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## PERSPECTIVE

# Conceptual framework for the definition of preclinical and prodromal frontotemporal dementia

Alberto Benussi<sup>1,2</sup> | Antonella Alberici<sup>2</sup> | Kiran Samra<sup>3</sup> | Lucy L. Russell<sup>3</sup> |  
 Caroline V. Greaves<sup>3</sup> | Martina Bocchetta<sup>3</sup> | Simon Ducharme<sup>4,5</sup> | Elizabeth Finger<sup>6</sup> |  
 Giorgio Fumagalli<sup>7,8</sup> | Daniela Galimberti<sup>7,8</sup> | Lize C. Jiskoot<sup>3,9</sup> | Isabelle  
 Le Ber<sup>10,11,12,13</sup> | Mario Masellis<sup>14</sup> | Benedetta Nacmias<sup>15</sup> | James B. Rowe<sup>16</sup> |  
 Raquel Sanchez-Valle<sup>17</sup> | Harro Seelaar<sup>9</sup> | Matthis Synofzik<sup>18,19</sup> | GENFI Consortium\* |  
 Jonathan D. Rohrer<sup>3</sup> | Barbara Borroni<sup>1,2</sup>

<sup>1</sup> Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

<sup>2</sup> Neurology Unit, Department of Neurological and Vision Sciences, ASST Spedali Civili, Brescia, Italy

<sup>3</sup> Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK

<sup>4</sup> Department of Psychiatry, Douglas Mental Health University Institute and Douglas Research Centre, McGill University, Montreal, Québec, Canada

<sup>5</sup> McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Québec, Canada

<sup>6</sup> Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada

<sup>7</sup> Fondazione Ca' Granda, IRCCS Ospedale Policlinico, Milan, Italy

<sup>8</sup> University of Milan, Milan, Italy

<sup>9</sup> Department of Neurology, Erasmus Medical Centre, Rotterdam, the Netherlands

<sup>10</sup> Paris Brain Institute – Institut du Cerveau – ICM, Sorbonne Université, Inserm U1127, CNRS UMR, Paris, France

<sup>11</sup> Centre de référence des démences rares ou précoces, IM2A, Département de Neurologie, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France

<sup>12</sup> Département de Neurologie, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France

<sup>13</sup> Reference Network for Rare Neurological Diseases (ERN-RND), Paris, France

<sup>14</sup> Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Toronto, Ontario, Canada

<sup>15</sup> Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, and IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy

<sup>16</sup> Department of Clinical Neurosciences, MRC Cognition and Brain Sciences Unit and Cambridge University Hospitals NHS Trust, University of Cambridge, Cambridge, UK

<sup>17</sup> Alzheimer's Disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain

<sup>18</sup> Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany

<sup>19</sup> Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany

## Correspondence

Jonathan Rohrer, Dementia Research Centre,  
 Department of Neurodegenerative Disease,  
 UCL Institute of Neurology, Queen Square,  
 London, UK.  
 E-mail: [j.rohrer@ucl.ac.uk](mailto:j.rohrer@ucl.ac.uk)

Jonathan D. Rohrer and Barbara Borroni  
 contributed equally to this work.

## Abstract

The presymptomatic stages of frontotemporal dementia (FTD) are still poorly defined and encompass a long accrual of progressive biological (preclinical) and then clinical (prodromal) changes, antedating the onset of dementia. The heterogeneity of clinical presentations and the different neuropathological phenotypes have prevented a prior clear description of either preclinical or prodromal FTD. Recent advances in

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\* See list of collaborators at the end of the article.

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therapeutic approaches, at least in monogenic disease, demand a proper definition of these prodementia stages. It has become clear that a consensus lexicon is needed to comprehensively describe the stages that anticipate dementia. The goal of the present work is to review existing literature on the preclinical and prodromal phases of FTD, providing recommendations to address the unmet questions, therefore laying out a strategy for operationalizing and better characterizing these presymptomatic disease stages.

#### KEYWORDS

definition, frontotemporal dementia, frontotemporal lobar degeneration, mild cognitive and/or behavioral and/or motor impairment, mild cognitive impairment, preclinical, presymptomatic, prodromal

Frontotemporal dementia (FTD) defines a genetically and pathologically heterogeneous group of neurodegenerative disorders with predominant degeneration of the frontal and/or temporal lobes, in which the main neuropathological hallmarks are represented by tau, TAR DNA-binding protein 43 (TDP-43), or fused in sarcoma (FUS) inclusions.<sup>1,2</sup> Clinically, it is characterized by progressive deterioration in behavior, personality, and/or language, often with parkinsonism and psychiatric features. Different phenotypes have been classically defined on the basis of presenting clinical symptoms: the behavioral variant of FTD (bvFTD), which is associated with early behavioral and personality changes;<sup>3</sup> the nonfluent or agrammatic variant of primary progressive aphasia (nfvPPA), with progressive deficits in speech, grammar, and word output; and the semantic variant of PPA (svPPA), a progressive disorder of semantic knowledge and naming.<sup>4</sup> A significant proportion of patients have associated extrapyramidal symptoms,<sup>5</sup> which may form part of either a progressive supranuclear palsy (PSP) or corticobasal syndrome (CBS),<sup>6</sup> and there is considerable clinical overlap with motor neuron disease (MND).<sup>7</sup>

The presymptomatic stages of FTD are still poorly defined and likely encompass a long accrual of progressive biological (preclinical) followed by clinical (prodromal) changes, antedating the onset of dementia. The heterogeneity of clinical presentations and the different neuropathological phenotypes have prevented a prior clear description of either preclinical or prodromal FTD. Recent advances in therapeutic approaches, at least in monogenic disease, make proper definition of these presymptomatic stages more urgent. As postulated for Alzheimer's disease (AD), the ability to intervene early may offer a chance to delay or even prevent neurodegeneration. In AD, the literature has suggested the conceptual framework of a preclinical biologically active process that precedes the onset of a prodromal or mild cognitive impairment (MCI) phase, which is then followed by dementia.<sup>8,9</sup> The heterogeneous presentation of FTD suggests that a wider set of clinical features might present in the prodromal phase compared to AD. Nonetheless, a similar conceptual framework to MCI could be translated to the FTD field. In this view, we may define a preclinical FTD stage in those subjects with an ongoing neuropathological process but without clinical abnormalities, and a prodromal stage in those subjects with the onset and progression of subtle clinical symptoms.

A privileged point of view for studying the preclinical and prodromal phases of FTD is provided by its genetic forms. Indeed, familial aggregation has been reported in a significant proportion of people with FTD (up to 40% of cases), with mutations in the microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*) gene, or a pathogenic expansion in the chromosome 9 open reading frame 72 (*C9orf72*) as the most common cause of monogenic disease.<sup>10</sup> Mutations in *MAPT* lead to abnormal tau accumulation, while *GRN* and *C9orf72* pathogenic variations are associated with TDP-43 deposition.<sup>11</sup> The study of family members bearing a pathogenic mutation has allowed the naturalistic observation of the shift from preclinical and prodromal status to overt disease. There is a wide variation in the age at onset, both within mutation class and within families with the same mutation at least in *GRN* and *C9orf72* mutations,<sup>12</sup> and possible disease modifiers have been recently reported, even though penetrance is high at age 75.<sup>13</sup>

Moreover, several studies have faced the challenge of detecting a clinical, biological, or imaging signature preceding the onset of dementia. A major contribution in this field has been provided by the international consortia devoted to the extensive evaluation of presymptomatic subjects carrying pathogenic mutations. The ongoing European- and Canadian-based Genetic Frontotemporal dementia Initiative (GENFI, [www.genfi.org](http://www.genfi.org)), the US-based Advancing Research & Treatment for Frontotemporal Lobar Degeneration/Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (ARTFL/LEFFTDS), and the Australian Dominantly Inherited Non-Alzheimer Dementias (DINAD) studies, have recruited cross-sectional and longitudinal data with the aim to identify early alterations in at-risk subjects before the expected onset of disease.<sup>12,14–16</sup> In addition, the recently established consortia in Latin America (Research Dementia Latin America [ReDLat]) and New Zealand (Genetic FTD Study [FTDGeNZ]) will be able to further contribute to the description of the natural history of the disease.<sup>17–20</sup> These studies collaborate together under the auspices of the FTD Prevention Initiative (FPI).<sup>12</sup>

It is therefore important for observational studies and clinical trials to determine specific parameters and measures of preclinical and prodromal FTD, to share a common lexicon when identifying patients in the earliest phases of disease. However, several outstanding issues still need proper analysis and scrutiny. To this end, the goal of the

**BOX 1** Unmet questions in preclinical and prodromal frontotemporal dementia

1. How do we define the onset of preclinical disease?
2. How do we define further stages of preclinical disease?
3. Is there a "no disease" phase in genetic FTD preceding the onset of preclinical disease?
4. How do we define onset of prodromal disease?
5. How may we assess mild cognitive and/or behavioral and/or motor impairment (MCBMI) due to FTD?
6. How do we include the prodromal neuropsychiatric features (particularly of *C9orf72*) within this framework?
7. How do we include mild features of parkinsonism or motor neuron disease within this scheme?
8. How do we define phenoconversion?
9. What modifies stage and progression of disease?

present work is to review the existing literature on the preclinical and prodromal phases of FTD, discussing and providing recommendations to the nine pressing questions that need a proper definition (see Box 1). This provides a starting point for operationalizing and better characterizing preclinical and prodromal disease stages of FTD. These recommendations should provide guidance for clinical and research applications, particularly at a time when therapeutic clinical trials are focusing on prodromal and preclinical stages of disease, promoting and harmonizing large-scale multicenter collaborative studies, and increasing funding from national and international agencies.

## 1 | HOW DO WE DEFINE THE ONSET OF PRECLINICAL DISEASE?

The onset of a preclinical disease stage may be theoretically defined by the occurrence of first signs of protein misfolding, presumably initially without either neuronal dysfunction or neurodegeneration, and with no clinical FTD-related symptoms. One of the key questions in the current literature is therefore how we define this switch from a "no disease" stage to a "preclinical stage" with available markers (see Figure 1).

Conceptually, while the disease process may be initiated through misfolded proteins forming neurotoxic oligomers, the first identifiable hallmark of a preclinical disease stage is the abnormal accumulation of pathogenic protein aggregates within cells, including (1) hyperphosphorylated tau, (2) TDP-43 immunoreactive inclusions, (3) FET family proteins (consisting of FUS, Ewing's sarcoma protein [EWS], and TATA-binding protein associated factor 2N [TAF15]), (4) dipeptide repeat proteins (DPR), or (5) still-to-be-defined proteins in those with frontotemporal lobar degeneration-ubiquitin proteasome system (FTLD-UPS) pathology.<sup>1,21</sup>

Reliable in vivo biomarkers able to predict the two main proteinopathies, namely tau or TDP-43, are not yet available. No TDP-43 positron emission tomography (PET) tracer has been investigated as of yet, and tau PET imaging studies have led to variable results, with the main limitation in the primary tauopathies being the non-specific/off-target binding and variable affinity for different tau species.<sup>22,23</sup> Sim-

ilarly, fluid biomarkers of tau and TDP-43 in cerebrospinal fluid (CSF) or blood have not shown specificity for FTLD pathology. While blood phosphorylated tau (p-tau<sub>181</sub> and p-tau<sub>217</sub>) assays have recently been shown to be useful to identify AD, they do not identify primary tauopathies including FTLD.<sup>24-27</sup> Markers of blood and CSF TDP-43 measurements have been developed but are not specific for TDP-43 pathology.<sup>28,29</sup> Phosphorylated TDP-43 markers and CSF TDP-43 real-time quaking-induced conversion reaction (RT-QuIC) may improve specificity,<sup>30,31</sup> but these results await confirmation. TDP-43 aggregates may be found even in a subset of AD patients, or in other neurodegenerative disorders or in some aged people, thus TDP-43 biomarkers may be not completely specific.<sup>32,33</sup>

Markers for the FET proteins have also not yet been developed. Recent work has identified the presence of a CSF measure that is specific to *C9orf72* expansion carriers. One of the key pathophysiological mechanisms in *C9orf72*-related disease is the accumulation of sense and antisense transcripts of the expanded repeats. These RNA transcripts serve as templates for the synthesis of DPRs through repeat associated non-ATG (RAN) translation. So far, only one of these, the glycine-proline-repeating protein or poly(GP), has been shown to be measurable in CSF,<sup>34-36</sup> being increased in *C9orf72* expansion carriers in both the presymptomatic and symptomatic phase, and normal in controls. This suggests it could be useful as a preclinical biomarker in genetic FTD.<sup>37-39</sup> Importantly, reports of autopsy studies in *C9orf72* expansion carriers have also described widespread DPR protein pathology prior to the formation of TDP-43 inclusions and neuronal loss,<sup>40-42</sup> suggesting that at least for *C9orf72* expansion carriers, the onset of the preclinical stage is defined by the presence of DPR proteins rather than TDP-43 pathology.

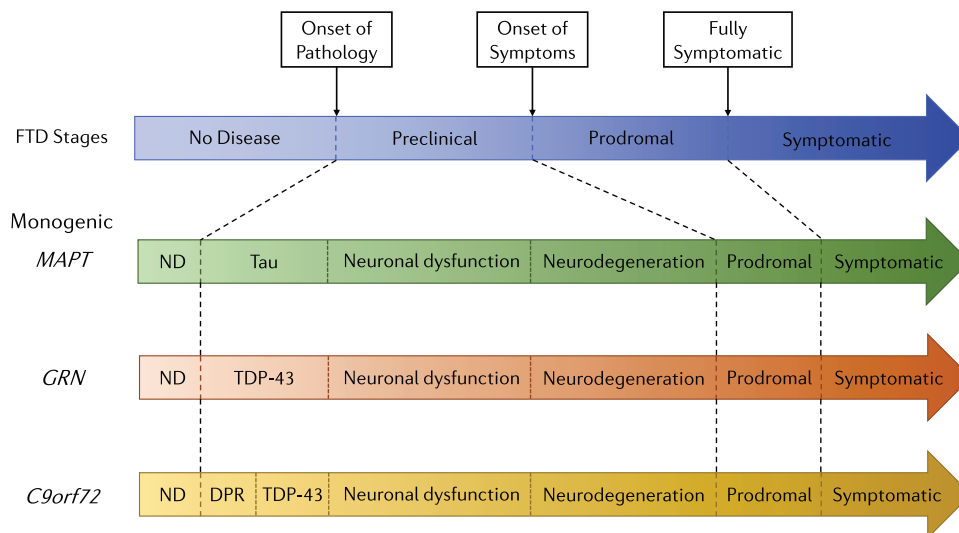
There is also a need for more studies examining the extent of neuropathological findings consistent with FTLD in healthy older people.

**Recommendation:** The preclinical phase of FTD should theoretically extend from the earliest signs of protein misfolding to the onset of the first clinical symptom of FTD. Based on current knowledge, the onset of a preclinical stage cannot be reliably identified with available biomarkers at this time except potentially for those with *C9orf72* expansions. We recommend that ongoing research aims to identify both PET tracers and fluid biomarkers that can sensitively and specifically show the presence of tau, TDP-43, and FET pathology.

## 2 | HOW DO WE DEFINE FURTHER STAGES OF PRECLINICAL DISEASE?

The preclinical disease stage may be characterized by when protein accumulation and misfolding is initiated, but later preclinical stages can also be defined. Accumulation of toxic proteins leads to neuronal dysfunction with multiple cellular mechanisms being affected, including the function of mitochondria and stress granules, autophagy, and transcription. The outcome of this is neuronal loss, that is, neurodegeneration. Both dysfunction and loss of neurons occur prior to the onset of clinical symptoms (see Figure 1).

<sup>18</sup>F-fluorodeoxyglucose (FDG)-PET detects changes in glucose metabolism in the brain with hypometabolism representing neuronal



**FIGURE 1** Disease stages in frontotemporal dementia (FTD). Natural history of FTD and monogenic FTD subtypes. *C9orf72*, chromosome 9 open reading frame 72; DPR, dipeptide repeat proteins; *GRN*, progranulin; *MAPT*, microtubule-associated protein tau; ND, no disease; TDP-43, TAR DNA-binding protein 43

dysfunction. Studies in AD suggest that FDG-PET may be abnormal prior to neuronal loss measured as atrophy on magnetic resonance imaging (MRI).<sup>43–46</sup> FDG-PET is also abnormal presymptomatically in genetic FTD,<sup>47–51</sup> and similar to AD, a few studies have now been performed suggesting that changes occur before structural MRI abnormalities.

Nonetheless, MRI represents one of the most powerful tools to study in vivo neurodegenerative disorders, with a wide range of possible approaches to explore incipient neurodegeneration.<sup>52,53</sup> The majority of imaging studies in preclinical FTD have used volumetric T1-weighted MRI to investigate changes in gray matter structure and to measure brain volume, the rate of brain atrophy, and the volumes of specific brain regions of interest.<sup>54–60</sup> In monogenic FTD, volumetric MRI analysis shows significant brain atrophy, first detectable in the insula, at least 10 years before expected symptom onset.<sup>14</sup> Diffusion-weighted MRI detects white matter damage including axonal loss. In genetic FTD, changes to diffusivity have been found in white matter tracts many years before symptom onset.<sup>61</sup> It needs to be further established if and how these subtle changes in gray and white matter found in T1 and diffusion imaging, respectively, may be used as a marker of early neurodegeneration in preclinical stages at the single subject level.

More recent studies have identified a possible fluid biomarker of neurodegeneration, albeit not specific for FTD. Neurofilament light chain (NfL) protein concentrations both in CSF and in blood reflect axonal degeneration and have been shown during the symptomatic period of FTD to be reflective of disease intensity and progression. In the presymptomatic period, analysis seems to suggest that levels change not long prior to symptom onset, increasing by 3- to 4-fold during conversion.<sup>62–64</sup> While longitudinal NfL measurements could be used to identify mutation carriers approaching symptom onset,<sup>65</sup> NfL needs to be further studied on a single subject basis, and in particular,

studies showing whether it is sensitive enough to detect neurodegeneration prior to early symptoms (i.e., prior to a prodromal stage).

**Recommendation:** Neuronal dysfunction can be measured in advance of neuronal loss with FDG-PET imaging but has been poorly studied in presymptomatic FTD thus far. Further studies are important to establish the earliest time at which dysfunction can be detected prior to structural MRI abnormalities, including investigation of newer measures of impaired neuronal function such as novel PET ligands, neurophysiological and magnetoencephalographic markers, and CSF measures of synaptic dysfunction. The onset of neuronal loss may be identifiable by MRI (especially with the advent of ultra-high-field 7T MRI) or fluid biomarkers such as NfL, but it remains unclear which is the most sensitive (early) or specific marker of neurodegeneration in FTD and what cut-offs or thresholds are to be applied, particularly at the single subject level.

### 3 | IS THERE A “NO DISEASE” PHASE IN GENETIC FTD PRECEDING THE ONSET OF PRECLINICAL DISEASE?

The conceptual timeline of FTD natural history typically includes a healthy stage, with “no disease,” followed by preclinical and prodromal disease to overt dementia (see Figure 1). In monogenic FTD subtypes, some biomarkers appear to be altered from birth and many are abnormal even in young adulthood. This raises the question whether there is a neurodevelopmental dimension to FTD, and the existence of a stage that is without disease, or without neuropathological abnormalities. By analogy with another genetic dementia, Huntington's disease, there may even be fetal neurodevelopmental abnormalities.<sup>66</sup>

Pathogenic loss-of-function mutations in *GRN* lead to haploinsufficiency, with blood and CSF levels of progranulin reduced to < 50% of



normal levels.<sup>67–72</sup> Low serum, plasma, or CSF progranulin levels have high accuracy in detecting pathogenic *GRN* mutations,<sup>72–75</sup> with low levels observed from the earliest time period in *GRN* mutation carriers, likely antedating TDP-43 neuropathology. At present, studies have not been performed in children (< 18 years) to understand whether levels are low from birth, but the assumption is that they are, given the known pathophysiology.<sup>73–75</sup>

As mentioned above, *C9orf72* expansion carriers have widespread DPR protein pathology early in life.<sup>40–42</sup> While similarly to *GRN* mutation carriers studies of fluid biomarkers show abnormal levels (here of raised poly[GP] concentrations) from at least the fourth decade of life,<sup>37,39,76,77</sup> and no studies have been performed in children, there is a less clear assumption of abnormal levels from birth and studies in a pediatric cohort would be highly informative.

**Recommendation:** Based on current knowledge it is not clear if a “no disease” stage exists after normal childhood development, for some forms of genetic FTD. For people with *GRN* mutations, there may well be a phase during which a biological disruption is ensuing, but which is not accompanied by an abnormal accumulation of specific pathologic proteins. For people with *C9orf72* expansions, the accumulation of DPRs appears to occur at least in young adulthood, but how early is unknown. Considering also the higher rate of developmental disorders in offspring of patients with FTD,<sup>78–81</sup> this has suggested the hypothesis of some forms of genetic FTD being neurodevelopmental disorders, in which the boundary with “no disease” is even more indistinct. Studies in pediatric at-risk genetic FTD cohorts, while ethically more complex, will be required to answer these questions more fully.

#### 4 | HOW DO WE DEFINE ONSET OF PRODROMAL DISEASE?

Prodromal FTD may be defined as the presence of subtle cognitive and/or behavioral changes (see Figure 1). Based on studies from large genetic cohorts, the cognitive prodromal phase may start with gradual and progressive executive dysfunction, occurring in isolation or associated with other cognitive changes, such as impaired social cognition or language disturbances. These may be accompanied by behavioral symptoms, such as apathy, disinhibition, loss of empathy, compulsive behavior, and change in appetite or subtle motor deficits,<sup>14,65,82–90</sup> which are observed by the patient, informant, or clinician, and represent a clear change from the person's usual behavior (see Box 2).

Unlike in AD, for which the concept of MCI was developed to define the prodromal stages,<sup>91–93</sup> no detailed characterization of prodromal FTD has been reported. The direct application of the term MCI to FTD is fraught with difficulties given the complex clinical presentation of FTD, which can be heralded by different phenotypes. Attempts to define MCI-like or prodromal stages in FTD have been undertaken with mixed results. Initial criteria for mild behavioral impairment (MBI) excluded serious memory complaints, ignoring cognitive functioning, despite its apparent importance for the early and accurate detection of FTD.<sup>94,95</sup> The term frontotemporal-MCI (FT-MCI) was later proposed, with criteria including also behavioral symptoms but not requir-

#### BOX 2 Proposed recommendation for clinical features of prodromal FTD

Gradual and progressive cognitive and/or behavioral and/or motor changes compared to prior functioning and reported by patient or informant, with preservation of independence in functional abilities of daily living, occurring along with one or more of the following features:

- Objective evidence of a dysexecutive syndrome, occurring in isolation or associated with other cognitive changes, such as impaired social cognition, as measured by tests with established specificity for FTD
- Language deficit, as measured by tests with established specificity for FTD
- Behavioral changes: apathy, disinhibition, loss of empathy, compulsive behavior, and change in appetite
- Signs and symptoms of parkinsonism or motor neuron disease

ing the onset to be insidious and progressive, creating potential confusion with delirium, mania, and other conditions.<sup>96</sup> The phonological similarity in naming with Petersen MCI criteria could also generate confusion.<sup>97</sup> Finally, provisional MBI criteria have been recently proposed, excluding patients younger than 50 years and not including cognitive disturbances.<sup>98</sup> Thus, a unifying characterization of prodromal FTD is currently lacking.

**Recommendation:** The onset of prodromal FTD is characterized by gradual and progressive cognitive and behavioral symptoms, which may be observed by the patient, informant, or clinician, as representing a clear change compared to prior functioning (see Box 2). Given that the onset of prodromal FTD can present with any of behavioral, cognitive, motor or language change, we suggest the label of mild cognitive and/or behavioral and/or motor impairment (MCBMI) to capture the complexity of the clinical phenotype under a single unifying characterization (see next section).

#### 5 | HOW MAY WE ASSESS MCBMI DUE TO FTD?

As with many other neurodegenerative conditions, behavioral and cognitive changes may be present in FTD years before the onset of manifest dementia. These changes clearly describe the switch from preclinical to prodromal disease stage, and a proper description of the first symptoms may further characterize MCBMI due to FTD. Up to now, the most meticulous description of prodromal clinical abnormalities has been performed in at-risk subjects carrying FTD-related pathogenic mutations.<sup>99</sup>

Results from the GENFI study have clearly shown that differences between mutation carriers and non-carriers in neuropsychological measures are apparent about 5 years before the expected onset of dementia, particularly in tests of naming (Boston Naming Test) and executive function (Trail Making Test Part B, Digit Span backward, and Digit Symbol Task), but not in immediate recall and verbal fluency.<sup>14</sup>

Previous studies performed in smaller cohorts of presymptomatic mutation carriers obtained somewhat similar findings.<sup>60,89,100–112</sup>

The wide heterogeneity of clinical presentation and disease progression has so far hindered a clear-cut identification of the core neuropsychological battery tests to adopt for defining MCBMI, both in genetic and in non-monogenic FTD, and for tracking the shift from pre-clinical to prodromal stages. Moreover, for a disease in which behavioral disturbances, including social misconduct, represent the majority of initial symptoms,<sup>113</sup> there is an urgent need to find appropriate standardized tools to detect subtle personality changes preceding the onset of disease.

The assessment of a minimum data set, exportable in different countries, is crucial to define the same outcome measure for clinical trials devoted to delaying or preventing the onset of disease. In this view, a study by the ARTFL/LEFFTDS consortium has shown that the Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (EXAMINER), a computerized battery developed to quantify many facets of executive functions, is a sensitive measure of cognitive changes in presymptomatic FTD.<sup>84</sup> Nonetheless, explicit criteria for the use of objective neuropsychological testing are currently lacking and should be defined to harmonize evaluations.

The Clinical Dementia Rating (CDR) plus National Alzheimer's Coordinating Center (NACC) FTLN rating scale (previously called the FTLN-CDR),<sup>114</sup> may be a promising measure to identify MCBMI, taking into consideration not only cognitive functions but also language impairment and behavioral and social functioning. Patients with MCI (including mild language impairment) and/or MBI, with relatively preserved functional independence, will have a global score of 0.5. Patients who appear clinically to have a dementia, irrespective of the particular FTD phenotype, will have a global score of  $\geq 1$ .<sup>115,116</sup> Recent studies have confirmed the high sensitivity of this scale in identifying patients in the early phases of disease, with very good inter-rater reliability,<sup>15,84,90,117–120</sup> although the low specificity may limit its use as a screening tool.<sup>117,118</sup> Nevertheless, the CDR plus NACC FTLN mostly relies on a co-participant/informant report and may lack objectivity. It also does not include measures of neuropsychiatric disturbance.

**Recommendation:** A provisional definition of MCBMI could rely on the CDR plus NACC FTLN score of 0.5; however, more objective neuropsychological and behavioral measures should be established. Furthermore, any scale aimed at detecting prodromal FTD should incorporate the neuropsychiatric symptoms seen in FTD (see below).

## 6 | HOW DO WE INCLUDE THE PRODROMAL NEUROPSYCHIATRIC FEATURES (PARTICULARLY OF *C9orf72*) WITHIN THIS FRAMEWORK?

A growing body of evidence describes neuropsychiatric symptoms as early markers of decline along the neurodegenerative spectrum.<sup>121</sup> This is of particular interest in prodromal FTD, in which behavioral symptoms represent the core feature of the disease. What is emerging is that, alongside behavioral symptoms already described in cur-

rent clinical criteria for FTD, such as disinhibition, apathy, loss of empathy, perseverative or compulsive behavior, and hyperorality, other neuropsychiatric symptoms are frequently reported. These manifestations, which are still not defined as FTD core symptoms, should be sought during evaluation and should be considered possible presenting symptoms in the prodromal stages.<sup>122</sup> In particular, anxiety and depression as well as hallucinations and delusions may be present in people with FTD, the latter highly expressed in *C9orf72* expansion carriers compared to the other FTD subtypes.<sup>123</sup> As mentioned above, such features are not captured well by current FTD scales such as the CDR plus NACC FTLN.

More complex, and relevant to the discussion above about the potential neurodevelopmental aspects of *C9orf72*-related FTD, is the presence of apparently lifelong personality traits in people with FTD, including autistic or schizotypy traits, features which may have changed little over time, but must be distinguished from behavioral changes, which evolve and progress over time and that might represent prodromal FTD. The former may end up being scored in symptom rating scales leading to the apparent presence of prodromal symptoms but in reality are not actually changes from a "baseline." These features are important to identify in the earliest FTD stages, allowing a better separation of FTD cases from phenocopies or other mimics.

**Recommendation:** Further evaluation of the frequency and phenotype of prodromal neuropsychiatric symptoms (particularly in *C9orf72* expansion carriers) is required, with a focus on longstanding autistic and schizotypy traits as well as more overt neuropsychiatric symptoms. Neuropsychiatric evaluation tools will have to consider past psychiatric or personality profiles to reliably identify new emerging prodromal symptoms.

## 7 | HOW DO WE INCLUDE MILD FEATURES OF PARKINSONISM OR MOTOR NEURON DISEASE WITHIN THIS SCHEME?

A significant percentage of patients with FTD have associated extrapyramidal symptoms, which can be nonspecific, not meeting criteria for a particular disorder, or may fit the criteria for either PSP (Richardson syndrome) or CBS.<sup>5,6,12,124–131</sup> In both sporadic and genetic FTD, movement disorders can sometimes be the initial presentation.<sup>132,133</sup> There is also considerable clinical overlap with MND.<sup>7</sup> Considering that all these diseases are included under the frontotemporal lobar degeneration umbrella term and that most pathogenic mutations may lead to one of these clinical syndromes, initial manifestations of parkinsonism or MND should be identified promptly in the early stages of disease, on par with cognitive and behavioral symptoms. At present, there are no movement disorder scales specific for FTD, although motor behavior may be clinically identified and quantifiable in the prodromal phase by scales designed for other diseases (e.g., the Unified Parkinson's Disease Rating Scale [UPDRS]; Progressive Supranuclear Palsy Rating Scale [PSPRS]; the Amyotrophic Lateral Sclerosis Functional Rating Scale [ALSFRS]).<sup>65,90,117,118,134</sup>

**Recommendation:** Motor symptoms are a common feature in FTD, and it may be argued that the onset of isolated movement disorders in the absence of cognitive symptoms could also be defined as a prodromal phase of FTD. We propose a unified approach, potentially including motor features in the prodromal FTD construct, that is, MCBMI. Further studies assessing isolated initial motor symptoms at the onset of sporadic FTD are required.

## 8 | HOW DO WE DEFINE PHENOCONVERSION?

Applying the definition of “dementia,” namely the presence of cognitive deficits that are significant enough to interfere with instrumental activities of daily living (IADLs), is still challenging in FTD. In early FTD disease stages, patients may present with preservation of IADLs,<sup>133,135,136</sup> at least as listed for assessment of other disorders, thus not satisfying the diagnosis of dementia, despite the presence of significant behavioral disturbances, executive deficits, or language impairment. Instead of measuring the impact on IADLs, which are somewhat loosely defined in clinical practice and that are useful indicators to track changes from a biological process to a clinical condition in AD, a broader neuropsychiatric approach may be more helpful to define conversion to FTD. In psychiatry, the presence of a mental disorder is defined as a condition that causes significant distress or impairment of personal functioning in social, occupational, or family activities, and must not be merely an expectable response to common stressors and losses.<sup>137,138</sup>

It is worth noting that the National Institute on Aging–Alzheimer's Association criteria specifically state that a diagnosis of dementia is appropriate in the setting of interference with the ability to function at work or at usual activities, and that the change represents a decline from prior functioning, with changes in personality or behavior plus one other more classic cognitive domains.<sup>139</sup>

As such, conversion to dementia could be defined by symptoms that lead to one or more of the following consequences: (1) the appearance of interference with IADLs, including IADLs relevant to the types of changes induced by FTD; (2) impairment of social/occupational abilities compared to prior functioning, despite preserved autonomy (e.g., normal independence but loss of relationships due to personality changes, inability to hold a job, inadequacy to parent children, language disturbances); (3) a global CDR plus NACC FTLD score  $\geq 1$ ; (4) fulfillment of consensus criteria for bvFTD or PPA.

The capability to translate abnormal behavior into different social and cultural contexts is yet to be achieved, and transcultural studies defining what is considered socially correct are still lacking. To this end, cooperative and multinational studies are warranted. Furthermore, important implications to consider include extreme behaviors that lead to legal issues such as sexual deviation (paraphilia) or economic difficulties that occur before the detection of a neurodegenerative condition. To this end, co-operative and multinational studies are needed.

**Recommendation:** The current concept of dementia relies on impairment of IADLs, but this may not be sufficient in defining FTD,

which may comprise impairment of social and occupational functioning adversely impacting a normal lifestyle. Integrating the psychiatric definition of a mental disorder along with the definition of dementia could be an attractive alternative to define the symptomatic phases of FTD and may capture a wider range of conversion.

## 9 | WHAT MODIFIES STAGE AND PROGRESSION OF DISEASE?

The risk of progression and natural history of preclinical and prodromal FTD may depend on modulating factors, for which the magnitude and interaction have yet to be determined. It has been postulated that certain lifetime experiences, including education, leisure activities, and occupational attainment, may be proxies of cognitive reserve and may modulate brain resistance and resilience.<sup>140,141</sup> In prodromal FTD, it has been shown that higher educational achievements are associated with greater gray matter volumes, suggesting that subjects with higher education are able to better counteract the detrimental effects of a pathogenetic mutation.<sup>13</sup> Bilingualism, another emerging aspect of cognitive reserve that has been shown to have an impact also in AD,<sup>142-144</sup> has been found to delay the onset of dementia in bvFTD but not in PPA.<sup>145</sup> Longitudinal studies have shown that increased education, but also active lifestyles, may also facilitate both brain reserve and brain maintenance in the prodromal stages of genetic FTD,<sup>146,147</sup> suggesting that cognitive reserve may confer clinical resilience, even in autosomal dominant FTD.

Along with modifiable modulators, even non-modifiable genetic factors have been identified and associated with age at disease onset in FTD. The most established genetic factor, at least in TDP-43 proteinopathies, is the transmembrane protein 106B (*TMEM106B*) gene.<sup>148</sup> It has been suggested that the *TMEM106B* rs1990622 polymorphism might modulate progranulin plasma levels, thus affecting age at symptom onset in *GRN* mutation carriers.<sup>149,150</sup> Accordingly, subjects with prodromal FTD due to *GRN* mutations and bearing the *TMEM106B* TT genotype showed greater functional brain damage than those with CT/CC *TMEM106B* genotypes.<sup>13,151</sup> In prodromal FTD-TDP-43 due to *C9orf72* expansion, the relationship is less clear, and it has been suggested that *TMEM106B* might be able to affect disease pathology, but with an opposite association.<sup>13,152,153</sup> This effect may be an example of the general phenomenon of epistasis, in which a genetic variant is beneficial on some genetic backgrounds but deleterious in others.<sup>152,154</sup> In the same view, other genetic modifiers, such as apolipoprotein E genotype or *MAPT* haplotypes, should be considered.

**Recommendation:** Increased cognitive reserve, comprising education, bilingualism, and active lifestyle, are protective factors for FTD progression, in preclinical, prodromal, and dementia phases. The *TMEM106B* TT polymorphism may increase the risk of progression to prodromal FTD in *GRN* carriers. Identification of disease modifiers is key to correctly ranking the risk of disease progression, to stage prodromal FTD and forecast duration of the MCBMI stage, and to select subjects, reducing heterogeneity and increasing statistical power of analysis in clinical trials.<sup>155</sup>



## 10 | CONCLUSIONS AND PERSPECTIVES

Developing the framework of preclinical disease stages as well as MCBMI-FTD continues to pose a challenge, and two aspects should be considered for future studies. On one hand, we should first carefully define the criteria of MCBMI, which may be conceptualized as a “risk state.” MCBMI may represent the prodromal state of FTD, and in some cases, it may refer to a neuropsychiatric condition different from FTD, especially in late-onset cases in which different neuropathologies including AD may coexist, or to a non-progressive or reversible stage. We need a proper definition of clinical features of MCBMI-FTD beyond the label of “mild FTD symptoms”; and to this, reliable biomarkers able to characterize the preclinical and prodromal stages are still clearly needed, as a definition solely based on clinical profile will have low specificity for sporadic cases, particularly in a psychiatric setting. Considering both clinical symptoms and supportive markers, in the near future we may suggest a proper classification of the prodromal stages of FTD to be used in clinical practice and in pharmacological and non-pharmacological trials.

There are some issues that should be considered regarding MCBMI-FTD. FTD is a relatively rare disorder<sup>156</sup> and with a stronger genetic trait than AD.<sup>12</sup> For these reasons, targeting MCBMI-FTD needs further remarks. It is plausible to speculate that markers of preclinical or prodromal FTD in genetic cases at risk of developing disease may be different from what we may observe in overt dementia. A debate is still open on definitions of outcomes in relatively small samples of subjects, with the proposal to identify new personalized endpoints.

The overall considerable proportion of subjects at risk of developing disease due to monogenic mutations, even though still to be established by multinational epidemiological studies,<sup>156,157</sup> and the possible differences with non-monogenic MCBMI-FTD, raise several questions. First, monogenic disease may help to build up the model of progression from the preclinical to the symptomatic stages. Whether this framework may be applied even in non-monogenic disease, in which the pre-test probability that behavioral or cognitive symptoms will lead to FTD is much lower, needs to be further addressed. Initial findings suggest that clinical presentations (including cognitive, behavioral, and motor) are very similar between genetic and sporadic FTD.<sup>158,159</sup>

Second, in MCBMI-FTD due to pathogenetic mutations we do not need diagnostic markers, but require prognostic markers, while in sporadic MCBMI-FTD we need both.

Most importantly, we should consider genetic MCBMI-FTD and sporadic MCBMI-FTD as distinct entities regarding treatment approaches. Pathological mutations, that is, *GRN*, *MAPT*, or *C9orf72*, result from specific pathogenetic mechanisms and thus have specific targets of treatment. Conversely, in those cases with unknown pathogenetic mutations, targets for disease-modifying treatments should be centered on the underlying proteinopathy, that is, tau or TDP-43, or nonpharmacological interventions targeting neurotransmitters or connectivity impairment.<sup>74,160</sup> Conversely, genetic and sporadic MCBMI-FTD can be considered comparable in symptomatic clinical trials and included regardless of the genetic or neuropathological background.

Finally, as with the symptomatic FTD stage, MCBMI-FTD also requires markers of phenotype prediction and markers of proximity to disease onset.

Several issues remain unanswered, including: how do we account for FTD phenocopies; what are the ethical issues in making an earlier diagnosis, informing subjects about biomarkers when it is still uncertain if it will progress to clinical FTD?

All the above considerations represent the roadmap of the recently established GENFI FTD Staging Working Group, whose main objectives will be to answer exhaustively the outstanding issues reported in the present proposal, to identify biomarkers in preclinical and prodromal FTD, and to plan larger collaborative international studies to test the utility and validity of this proposed new approach.

Our ability to carefully characterize the preclinical and prodromal stages of FTD will help in early disease detection, in enabling patient stratification, and in tailoring therapeutic selection for each patient.

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- **Sarah Anderl-Straub** Department of Neurology, University of Ulm, Ulm, Germany
  - **Christin Andersson** Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
  - **Anna Antonell** Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain
  - **Silvana Archetti** Biotechnology Laboratory, Department of Diagnostics, ASST Brescia Hospital, Brescia, Italy
  - **Andrea Arighi** Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy
  - **Mircea Balasa** Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain
  - **Myriam Barandiaran** Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, San Sebastian, Gipuzkoa, Spain; Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain
  - **Nuria Bargalló** Imaging Diagnostic Center, Hospital Clínic, Barcelona, Spain
  - **Robart Bartha** Department of Medical Biophysics, The University of Western Ontario, London, Ontario, Canada; Centre for Functional and Metabolic Mapping, Robarts Research Institute, The University of Western Ontario, London, Ontario, Canada
  - **Benjamin Bender** Department of Diagnostic and Interventional Neuroradiology, University of Tübingen, Tübingen, Germany
  - **Maxime Bertoux** Inserm 1172, Lille, France
  - **Anne Bertrand** Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP – Hôpital Pitié-Salpêtrière, Paris, France
  - **Valentina Bessi** Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy
  - **Sandra Black** Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Toronto, Canada
  - **Sergi Borrego-Ecija** Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain
  - **Arabella Bouzigues** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
  - **Jose Bras** Center for Neurodegenerative Science, Van Andel Institute, Grand Rapids, Michigan, MI 49503, USA
  - **Alexis Brice** Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP – Hôpital Pitié-Salpêtrière, Paris, France
  - **Rose Bruffaerts** Laboratory for Cognitive Neurology, Department of Neurosciences, KU Leuven, Leuven, Belgium
  - **Chris R. Butler** Nuffield Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford, Oxford, UK
  - **Agnès Camuzat** Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP – Hôpital Pitié-Salpêtrière, Paris, France
  - **Marta Cañada** CITA Alzheimer, San Sebastian, Gipuzkoa, Spain

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## APPENDIX A

List of collaborators in the GENFI consortium

- **Sónia Afonso** Instituto Ciências Nucleares Aplicadas a Saude, Universidade de Coimbra, Coimbra, Portugal
- **Maria Rosario Almeida** Faculty of Medicine, University of Coimbra, Coimbra, Portugal

- **Valentina Cantoni** Centre for Neurodegenerative Disorders, Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
- **Paola Caroppo** Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
- **David Cash** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Miguel Castelo-Branco** Faculty of Medicine, University of Coimbra, Coimbra, Portugal
- **Olivier Colliot** Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France
- **Rhian Convery** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Thomas Cope** Department of Clinical Neuroscience, University of Cambridge, Cambridge, UK
- **Adrian Danek** Neurologische Klinik und Poliklinik, Ludwig-Maximilians-Universität, Munich
- **Alexandre de Mendonça** Laboratory of Neurosciences, Institute of Molecular Medicine, Faculty of Medicine, University of Lisbon, Lisbon, Portugal
- **Vincent Deramecourt** Univ Lille, France
- **Giuseppe Di Fede** Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
- **Alina Díez** Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain
- **Diana Duro** Faculty of Medicine, University of Coimbra, Coimbra, Portugal
- **Chiara Fenoglio** Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy
- **Camilla Ferrari** Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy
- **Catarina B. Ferreira** Laboratory of Neurosciences, Institute of Molecular Medicine, Faculty of Medicine, University of Lisbon, Lisbon, Portugal
- **Nick Fox** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Morris Freedman** Baycrest Health Sciences, Rotman Research Institute, University of Toronto, Toronto, Canada
- **Aurélié Funkiewiez** Centre de référence des démences rares ou précoces, IM2A, Département de Neurologie, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France
- **Alazne Gabilondo** Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain
- **Serge Gauthier** Alzheimer Disease Research Unit, McGill Centre for Studies in Aging, Department of Neurology & Neurosurgery, McGill University, Montreal, Québec, Canada
- **Stefano Gazzina** Neurology, ASST Brescia Hospital, Brescia, Italy
- **Alexander Gerhard** Division of Neuroscience and Experimental Psychology, Wolfson Molecular Imaging Centre, University of Manchester, Manchester, UK
- **Giorgio Giaccone** Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
- **Ana Gorostidi** Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain
- **Caroline Graff** Center for Alzheimer Research, Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Bioclinicum, Karolinska Institutet, Solna, Sweden
- **Rita Guerreiro** Center for Neurodegenerative Science, Van Andel Institute, Grand Rapids, Michigan, MI 49503, USA
- **Carolin Heller** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Tobias Hoegen** Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany
- **Begoña Indakoetxea** Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, San Sebastian, Gipuzkoa, Spain; Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain
- **Vesna Jelic** Division of Clinical Geriatrics, Karolinska Institutet, Stockholm, Sweden
- **Hans-Otto Karnath** Division of Neuropsychology, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany
- **Ron Keren** The University Health Network, Toronto Rehabilitation Institute, Toronto, Canada
- **Gregory Kuchcinski** Univ Lille, France
- **Robert Laforce** Clinique Interdisciplinaire de Mémoire, Département des Sciences Neurologiques, CHU de Québec, and Faculté de Médecine, Université Laval, QC, Canada
- **Maria Landqvist Waldo** Department of Clinical Sciences, Clinical Sciences Helsingborg, Lund, Lund University, Lund, Sweden
- **Tobias Langheinrich** Division of Neuroscience and Experimental Psychology, Wolfson Molecular Imaging Centre, University of Manchester, Manchester, UK
- **Thibaud Lebouvier** Univ Lille, France
- **Maria João Leitão** Centre of Neurosciences and Cell Biology, Universidade de Coimbra, Coimbra, Portugal
- **Johannes Levin** Neurologische Klinik und Poliklinik, Ludwig-Maximilians-Universität, Munich
- **Albert Lladó** Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain
- **Gemma Lombardi** Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy
- **Jolina Lombardi** Department of Neurology, University of Ulm, Ulm
- **Sandra Loosli** Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany
- **Carolina Maruta** Laboratory of Language Research, Centro de Estudos Egas Moniz, Faculty of Medicine, University of Lisbon, Lisbon, Portugal

- **Simon Mead** MRC Prion Unit, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK
- **Lieke Meeter** Department of Neurology, Erasmus Medical Center, Rotterdam, Netherlands
- **Gabriel Miltenberger** Faculty of Medicine, University of Lisbon, Lisbon, Portugal
- **Rick van Minkelen** Department of Clinical Genetics, Erasmus Medical Center, Rotterdam, Netherlands
- **Sara Mitchell** Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Toronto, Canada
- **Katrina Moore** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Fermin Moreno** Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, San Sebastian, Gipuzkoa, Spain
- **Annabel Nelson** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Jennifer Nicholas** Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK
- **Linn Öjjerstedt** Center for Alzheimer Research, Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Bioclinicum, Karolinska Institutet, Solna, Sweden
- **Jaume Olives** Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain
- **Markus Otto** Department of Neurology, University of Ulm, Ulm, Germany
- **Sebastien Ourselin** School of Biomedical Engineering & Imaging Sciences, King's College London, London, UK
- **Jessica Panman** Department of Neurology, Erasmus Medical Center, Rotterdam, Netherlands
- **Janne M. Papma** Department of Neurology, Erasmus Medical Center, Rotterdam, Netherlands
- **Florence Pasquier** Univ Lille, France
- **Yolande Pijnenburg** Amsterdam University Medical Centre, Amsterdam VUmc, Amsterdam, Netherlands
- **Cristina Polito** Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", Nuclear Medicine Unit, University of Florence, Florence, Italy
- **Enrico Premi** Stroke Unit, ASST Brescia Hospital, Brescia, Italy
- **Sara Prioni** Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
- **Catharina Prix** Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany
- **Rosa Rademakers** Department of Neurosciences, Mayo Clinic, Jacksonville, Florida, USA
- **Veronica Redaelli** Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
- **Daisy Rinaldi** Centre de référence des démences rares ou précoces, IM2A, Département de Neurologie, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France
- **Tim Rittman** Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
- **Ekaterina Rogaeva** Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Canada
- **Adeline Rollin** CHU, CNR-MAJ, Labex Distalz, LICEND Lille, France
- **Pedro Rosa-Neto** Translational Neuroimaging Laboratory, McGill Centre for Studies in Aging, McGill University, Montreal, Québec, Canada
- **Giacomina Rossi** Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
- **Martin Rossor** Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK
- **Isabel Santana** University Hospital of Coimbra (HUC), Neurology Service, Faculty of Medicine, University of Coimbra, Coimbra, Portugal
- **Beatriz Santiago** Neurology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
- **Dario Saracino** Sorbonne Université, Paris Brain Institute - Institut du Cerveau - ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France
- **Sabrina Sayah** Sorbonne Université, Paris Brain Institute - Institut du Cerveau - ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France
- **Elio Scarpini** Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy
- **Sonja Schönecker** Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany
- **Matthias Schroeter** Max Planck Institute for Human Cognitive & Brain Sciences, Leipzig & Clinic for Cognitive Neurology, University Leipzig, Germany
- **Rachelle Shafei** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Christen Shoemsmith** Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada
- **Sandro Sorbi** Department of Neurofarba, University of Florence, Italy
- **Imogen Swift** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Miguel Tábuas-Pereira** Neurology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
- **Yolande Pijnenburg** Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands
- **Fabrizio Tagliavini** Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
- **Mikel Tainta** Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain
- **Ricardo Taipa** Neuropathology Unit and Department of Neurology, Centro Hospitalar do Porto - Hospital de Santo António, Oporto, Portugal

- **David Tang-Wai** The University Health Network, Krembil Research Institute, Toronto, Canada
- **Carmela Tartaglia** Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Canada
- **David L. Thomas** Neuroimaging Analysis Centre, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, Queen Square, London, UK
- **Paul Thompson** Division of Neuroscience and Experimental Psychology, Wolfson Molecular Imaging Centre, University of Manchester, Manchester, UK
- **Hakan Thonberg** Center for Alzheimer Research, Division of Neurogeriatrics, Karolinska Institutet, Stockholm, Sweden
- **Carolyn Timberlake** Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
- **Pietro Tiraboschi** Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
- **Emily Todd** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Philip Van Damme** Neurology Service, University Hospitals Leuven, Belgium; Laboratory for Neurobiology, VIB-KU Leuven Centre for Brain Research, Leuven, Belgium
- **Rik Vandenberghe** Laboratory for Cognitive Neurology, Department of Neurosciences, KU Leuven, Leuven, Belgium
- **Mathieu Vandenbulcke** Geriatric Psychiatry Service, University Hospitals Leuven, Belgium; Neuropsychiatry, Department of Neurosciences, KU Leuven, Leuven, Belgium
- **John C. van Swieten** Department of Neurology, Erasmus Medical Centre, Rotterdam, Netherlands
- **Michele Veldsman** Nuffield Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford, Oxford, UK
- **Ana Verdelho** Department of Neurosciences and Mental Health, Centro Hospitalar Lisboa Norte - Hospital de Santa Maria & Faculty of Medicine, University of Lisbon, Lisbon, Portugal
- **Jorge Villanua** OSATEK, University of Donostia, San Sebastian, Gipuzkoa, Spain
- **Jason Warren** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Carlo Wilke** Department of Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany; Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany
- **Ione Woollacott** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Elisabeth Wlasich** Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany
- **Henrik Zetterberg** Dementia Research Institute, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK
- **Miren Zulaica** Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain