortex, hypothalamus reward structures, and regions supporting semantic knowledge (Ahmed et al., 2016b). Taken together, mouse models may contribute to the understanding of underlying mechanisms in semantic deficits in FTD by using ultrasonic vocalization as a surrogate readout for changes in 'language' formation, but it is unlikely that using a single one species will ever capture the complexity of human language. As such, the study of species with more complex vocalization patterns (e.g. song birds) may prove helpful to elucidate language features of FTD.

Eating behavior and metabolism in FTD

Eating behavior and metabolism in humans

Alterations in eating behavior (hyperphagia or preference for sweet foods) are one of the diagnostic criteria for bvFTD (Ahmed et al., 2014a; Ahmed et al., 2016b; Ahmed et al., 2016c; Ikeda et al., 2002; Rascovsky et al., 2011). It is increasingly recognized that such changes are also present in sv-PPA (Ahmed et al., 2014a; Ikeda et al., 2002). Eating changes affect metabolism and possibly disease progression and prognosis (Ahmed et al., 2014b). Patients with FTD and in particular bvFTD have been shown to have an increased body mass (BMI) index, which has been suggested anecdotally to be less than expected for their caloric intake. Changes in HDL cholesterol and triglyceride levels, with increased fasting serum

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insulin, further suggest a state of insulin resistance (Ahmed et al., 2014b). In ALS a contrasting metabolic pattern has been observed including a state of hypermetabolism (Desport et al., 2005), with low BMI (Dupuis et al., 2011; Jawaid et al., 2010a), but similarly to FTD, hyperlipidemia including increased triglyceride levels (Dupuis et al., 2008) and peripheral insulin resistance (Jawaid et al., 2010b). These variables have been found to affect disease progression in ALS with an increased triglyceride level (Dorst et al., 2011), increased low density lipoprotein (LDL) to high density lipoprotein (HDL) ratio (Dupuis et al., 2008) and the presence of diabetes mellitus thought to be protective against disease progression (Dupuis et al., 2008; Jawaid et al., 2010b). In ALS, low BMI has been associated with worse prognosis; however, it has also been shown that as ALS patients develop cognitive impairment, their BMI increases, suggesting that BMI patterns in ALS in addition to being influenced by peripheral factors, such as muscle wasting, may be centrally mediated (Ahmed et al., 2014c).

Eating behavior and metabolism in mouse models

A detailed understanding of eating behavior and metabolic changes in current FTD mouse models is lacking. There is the suggestion that metabolic changes may be associated with the process of neurodegeneration with several mouse models including TDP-43 and *C9ORF72* associated with weight loss (Chew et al., 2015; Chiang et al., 2010; Dupuis et al., 2004; Shan et al., 2010; Xu et al., 2010). Recent studies have also shown that high fat diet-induced obesity exacerbates tau pathology in mutant tau transgenic mice (Koga et al., 2014; Leboucher et al., 2013). Similarly, it has being shown that diabetes exacerbates tau deposition (Ke et al., 2009), suggesting cross-talk between metabolism and brain pathology in FTD. Furthermore, recent studies in normal mice have suggested that both excitatory and inhibitory input to similar neural correlates to those suggested to be involved in humans with FTD (Ahmed et al., 2015; Perry et al., 2014) results in hyperphagic behavior and sucrose preference, showing that the lateral hypothalamus connects to the reward centers in the ventral tegmental area, that may mediate sucrose preference (Nieh et al., 2015). Future studies

need to determine the effects of neuronal expression of FTD mutant proteins on metabolic parameters and regulation of weight in mice, potentially providing important insights as to what controls eating and metabolism in FTD.

Several ALS mouse models also present with alterations in energy metabolism. For example, mutant *SOD1* mouse models demonstrate hypermetabolism (Dupuis et al., 2004), with a delayed disease onset and increased survival mediated by a high fat diet, while caloric restriction shortens the lifespan and induces lipid peroxidation, inflammation and apoptosis (Dupuis et al., 2004; Patel et al., 2010). A recent study in ALS (Vercruysse et al., 2016) revealed that hypothalamic neurons producing proopiomelanocortin (POMC) were decreased and the endogenous melanocortin inhibitor agouti-related peptide (AGRP) (a known appetite stimulator), increased in mice expressing amyotrophic lateral sclerosis-linked mutant SOD1(G86R). Consistent with a defect in the hypothalamic melanocortin system, food intake after short-term fasting was increased in SOD1(G86R) mice. These findings were replicated in two other amyotrophic lateral sclerosis mouse models based on TDP-43 (Tardbp) and FUS mutations. These findings show a potential correlation with human studies with AGRP found to be elevated in FTD patients and associated with abnormal eating behavior and changes in BMI (Ahmed et al., 2015).

Motor Symptoms and FTD

Motor symptoms in humans

Motor symptoms are a common feature of FTD; a significant proportion of patients develop symptoms reminiscent of Parkinson's disease (i.e., parkinsonism) (Siuda et al., 2014), and FTD and ALS are part of a disease continuum with overlapping clinical presentations (Burrell et al., 2016). Accordingly, 10-15% of FTD patients have concomitant ALS, while 25-60% show evidence of motor neuron dysfunction insufficient to reach criteria for ALS (Burrell et al., 2011; Josephs et al., 2006b; Lomen-Hoerth et al., 2002). Conversely, cognitive testing of ALS patients revealed frequent frontal executive (Ringholz et al., 2005) and language deficits

(Caselli et al., 1993) (Duffy et al., 2007), and behavioral features including apathy, loss of empathy, emotional lability and, less commonly, gluttony, behavioral stereotypes and compulsions (Gibbons ZC, 2008), typical of FTD. Therefore, it has been suggested that FTD and ALS represent extremes of a disease spectrum (Clark and Forman, 2006). Between 10-50% of FTD patients develop features of parkinsonism (Siuda et al., 2014), most frequently observed in 'FTD with Parkinsonism linked to chromosome 17q' (FTDP-17) (Wszolek et al., 2006), with mutations also identified in *MAPT* and *GRN* (Siuda et al., 2014). Furthermore, poly-GC-repeat expansions in *C9ORF72* have been associated with parkinsonism (Park and Chung, 2013). At autopsy, ALS-like motor symptoms are typically associated with TDP-43 pathology, while parkinsonism tends to be associated with tau pathology (Siuda et al., 2014).

Motor symptoms in mouse models

Interestingly, motor deficits were the first prominent motor phenotype described in non-mutant and mutant tau transgenic mouse models of FTD [ALZ17, JNPL3] (Lewis et al., 2000; Probst et al., 2000). In several of the tau models, motor deficits have been described in association with muscle weakness and postural changes [JNPL3(P301L)] (Lewis et al., 2000), paraparesis [Tau P301S (Line PS19)] (Yoshiyama et al., 2007) and dystonic features [Tau R406W] (Tatebayashi et al., 2002). Furthermore, we have described an FTD mutant line, K3, which developed all aspects of FTD-associated parkinsonism including early resistance to L-dopa treatment (Ittner et al., 2008). These mouse models have been instrumental in developing tau-targeted treatments, in particular due to the early-onset progressive motor phenotype (Ittner et al., 2015; van Eersel et al., 2010). Other FTD mouse models have presented with motor deficits. For example, TDP-43 transgenic mouse models are reported to show a wide range of changes from limited motor impairments (Wegorzewska et al., 2009), decreased grip strength and gait abnormalities, to profound muscle weakness (Tsao et al., 2012; Wegorzewska et al., 2009; Wils et al., 2010; Xu et al., 2010). This includes more recent mutant TDP-43 mouse models with controllable transgene expression and rapid development of motor and behavioral deficits, together with FTD-like biochemical and histopathological

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changes (Ke et al., 2015; Walker et al., 2015). It would be of interest to differentiate between motor phenotypes due to muscle wasting, and those resulting from neuronal dysfunction. Here, the association of motor deficits and atrophy/pathology of specific brain regions in human FTD may assist in analyzing specific brain area and structures in FTD mouse models, to elucidate underlying molecular pathomechanisms. Furthermore, motor phenotypes in FTD mouse models, even if not resembling a dominant clinical feature of the human disease, should be used as simple functional surrogate readouts for molecular studies and drug development (van Eersel et al., 2010).

Future directions

While commonly used constitutively expressing FTD mouse models have been instrumental in studying biochemical and histological aspects of FTD and to test therapeutic interventions, they have certain limitations. For example, spread of neuropathological changes which has been documented in humans is difficult to replicate in mouse models with the 'all or none' pattern of constitutive transgene expression. This is of particular relevance given the increasing interest in pathological spread in a prion-like manner and network involvement in FTD and ALS. (Braak et al., 2013; Ludolph and Brettschneider, 2015; Tan et al., 2015). It is increasingly recognized that FTD, rather than reflecting a single protein or neuronal area, represents systems or network degeneration (Ahmed et al., 2016a; Eisen and Turner, 2013; Irish et al., 2012b; Warren et al., 2013). Models proposed include "molecular nexopathies" which suggests that proposed deposition and propagation of proteins along particular networks potentially in a prion-like manner is responsible for phenotypic FTD presentations (Warren et al., 2013). The extension of proposals such as this into animal models offers the potential to not only understand different phenotypic presentations in FTD, but also to trial treatments targeted at particular networks and examine the effects of developmental, environmental and social modifications on the expression of disease phenotypes.

Neuronal network aberrations have been described for transgenic mouse models using electroencephalography (Hall et al., 2015), imaging (Busche et al., 2008), and computational methods to mine EEG data for network performance. Several recording types appear particularly relevant as their network features and can be related to cognitive performance by computational means; hippocampal recordings from the *cornu ammonis* (CA) region for example provide insight on performance and topology of pyramidal/interneuronal connections that are reflected in EEG gamma and theta oscillations and their phase-coupling (Buzsaki and Moser, 2013). Spontaneous and induced hyperexcitability have also been observed in tau transgenic mouse models (Garcia-Cabrero et al., 2013). However, detailed analysis of network topology by EEG or electrophysiology of single cells *in situ* in tau transgenic mice has not been performed. Network alterations in FTD mouse models using, TDP-43 overexpression or C9ORF72 repeat expansion have also not been addressed. Recently optogenetics have made manipulation of neuronal systems in vivo feasible (Marton and Sohal, 2015). Combining functional network analysis by EEG, electrophysiology or imaging with induced changes in activity of specific neuronal ensembles by optogenetics is likely to prove a valuable tool to address whether network aberrations can be manipulated or even reversed by specifically targeting subsets of neurons (e.g. interneurons). Insights from these induced network outputs can then be correlated with cognitive performance.

The use of transgenic promoters with high expression levels, which may be needed to achieve pathology within the life-time of a mouse, limits the ability of cells to regulate protein levels, including during brain development. Although, mutant proteins may be similarly present during development in human mutation carriers, unphysiological levels at embryonic and/or early post-natal stages may have developmental effects that contribute to later phenotypes (Cannon et al., 2012). Using inducible promoters and expression in mature brains is an elegant way to circumvent this problem, and has been used in a number of more recent tau and TDP-43 transgenic mouse models (Santacruz et al., 2005; Xu et al., 2010). Notably, we have recently used inducible human mutant TDP-43 mice to show that short term suppression

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of pathological TDP-43 results in significant improvements of functional deficits, supporting the development of future compounds that target TDP-43 directly to treat FTD (Ke et al., 2015). Furthermore, the availability of advanced genome-editing technologies, such as CRISPR (LaFountaine et al., 2015), allows simple introduction of pathogenic mutations into endogenous mouse genes, or exchange parts or whole loci to humanize the murine gene product, while still using endogenous promoters, as recently reported for the *amyloid-β precursor protein* (*APP*) locus (Saito et al., 2014). Similar humanized FTD models may advance our current understanding of the disease and overcome limitations of current transgenic lines.

While some human FTD cases present with a single type of pathology at autopsy, the heterogeneity of the disease, both pathologically and clinically, is remarkable (Rohrer et al., 2011). Typically, transgenic mouse models express one pathogenic factor, such as mutant tau or TDP-43, which assist in understating specific disease mechanism, but limits translation to the heterogeneous pathology seen in humans. Combinatorial approaches, by intercrossing different transgenic lines, have had a significant impact on understanding disease mechanisms in AD (Ittner et al., 2010; Kulic et al., 2011; Lewis et al., 2001; Oddo et al., 2003). Similar combinatorial approaches utilizing existing FTD models with different transgenes, or in the future by introducing multiple humanized FTD genes, may provide a similar advance in understanding the pathogenesis of FTD.

As outlined above, the clinical presentation of FTD includes a wide range of functional changes, with behavioral, memory, language, eating/metabolic, and motor deficits, in addition to variable neuropathology. Here, FTD mouse models may only recapitulate single or a small number of the clinical features. Accordingly, few FTD mouse model studies have attempted to address multiple aspects of the clinical symptoms, focusing instead on specific phenotypes. While this appears to be a disadvantage at first sight, it offers the opportunity to reduce the

complexity of the human disease to tractable 'building blocks' and allows studying underlying mechanisms of distinct aspects of disease. Combinations of models may then be used to 'rebuild' the complexity of the human disease and inform the cross-impact of individual aspects on each other, to eventually elucidate FTD in its entirety. Future studies of FTD mouse models should consider overlapping, including comprehensive functional testing with complementary paradigms. Furthermore, using established associations between functional deficits and localization of pathology in human FTD should guide the functional analysis of mouse models, rather than retrospective matching of phenotypes to clinical symptoms and pathology. The development of new techniques to examine differing functional deficits across multiple domains (Table 2) may improve hypothesis testing and translation, and thus advance our understanding of human pathophysiology.

Inter-individual genetic and environmental variability in humans contributes to significant differences in disease presentation across patients, including for example incomplete penetrance in *C9ORF72* mutation carriers or varying age of onset (Hodges, 2012).Typically, when generating transgenic mouse models of FTD and other diseases, researchers go to great lengths to achieve identical genetic backgrounds, that is by backcrossing on defined inbred strains (such as C57BL/6J) over more than 10 generations, in order to control for variability and reduce the sample sizes needed to carry out an experiment. This is particularly important for behavioral testing, where variability in genetic backgrounds could result in inconsistent results and the need for very large group sizes. While advocating for clean genetic backgrounds when establishing new transgenic mouse lines, inbred lines likely fail to capture varying phenotypes due to the impact of environmental factors on genetic variability. Utilizing new platform resources with defined variability of genetic backgrounds in mice, such as the Collaborative Cross may in the future allow genetic modifiers in FTD mouse models to be addressed (Bogue et al., 2015) to provide new insight into the pathological and clinical variability of FTD in humans. Such approaches, however, are labor-, resource- and

cost-intensive and will depend on well-defined models of FTD with highly penetrant phenotypes, and are therefore only likely to succeed within large research collaborations. Another approach may be to use the concept of endophenotypes which are heritable traits that are considered to be more highly associated with a gene based neurological deficit than a disease phenotype itself. These endophenotypes can be present in the non- affected relatives of patients affected with disease and suggestions have been made to utilize this approach in diseases such as schizophrenia (Amann et al., 2010; Desbonnet et al., 2009). This approach may aid in understanding underlying disease pathomechanisms and trialing treatments. Taken together, we propose that an approach of (re-)examining FTD mouse models based on functional impairment in human patients will help to elucidate the underlying process of neurodegeneration in FTD (Figure 1). Examining FTD mouse models driven by functional impairment from humans across multiple pathologies and genetic changes will elucidate the specific networks involved and therefore may have greater clinical applicability. Defining FTD mouse models, in isolation or in combination, based on functional deficits driven by clinical observations may also improve drug development and testing. Therefore, complementing the current neuropathology-driven approach of matching pathology to single symptoms with a more functional approach offers unique potential to improve translation of animal models to humans. We suggest that this approach will aid the development of new therapeutic strategies in the hope of modifying disease prognosis and progression.

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Table 1: Clinical and imaging features of FTD

	bvFTD	sv-PPA	PNFA	AD for comparison
Cognitive Domains				
Episodic memory	++	intact	intact	+++
Executive function	+++	intact	intact	++
Orientation	intact	intact	intact	+++
Spatial memory	intact	intact	intact	+++
Eating behavior	+++	++	+	intact
Emotion processing	+++	+++	+	+
Theory of mind	+++	++	intact	intact
Empathy	+++	++		intact
Language	Can develop semantic deficits	Prominent semantic deficits	Non-fluent spontaneous speech, agrammatism, apraxia of speech, anomia.	Can present with language impairment
Predominant areas of atrophy	Frontoinsular cortices, medial prefrontal cortex, spreading to include lateral and medial temporal regions including hippocampus	Anterior temporal cortices (asymmetric). Including hippocampus, spreads to contralateral hemisphere and ventromedial prefrontal cortex.	Asymmetric changes affecting the dominant hemisphere, usually left sided	Medial temporal lobes (entorhinal, parahippocampal, hippocampus), posterior parietal cortices, spreads to frontal and lateral temporal lobes.
Predominant pathological protein deposition	TDP-43, Tau, FUS	TDP-43 type C	Tau or TDP-43 type A	Tau and amyloid

bvFTD= behavioural variant frontotemporal dementia; sv-PPA= semantic variant primary progressive aphasia; PNFA= progressive non-fluent aphasia; AD= Alzheimer's disease. Number of + reflects degree of deficit reported in the literature, increasing number of + reflects increasing deficits.

Table 2: Potential approaches to examine functional deficits between humans and mouse models

Functional domains	Deficits in humans with FTD	Deficits shown in mouse models	Extended approaches to examine these domains in mouse models
Behaviour	Pervasive behavioral changes, apathy, disinhibition, impulsivity, executive dysfunction	Hyperactivity, apathy, anxiety, repetitive behaviors (Cook et al., 2014; Pennanen et al., 2006; Przybyla et al., 2016; Van der Jeugd et al., 2016).	Complex test batteries to exclude confounding memory/motivation deficits; automated touchscreen operant chambers.
Socioemotional cognition	Deficits in emotion processing, lack of empathy	Reduced sociability(Alfieri et al., 2014; Chew et al., 2015; Filiano et al., 2013; Gascon et al., 2014; Takeuchi et al., 2011)	Skin conductance, pupillary response, autonomic function in relation to emotional stimuli
Memory	Episodic memory deficits increasingly recognised	Episodic memory deficits shown on water maze test (Custer et al., 2010; Ghoshal et al., 2012; Santacruz et al., 2005; Swarup et al., 2011).	automated touchscreen operant chambers
Language	Deficits in semantic knowledge and speech output depending on variant.	Reduced vocalisations(Menuet et al., 2011)	Explore mouse vocalisations in different test paradigms
Eating and metabolism	Hyperphagia, rigidity, sucrose preference. Suggestion less weight gain than expected for intake	Eating behaviour not examined. Several models show weight loss(Chew et al., 2015; Chiang et al., 2010). Diet may alter tau deposition (Koga et al., 2014; Leboucher et al., 2013). Several ALS models show hypermetabolism(Dupuis et al., 2004; Patel et al., 2010)	Analyses of weight, fat composition, dietary intake and nutrient preference; metabolic cages
Motor	Parkinsonism, muscle weakness	Weakness, dystonia, Parkinsonism	Examine for relationship between

	and ALS.	(Ittner et al., 2015; Ittner et al., 2008; Lewis et al., 2000; Tatebayashi et al., 2002; Tsao et al., 2012)	muscle wasting weakness and parkinsonian features

Figure 1: Mouse models and reported functional deficits

Figure showing the functional impairments reported in available mouse models and future directions for research to improve clinical and pathological utility of mouse models.

MOUSE MODELS

C9ORF72
Behavioral
Motor changes

TDP-43
Motor changes
Behavioural
Memory

TAU
Motor
Behavioural
Memory

PROGRANULIN
Behavioural changes

VCP
Behavioural/
Social

Future mouse models should focus on differentiation of brain areas

Mapping Brain networks

Explain heterogeneity across pathology and genetics