Title
Multimodal imaging in familial FTLD: phenoconversion and planning for the future

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growth factor, glutamate, etc), and ischaemic stimulation. The approach proposed by Akerman *et al.* has some unique and valuable features: (i) it is specific for allodynia and thus provides a clearly identified biological target ready for future in-depth investigations; (ii) it provides a collimated human/animal paradigm that is likely to minimize some of the intrinsic limitations of the individual approaches when used alone; and (iii) it relies on an efficient abortive/inhibiting treatment, which represents a powerful probe for further dissecting out the mechanisms involved in allodynia occurrence, persistence and resolution. This latter point seems particularly interesting when considering that sumatriptan does not cross the blood–brain barrier. One intriguing hypothesis is that in the minority of allodynic patients who do not respond to sumatriptan, the main mechanism of allodynia is sensitization of second-order neurons of the trigeminovascular system as a consequence of repeated peripheral activation of first-order neurons, whereas a response to sumatriptan limits the site of the aberrant mechanisms to the periphery (first-order neurons).

This new comprehensive approach to modelling migraine and allodynia *in vivo* will be the starting point for further research into the cellular and molecular determinants of allodynia. It will also open up the possibility of studying allodynia using additional strategies in humans, namely morphological and functional neuroimaging, biochemical and genetic evaluation, as well as more advanced electrophysiological techniques. These clinical and preclinical models may also help identify biomarkers for subgroups of patients with allodynia, should such subgroups exist, and hopefully provide a scientific basis for adapting and optimizing migraine treatment to a specific patient's endophenotype.

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Competing interests

The authors report no competing interests.

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Multimodal imaging in familial FTLD: phenoconversion and planning for the future

This scientific commentary refers to 'Longitudinal multimodal MRI as prognostic and diagnostic biomarker in presymptomatic familial frontotemporal dementia', by Jiskoot *et al.* (doi:10.1093/brain/awy288).

Investigators are increasingly using clinical, neuropsychological, biofluid and imaging measures in patients with familial frontotemporal lobar degeneration (FTLD) to improve understanding of the neuropathological substrate of evolving FTLD pathology and to plan for future clinical trials. Molecular alterations are predicted to lead to changes in grey and/or white matter indices on brain MRI, and these MRI changes are predicted to precede the onset of neuropsychological abnormalities and the clinical features of overt symptomatic FTLD (Fig. 1A). In this issue of *Brain*, Jiskoot and co-workers test these predictions by investigating longitudinal MRI changes in members of familial

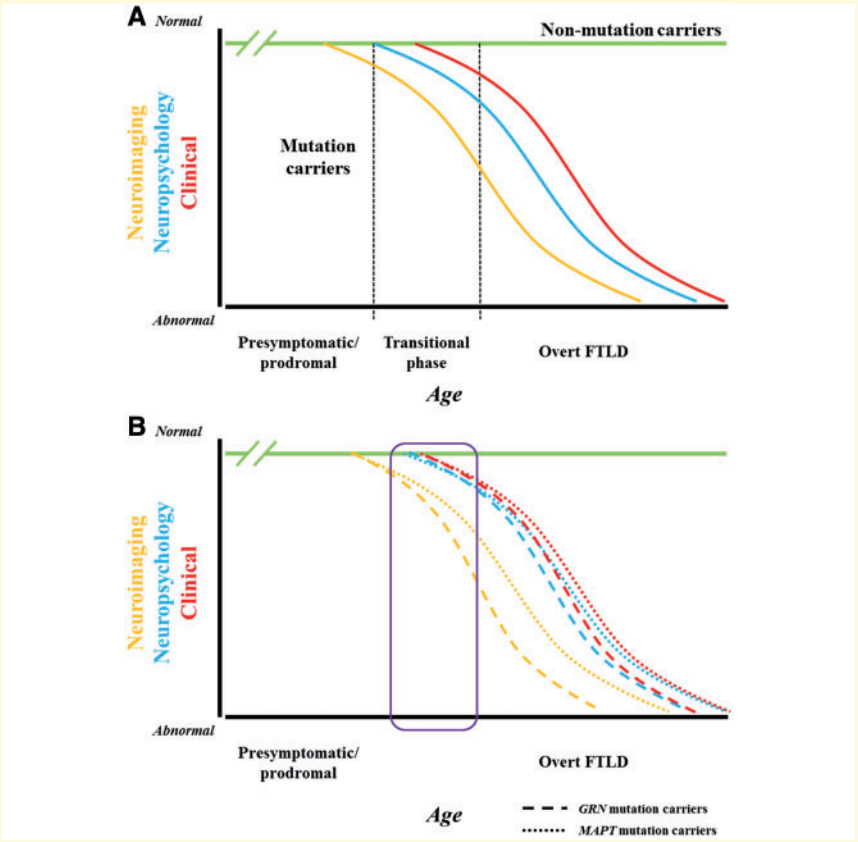

Figure 1 Implications of research findings on the hypothesized framework of evolving familial FTLD. (**A**) Hypothesized framework of evolving familial FTLD. Compared to non-mutation carrier relatives in familial FTLD kindreds (green line), one would expect that among mutation carriers, molecular alterations would lead to changes in grey and/or white matter indices on brain MRI (orange curve), and these MRI changes would precede the onset of neuropsychological abnormalities (blue curve) and overt clinical features of symptomatic FTLD (red curve). Presumably the curves would be sinusoidal—similar to other neurodegenerative disorders such as Alzheimer's disease—with a slow initial slope, then an acceleration phase, then a deceleration phase, followed by a terminal gradual change. Inherent in this framework would be a transitional phase (represented by the column bounded by hashed vertical lines) with variable degrees of neuropsychological abnormalities (particularly in social cognition, executive functioning and language functioning) plus subtle clinical changes (such as mild apathy, disinhibition, altered food preferences, reduced empathy, declines in executive functioning and receptive or expressive language functioning) prior to the development of an overt FTLD phenotype such as behavioural variant frontotemporal dementia or primary progressive aphasia. (**B**) Implications of Jiskoot *et al.* data on the familial FTLD framework. The data in this manuscript relate to eight individuals—five *MAPT* mutation carriers who all converted to behavioural variant frontotemporal dementia and three *GRN* mutation carriers who all converted to non-fluent variant primary progressive aphasia—who were assessed over a 2–4 year timespan (roughly encompassed by the purple rectangle). The data suggest that indices of grey and white matter integrity changed prior to the onset of overt FTLD, with subtle neuropsychological changes around the time of conversion. Plus, the slopes of the imaging and neuropsychological/clinical changes in the *GRN* mutation carriers appeared to be steeper than those in the *MAPT* mutation carriers. With only three timepoints in six of the cases and two time points in the other two, it is difficult to determine if an initial slow slope evolved to a more rapid acceleration phase, as implied by these curves. Furthermore, while the period of assessment likely included the transitional phase between normal neurological functioning and overt FTLD for at least some of these cases, it is challenging to characterize this further based on the available data. Regardless, the longitudinal data in this paper provide intriguing preliminary support for the hypothetical familial FTLD model described above.

FTLD kindreds who were asymptomatic at baseline (Jiskoot *et al.*, 2019).

The investigators analysed grey and white matter indices on brain MRI in the prodromal phase of familial FTLD in kindreds with mutations in the genes encoding microtubule-associated protein tau (*MAPT*) or progranulin (*GRN*). The team compared findings on white matter integrity (using fractional anisotropy), diffusion tensor imaging (DTI) and grey matter volume in persons who evolved from asymptomatic to overt FTLD (converters; $n = 8$) to those in asymptomatic mutation carriers (non-converters; $n = 35$) and non-carriers ($n = 30$) from the same families. They found lower fractional anisotropy values in white matter regions (genu corpus callosum, forceps minor, uncinate fasciculus, and superior longitudinal fasciculus) and smaller grey matter volumes (prefrontal, temporal, cingulate, and insular cortex) over time in converters, which were present from 2 years before overt FTLD. Furthermore, they found that (i) MRI changes evolved more rapidly in *GRN* compared to *MAPT* converters; (ii) *MAPT* converters showed more decline in the uncinate fasciculus than *GRN* converters; and (iii) fractional anisotropy in corpus callosum declined more in *GRN* than *MAPT* converters. Subtle changes on neuropsychological measures were also suggested in the late presymptomatic phase. Jiskoot *et al.* concluded that there is evolving frontotemporal pathology near symptom onset and that these findings highlight the value of multimodal MRI as a prognostic biomarker in familial FTLD. While there are only eight converters in this analysis and sweeping conclusions are not appropriate, one could map the findings into the familial FTLD framework as shown in Fig. 1B.

These data extend what has been suggested on the basis of cross-sectional and longitudinal analyses (Rosen *et al.*, 2002*a*, *b*; Knopman *et al.*, 2009; Whitwell *et al.*, 2010, 2012, 2015; Rohrer *et al.*, 2015). Indeed, these results support the utility of longitudinal MRI in characterizing familial FTLD in the presymptomatic phase. Prior data, particularly from

the Genetic Frontotemporal Dementia Initiative (GENFI) consortium (Rohrer *et al.*, 2015), had suggested that MRI changes precede the onset of FTLD symptoms, possibly by as much as 10 years. That analysis used cross-sectional data and estimated ages of onset for asymptomatic individuals based on familial age of onset, but it is well accepted in the field that the highly variable age of onset in familial FTLD makes predictions of symptom onset tenuous. The findings by Jiskoot *et al.* are therefore notable because they confirm through prospective longitudinal analysis that brain volume and white matter integrity start to decline before overt symptom onset. However, their analysis suggested that these changes may begin about 2 years before symptom onset (they did not detect much difference 4 years prior to symptom onset). While general conclusions should not be made based on such a small sample, the findings clearly highlight the value of prospective longitudinal assessment for addressing this issue. Furthermore, while there are ample data indicating differences in the topography of degeneration across symptomatic *MAPT*, *GRN* and chromosome 9 open reading frame 72 (*C9orf72*) mutation carriers (Whitwell *et al.*, 2012), this is one of the first studies to show topographic differences between genetic groups using longitudinal data.

Jiskoot *et al.* performed their study using a 3 T MRI scanner, available at many clinical and research centres, and using standard image analysis packages. These aspects of the study make the results more generalizable, but it is important to note that many centres still use 1.5 T scanners, and prior studies have indicated that field strength affects the power to detect longitudinal changes (Pankov *et al.*, 2015). Furthermore, all subjects were scanned in the same machine. Although there have been great advances in methods for harmonizing acquisition procedures across centres and scanners (Jack *et al.*, 2015), differences in scanner platforms and software still influence image characteristics, introducing noise into multicentre studies and decreasing sensitivity to detect change. Also, harmonization procedures are most advanced for T_1-weighted MRI that quantifies volumetric changes, whereas harmonization for other types of imaging such as DTI is less well developed. All of these considerations underscore the importance of replicating and expanding these findings in a larger, multisite setting. If more advanced imaging techniques such as DTI really bring unique value for prediction, then additional technical developments will be needed to make this procedure perform optimally in a multisite setting.

The issue of a transitional stage between normal neurological functioning and overt FTLD also warrants comment. Jiskoot *et al.* analysed neuropsychological and imaging data using the onset of an overt FTLD syndrome—behavioural variant FTD (bvFTD) or a subtype of primary progressive aphasia (PPA)—as representing 'symptom onset' and hence conversion. By inference, the imaging changes identified were occurring during a transitional stage in at least some of the cases. The authors acknowledge the difficulty of identifying the exact timing of conversion, and discuss the concept and variable nomenclature of a transitional stage—similar to mild cognitive impairment in the evolution to Alzheimer's disease dementia—in FTLD. However, they did not characterize the clinical features of this transitional stage. This is an important issue because clinicians and researchers will need guidance for when to pursue longitudinal imaging to look for the types of changes identified by Jiskoot *et al.* Data presented in the paper show a trend of mildly increased scores on the Neuropsychiatric Inventory Questionnaire, which captures some of the key neuropsychiatric FTLD features, in the non-converters compared to the non-carriers. Further studies may ultimately demonstrate that neuropsychiatric changes, or other clinical changes, are an early indicator of transition, and lead to a uniform set of operational criteria and terminology for this phase. Additional indicators of transition may ultimately come from protein biomarkers, hopefully measurable from peripheral blood (Rojas *et al.*, 2016).

The authors also plot clinical, neuropsychological and imaging data for the eight converters at 4 years prior to conversion (when data were available), 2 years prior to conversion and at conversion. The Z-scores for the clinical and neuropsychological data are near 0 for almost every case at the evaluation 2 years prior to conversion. This suggests either that these measures are poorly sensitive to evolving FTLD, or that evaluating familial FTLD subjects every 2 years is insufficient to capture evolving features when nearing phenoconversion.

The findings from Jiskoot *et al.* and other reports, underscore the importance of these imaging modalities in familial FTLD clinical trials. Comprehensive prospective assessments consisting of longitudinal clinical, neuropsychological, biofluid and neuroimaging studies of a large number of patients with familial FTLD will be required to predict phenoconversion (that is, when and to what major phenotype—bvFTD versus PPA versus other), to identify the optimal outcome measures, and to estimate sample sizes for clinical trials. The success of future trials of disease-modifying therapies for familial FTLD—presumably using agents that affect tau pathophysiology in *MAPT* mutation carriers, progranulin ± TDP-43-related pathophysiology in *GRN* mutation carriers, and chromosome 9 repeat-associated non-standard (RAN) translation products ± TDP-43-related pathophysiology in *C9orf72* mutation carriers—will likely require the identification of familial FTLD mutation carriers who have undergone at least two longitudinal evaluations prior to commencing therapy in order to assess whether the slope of change on MRI indices is altered during a clinical trial. Furthermore, regulators will likely require that sufficient natural history data have been acquired to determine which neuropsychological and clinical measures, and clinical outcomes, can best show that any intervention has delayed the onset of symptomatic FTLD. There are several prospective multisite studies that involve familial FTLD kindreds in progress (e.g. GENFI,

ARTFL, LEFFTDS), and willingness among members of familial FTLD kindreds to participate in natural history studies is high. In addition, several interventions that may impact FTLD-related proteinopathies are nearing clinical trial readiness. The future thus appears bright for disease-modifying familial FTLD trials. The data by Jiskoot *et al.* underscore the importance of multimodal MRI, as well as a comprehensive battery of clinical and neuropsychological measures, in ongoing observational and future clinical trials.

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Competing interests

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Generating truth from error: insights from neurodevelopmental disorders

This scientific commentary refers to 'Impaired forward model updating in young adults with Tourette syndrome', by Kim *et al.* (doi:10.1093/brain/awy306).

> 'If only *one* person had, *once*, made a bodily movement—could the question exist, whether it was voluntary or involuntary?' (Wittgenstein, 1980).

In the answer are revealed two incontestable features of the biology of voluntary action, incontestable because they are conceptually given and so impregnable to empirical attack. First, to be able to say of someone that she acted voluntarily we must be able to say that she could have acted otherwise even if, in the event, she did not. This implies a plurality of condition-movement associations—including the absence of movement—and a mechanism for selecting between them. A substrate that instantiates this, neurally or mechanically, can only be described as embodying a model, for that is what a set of rules of conditional transformation is. Second, to be able to act voluntarily one must be able to act as one has never acted before, for the learnt acquisition of any ability implies it must have been novel, once, and the ability here must be autonomously acquired. So, the model must be generative, capable of interpolating across the high