

2 Conceptualizing cognition and behaviour 3 across amyotrophic lateral sclerosis and 4 frontotemporal dementia

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11 Abstract

12 Cognitive and behavioral dysfunction in frontotemporal dementia (FTD) evolves along a
13 clinical continuum from a clinically silent stage of disease, through a prodromal period,
14 often referred to as mild cognitive impairment (MCI) and/or mild behavioral impairment
15 (MBI), and into a clinically manifest stage recognized by the syndromes of behavioral
16 variant FTD and primary progressive aphasia (PPA). Similar cognitive and behavioral
17 manifestations of varying severity are also encountered in individuals with amyotrophic
18 lateral sclerosis (ALS).

19 Notwithstanding this phenotypic overlap as well as a degree of shared genetic risk and
20 underlying pathology, the approach to phenotypic characterization and description
21 meaningfully differs between the ALS and FTD communities. The problem is particularly
22 evident within the ALS community when describing impairment in the prodromal vs.
23 clinically manifest disease stages. Pertinent considerations include the nature of cognitive
24 and behavioral assessments, the nosology used to describe symptoms identified including
25 those encompassed by the terms ‘behavioral’ and ‘neuropsychiatric’, the operationalized
26 criteria that define prodromal syndromes and clinically manifest disease, and the extent to
27 which these criteria rely on longitudinal (vs. cross-sectional) data.

28 A multi-stakeholder workshop, held in London, Ontario (May 12-14, 2025), brought together
29 neurologists, psychiatrists, neuropsychologists, neuropathologists, neuroscientists, and

neurogeneticists studying ALS and FTD, to promote inter-disciplinary dialogue and to define a research agenda that might be jointly tackled to address these critical issues. A new nosology for classifying frontotemporal-related behavioral and neuropsychiatric dysfunction, which could be used to support empirical evidence collection, is proposed alongside a list of cognitive, language, behavioral and neuropsychiatric symptoms to be considered in the evaluation of individuals with ALS. Research priorities for each of the ALS and FTD communities, as well as initiatives that should be undertaken jointly, are highlighted. The long-term goal is to harmonize approaches to phenotypic characterization, the nosology used to describe symptoms, and the criteria used to define landmark stages along the clinical continua of the motor neuron and frontotemporal axes irrespective of clinical stage.

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17 Introduction

18 Behavioral and cognitive dysfunction are the defining clinical features of frontotemporal
 19 dementia (FTD), but *formes frustes* are also recognized, some of which may be transitional
 20 states between clinically silent and clinically manifest syndromes ^{1, 2}. Varying terms have
 21 been used to describe these prodromal stages of disease that have been broadly captured
 22 by the terms mild cognitive impairment (MCI) and mild behavioral impairment (MBI).
 23 Cognitive and behavioral symptoms that resemble those seen in FTD are also known to
 24 occur in individuals with amyotrophic lateral sclerosis (ALS), a closely related
 25 neurodegenerative disorder that shares genetic risk and underlying pathology with some
 26 forms of FTD. Indeed, the terms ALS with cognitive impairment (ALSci) and ALS with
 27 behavioral impairment (ALSbi) have been used to capture MCI and MBI when they occur in
 28 the context of ALS, and the term ALS-FTD reserved for the co-occurrence of clinically
 29 manifest motor neuron disease and FTD ³. The study of clinically unaffected pathogenic

variant carriers at elevated risk for ALS (and FTD) has also revealed that MCI and MBI may precede the development of clinically manifest ALS⁴.

The Miami Framework offers a unified approach to specifying the pleiotropic clinical manifestations of ALS and FTD⁵. This framework conceptualizes (at least) three phenotypic axes (motor neuron, frontotemporal and extrapyramidal), with a clinical continuum along each axis whereby phenotypic manifestations of disease progress from being clinically silent, to a prodromal stage when subtle symptoms or signs begin to emerge^{6, 7, 8}, and finally to a clinically manifest stage of disease. Importantly, while the Miami Framework envisages MCI/MBI as the prodrome to a fully manifest FTD syndrome, it also recognizes that MCI/MBI may precede the emergence of a clinically manifest syndrome (e.g. ALS) on a different axis. In other words, a cognitive/behavioral predominant prodrome may precede the emergence of a motor-predominant fully manifest disease, and a motor prodrome (mild motor impairment^{6, 7}) may precede the emergence of FTD. Moreover, although the term 'prodrome' is used broadly to describe the milder/earlier stages of phenotypic expression along each axis, a prodromal state does not necessarily progress to a clinically manifest state in the same (or a different) axis – i.e. it may arrest at the prodromal stage (Figure 1).

The importance of evaluating non-motor symptoms in the context of ALS is underscored by several factors. First, families are often puzzled and distressed by non-motor symptoms exhibited by their family member with ALS. Without an explanation of these symptoms as a part of the patient's illness by a physician, families may adopt alternative explanations that are deleterious to family relationships (e.g., the ALS patient is willfully stubborn, cruel, or uncaring). Second, non-motor symptoms have been associated with poorer quality of life⁹ and shorter survival¹⁰. Finally, a full and accurate assessment of non-motor symptoms in ALS is needed to understand and distinguish non-motor symptoms of ALS from non-pathological psychological reactions to motor symptoms, especially since some non-motor symptoms may be addressable with symptomatic treatments.

While the spectral relationship between ALS and FTD is now well established, there are many issues to resolve. For example, the revised Strong criteria used to define MCI/MBI in individuals with clinically manifest ALS (ALS_{bi}, ALS_{ci}, ALS_{cbi})³ differ from those used to define MCI/MBI among pathogenic variant carriers prior to motor phenoconversion (MCI-frontotemporal [MCI-ft], MBI-ft)¹. This discrepancy reflects, in part, the revised Strong criteria's emphasis on cross-sectional assessments, whereas evidence of longitudinal

decline is prioritized in the pre-symptomatic stage of disease. Similarly, a host of different operational definitions of MCI and MBI have been proposed by the ALS and FTD communities¹¹⁻¹⁵, with the prevalence estimates varying widely depending on the criteria applied⁴. Also unknown is whether the MCI/MBI phenotype that precedes ALS is the same as that which precedes FTD. These and other questions were the focus of discussion at a Workshop entitled *Phenotype and Biology of ALS Frontotemporal Spectrum Disorders* held in London, Ontario (May 12-14, 2025). These discussions highlighted priority areas for research that will be essential to advance our understanding of the earliest stages of FTD across the ALS-FTD spectrum.

Behavioral, neuropsychiatric and cognitive manifestations

The term FTD encompasses clinical syndromes that are typically characterized either by prominent behavioral symptoms (behavioral variant FTD [bvFTD]), or by a primary language disorder (primary progressive aphasia [PPA]), with the latter most commonly a non-fluent/agrammatic variant or a semantic variant. However, there are less common behavioral and language syndromes within FTD that include, for example, right temporal variant FTD¹⁶, primary progressive apraxia of speech¹⁷, and logopenic variant PPA (in the absence of Alzheimer's disease pathology)¹⁸.

While bvFTD is considered primarily a behavioral syndrome, often accompanied by executive dysfunction, some view it as a disorder of social cognition with resulting aberrant behaviors¹⁹. In addition, a proportion of individuals with bvFTD exhibit language deficits (e.g. impaired word naming or object knowledge, and grammatical deficits) or memory dysfunction. As criteria for defining bvFTD have evolved from Lund-Manchester²⁰ to those proposed by Neary et al.²¹, to the contemporary set described by Rascovsky et al.²², different symptoms have been considered and varying terms have been used to describe the same behavioral manifestations of FTD. At the core, however, are three broad classes of symptoms – a diminution of customary behaviors (manifestations include apathy and loss of sympathy/empathy), emergence of behaviors that are ordinarily absent (manifestations of behavioral dysregulation), and neuropsychiatric symptoms (including affective states, and, less commonly, perceptual and ideational disorders, Table 1).

We recognize that the term 'neuropsychiatric', in the context of bvFTD, has historically been used to mean different things. Some have used the term interchangeably with 'behavioral'.

Others have used it to encompass a broad range of symptoms including psychosis (i.e. delusions and hallucinations), affective symptoms (e.g. dysphoria, euphoria)²³, and an array of other symptoms and states (e.g. irritability, lability, agitation, aggression, elation, aberrant motor behavior, hypersexuality, hyper-religiosity, impaired sleep and altered sense of humor)²⁴. It is precisely because of the inconsistent use of the term ‘neuropsychiatric’ in the past and the overlap between behavioral and neuropsychiatric symptoms when the latter is broadly construed, that we propose a more precisely defined usage of the term (Table 1). It is worth noting that some neuropsychiatric symptoms, more precisely defined to encompass affective, perceptual and ideational features, may have value as criteria for designating MBI. For example, some studies have reported a higher frequency of neuropsychiatric symptoms in *C9orf72* repeat expansion carriers²⁵ and more broadly among patients with ALS²⁶. However, even though psychosis is reported to be more common among *C9orf72* repeat expansion than other gene mutation carriers^{27, 28}, at least one analysis found this phenotypic feature to be sufficiently infrequent that it was not included in the criteria proposed for prodromal disease¹⁵. Moreover, a prospective study of *MAPT* carriers found that mood and anxiety disorders were more prevalent among non-carrier family members²⁹. It should also be noted that some neuropsychiatric symptoms may confound determination of whether a behavioral symptom such as apathy, is independently present and should be counted among criteria for designating MBI. Disentangling the two is complex and requires focused assessment and clinical judgement. For example, a lack of expected dysphoria may be a symptom of bvFTD in a patient who seems untroubled by learning their diagnosis, suggesting that they have emotional blunting (while recognizing that poor insight or anosognosia might also contribute). Similarly, apathy in the context of self-reported moderate-to-severe symptoms of depression should be considered with more circumspection. Importantly, apathy is more emotionally and ideationally neutral, while depression, by contrast, is characterized by negative emotions and thoughts³⁰. It is also worth noting that while behavioral symptoms can be directly observed, neuropsychiatric symptoms that likely reflect internal states, are more difficult to assess, especially in the context of impaired insight.

The most common language syndromes of FTD are of two main variants – non-fluent (nfvPPA) and semantic variant (svPPA, also known as semantic dementia, SD). The primary feature of PPA is difficulty with language from onset and for the first two years after symptom onset. Criteria also stipulate that impaired language is the principal cause of impaired daily activities. The distinguishing characteristics of nfvPPA are agrammatism, effortful/halting speech, and impaired naming, while the core features of svPPA include loss of object knowledge, impaired word naming, and object agnosia³¹. A related disorder

1 is primary progressive apraxia of speech, where the principal deficit relates to articulation
 2 of speech and sequencing sounds within a word ^{32, 33}.

3
 4 The cognitive and behavioral manifestations of ALS have been articulated differently.
 5 Specifically, the criteria for ALSbi (which is the equivalent of MBI in those with ALS) build
 6 upon the Rascovsky criteria for bvFTD. Apathy is the prevailing symptom, although
 7 disinhibition, loss of sympathy/empathy, perseveration, and hyperorality are observed. The
 8 criteria for ALSbi also incorporate additional features of loss of insight and psychosis ³. The
 9 criteria for ALSci (which is the equivalent of MCI in those with ALS) emphasize phonemic
 10 verbal fluency deficits, but also include other aspects of executive function and social
 11 cognition, as well as language impairment that cannot be explained by verbal fluency
 12 deficits (e.g. spelling, naming). The focus on phonemic verbal fluency stems from early
 13 reports of lower average phonemic verbal fluency performance among ALS individuals
 14 compared to the cognitively unimpaired, even when accounting for motor symptoms ³⁴.
 15 While a meta-analysis showed a medium to large pooled effect size for phonemic fluency
 16 ³⁵, the literature on the frequency with which phonemic verbal fluency scores fall below a
 17 normative threshold in ALS, is quite mixed ³⁶⁻⁴², varying in part according to the normative
 18 data used to define abnormalities ⁴³. It is also the case that the frequency of semantic
 19 deficits in ALS is relatively low ⁴⁴⁻⁴⁶ despite their prevalence in svPPA, mixed bvFTD/svPPA
 20 phenotypes, and right temporal variant bvFTD. Moreover, defining apathetic behavior and
 21 verbal fluency deficits in the context of motor manifestations of ALS are challenging
 22 particularly given heterogeneous involvement of limb and bulbar sites, respectively.

23
 24 The discordance between criteria for cognitive and behavioral impairment in FTD and ALS
 25 is similarly noteworthy. Most striking is how cognition and behavior are parsed and how
 26 cognitive and behavioral deficits are relatively weighted. The FTD community distinguishes
 27 language dysfunction (PPA) from a predominantly behavioral syndrome (bvFTD) that may
 28 also be accompanied by executive dysfunction with relative sparing of memory and
 29 visuospatial functions, but recognizes that many patients progress to a mixed phenotype
 30 with both language and behavioral impairment. Importantly, executive dysfunction is only
 31 one of six features, which when combined with two behavioral features, meets criteria for
 32 diagnosis of bvFTD (and is not required to declare prodromal disease). By contrast, in ALS
 33 the cognitive and behavioral features are addressed separately as prodromal states (i.e.
 34 before progression to ALS-FTD). The assessment of cognition in ALS centers around
 35 executive function and language (often jointly evaluated through tests of verbal fluency),
 36 but does not preclude involvement of other domains. Critically, the ALS community views

social cognition as an executive function, whereas the FTD community views social cognition as the principal driver of behavioral dysfunction.

Moreover, the criteria for ALSbi are permissive, such that the diagnosis can be reached by relying on apathy alone, which is challenging to disentangle from depressed mood and reduced activity secondary to motor symptoms. While both the Rascovsky and revised Strong criteria require that a comorbid psychiatric disorder (e.g. depression or adjustment disorder upon receiving a diagnosis) not account for the observed behavioral changes, this nuance is often lost among ALS specialists when the revised Strong criteria are operationalized. It is also worth noting that the proposed criteria for a prodromal behavioral disturbance (MBI) include additional features not included in the Rascovsky bvFTD criteria, possibly reflecting the evanescent nature of behavioral symptoms or simply a function of the motivation to improve sensitivity for detecting a prodromal state^{3, 15}. One practical implication of this discordance is that someone with MBI (or ALSbi) may not go on to meet criteria for a fully manifest FTD syndrome even if their behaviors worsen if the specific symptoms (e.g. psychosis or loss of insight) do not count among the criteria for bvFTD.

Tools for assessing functions dependent on the frontotemporal lobes

Cognitive/behavioral neurologists and neuropsychiatrists rely primarily on a detailed clinical evaluation, including an interview with a care/study partner, for their assessment of cognitive and behavioral function. This is usually supplemented by assessment of the individual with a formal neuropsychological battery as well as administration of structured surveys of cognitive and behavioral change to the care/study partner. Several measures of behavioral and neuropsychiatric signs and symptoms associated with frontal dysfunction have been published and validated, including the Frontal Systems Behavior Scale⁴⁷, and the Frontal Behavioral Inventory^{48, 49}. In addition, an array of instruments may be used to capture the frequency of neuropsychiatric symptoms in FTD – including the Neuropsychiatric Inventory-Questionnaire^{50, 51}, the Cambridge Behavioral Inventory⁵², the Frontotemporal Dementia Rating Scale²³, and the GENFI neuropsychiatric symptom scale²⁴. However, not all symptoms captured by these scales necessarily reflect behavioral and neuropsychiatric symptomatology as conceptualized in Table 1, nor do they differentiate between disease-related changes with neurobiological underpinning and psychosocial responses to a terminal disease. When individuals with FTD are evaluated in the research context, these sources of data are integrated, often through a multidisciplinary case conference discussion, to designate a research diagnosis and a specific structured

interview facilitates assignment of ratings on the eight domains of the National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration (FTLD) module (CDR + NACC FTLD), that determine the global and sum of boxes scores ^{14, 53}.

The assessment of non-motor (i.e. cognitive, behavioral and neuropsychiatric) manifestations of ALS-FTD is inherently more challenging than that of motor symptoms and signs. In part this derives from the more concrete nature of weakness than behavior, where the latter is characterized by larger pre-morbid variability, difficulty discerning change against a background of pre-morbid state, the necessary reliance on third party reporting, the relatively high prevalence of psychiatric illness in the general population ⁵⁴, and the increased emotional distress and frequency of psychiatric illness in patients with ALS. While FTD specialists have expertise in parsing these complexities, the task is more complex for ALS neurologists, with subspecialty training in neuromuscular disease rather than cognitive/behavioral neurology or neuropsychiatry. ALS neurologists typically lean more heavily on the results of the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) ⁵⁵ and a formal neuropsychological test battery, alongside information gleaned from study/care partner completed standardized questionnaires. The ECAS has been reported to provide good sensitivity and specificity against a full neuropsychology battery in individuals with ALS ³⁷, is brief (20 to 30 mins) and is designed to accommodate motor disability. However, we currently lack data validating reliance on the ECAS alone (i.e., without a full neuropsychological assessment) as a tool to evaluate cognitive and behavioral function or decline in the pre-symptomatic state ⁵⁶. Moreover, the ECAS must be used together with measures of mood and anxiety to have confidence that ascertainment of apathy is not confounded by depression or an adjustment disorder, for example. This is especially important if the designation of MBI rests on apathy alone (per revised Strong criteria for ALSbi). Moreover, to the extent that the evaluation of behavioral function relies heavily on study/care partner reports, the information received may be colored by the characteristics of the study/care partner and their relationship to the individual with ALS or FTD. This may influence the nature and quality of the information provided ^{57, 58}, and provides a rationale for seeking input from multiple study/care partners.

There is an opportunity to address these structural differences in the approach to evaluating cognitive and behavioral dysfunction by using materials developed by the FTD community to train ALS neurologists in cognitive and behavioral phenotyping. As an example, ALS neurologists might refer to a list of probes about cognition and behavior such as those summarized in Table 2, to guide the clinical interview of both the carrier/patient and the study partner or caregiver. These items are based on the clinical expertise of FTD

clinicians and their utility in an ALS population is not yet established. However, by more actively enquiring about potential cognitive and behavioral symptoms, ALS neurologists will be better placed to make appropriate referrals, contribute to multi-specialty consensus discussions, and gradually acquire greater comfort and expertise in evaluating these important manifestations of disease. A shorter-term solution might emerge from a formal cross-comparison of MCI and MBI designations using different sources of data in the same population. For example, the approach used by the ALS community, placing heavy reliance on formal neuropsychological testing and care/study partner surveys, might be compared with the designation of a prodromal state based on the CDR plus NACC FTLD score. A third, potentially complementary, approach, would be to ensure that both ALS and FTD neurologists participate in multi-specialty discussions, to help ensure consistency in assignment of consensus-based research diagnoses.

Terminology

An array of terms has been used to describe the cognitive manifestations of the ALS-FTD spectrum. Examples include ‘deficit’, ‘dysfunction’, ‘impairment’ and ‘decline’. The challenge is that these terms are sometimes used interchangeably but are intended to convey different ideas, causing conceptual confusion. A potential resolution would be the adoption of a standardized set of terminology, as recently proposed⁴. The proposal is that the term ‘sub-threshold cognitive performance’ be used to describe scores on an objective test of cognition that fall below a specified cut-off compared to appropriate normative data; that ‘decline’ be used to capture self-reported worsening of cognitive function or the situation where scores on psychometric tests fall by a specified amount compared to prior performance; and that ‘impairment’ be reserved to describe those with deficits or decline that meet recognized/established criteria for classification into a category such as MCI. It is also essential to avoid conflating group level differences in cognitive performance (e.g. lower average verbal fluency in ALS compared to cognitively unimpaired individuals) with frequency of impairment – a particular group may, on average, have worse performance than another group, but this does not necessarily indicate that people in one group are more frequently classified as having cognitive impairment. These challenges are compounded by a paucity of robust and appropriate normative data for some commonly used tests, which in turn, impedes the ability to correctly classify an individual at risk for, or with manifest ALS or FTD, as “impaired”.

Complexity also arises from the use of different instruments and criteria for designation of cognitive or behavioral impairment. For example, the North American and European FTD communities have relied heavily on the CDR + NACC FTLD⁵³, with a global score of 0.5

used to indicate mild (or indeterminate) impairment and a global score of 1 indicating the presence of clinically manifest FTD, meaning the patient has dementia. Although revised scoring methods⁵³ reduce the dependency of the CDR plus NACC FTLD global score on memory and allow impairment in behavioral or language domains to contribute to disease severity, core FTD features such as loss of sympathy/empathy and emotional blunting may produce less overt functional impairment; and motor symptoms (including those relevant to ALS) are not assessed. This paradigm focuses exclusively on cognition and behavior. Others within the FTD community have proposed a variety of different criteria for designating MCI and MBI – frontotemporal mild cognitive impairment¹¹, mild cognitive and/or behavioral and/or motor impairment (MCBBI)¹³, and mild behavioral and/or cognitive impairment in bvFTD (MBCI-FTD)¹⁵. The ALS community, by contrast, has favored differentiation of cognitive and behavioral symptoms, proposing the constructs of ALSci and ALSbi in the clinically manifest ALS population³, and the terms mild cognitive impairment (MCI-ft) and mild behavioral impairment (MBI-ft) among those at risk for, but who have not (yet) developed ALS or FTD¹.

Criteria for cognitive and behavioral impairment

Within the FTD community, there are established diagnostic criteria for clinically manifest disease (bvFTD, nvPPA and svPPA), although some recent data suggest that revisions might be needed⁵⁹⁻⁶¹. In parallel and as noted above, several different sets of criteria have been proposed to describe mild cognitive/behavioral impairment as a prodromal stage of these diseases. In addition to the discordance across these approaches to defining prodromal disease, there is also a disconnect between criteria for prodromal disease and those for clinically manifest disease. The net effect is that there is not a seamless continuum across the spectrum of frontotemporal dysfunction. As an example, the Rascovsky criteria for possible bvFTD do not require functional impairment, and therefore, someone with the same behavioral and cognitive profile might be classified as having MBCI-FTD or possible bvFTD.

Similarly, different rubrics have been proposed for defining MCI and MBI among individuals with clinically manifest ALS versus among pathogenic variant carriers at elevated risk for ALS. The result is that if the published criteria are applied, the same individual might “evolve” from having MCI and MBI while pre-symptomatic for ALS to having no ‘diagnosis’ of cognitive or behavioral impairment following phenoconversion to ALS, even without any actual change in cognitive or behavioral function. Within the ALS community, therefore,

1 there is a pressing need to integrate the criteria for a prodromal stage of disease along the
2 frontotemporal axis (i.e. mild cognitive and mild behavioral impairment) irrespective of
3 stage along the clinical continuum of the motor axis – i.e. designation of MCI/MBI should
4 not change simply by virtue of the stage of disease along the motor neuron axis.

5
6 Integration of conceptual frameworks across the ALS and FTD communities is equally
7 important but will be more challenging. In part this reflects divergent approaches based on
8 tools available to clinicians with different subspecialty training (see above). In part,
9 however, there may be real differences in the nature of cognitive and behavioral deficits
10 among those destined to develop FTD versus those destined to develop (or have
11 developed) ALS⁶². Relatively few studies have examined differences in the cognitive and
12 behavioral profiles of individuals with ALS, ALS-FTD, and FTD, and the limited evidence
13 available has produced mixed findings⁶³⁻⁶⁶. As these studies are cross-sectional it is
14 possible that any observed differences are confounded by motor symptoms; for example,
15 individuals with ALS-FTD may be less able to exhibit impulsive or repetitive behaviors due
16 to physical limitations. Similarly, it is essential to distinguish an ALS patient's physical
17 inability to engage in activities of interest, from apathy, anhedonia, or a lack of motivation.
18 Further exploration, including longitudinal studies, is an important research priority, which
19 may also shed light on the extent to which aberrant behaviors might reflect an exacerbation
20 of premorbid traits. It will also be necessary to carefully consider and disentangle the
21 extent to which reported behaviors truly reflect a behavioral change rather than simply the
22 perspective of the study partner for unrelated reasons. For example, a spouse's report of
23 reduced sympathy/empathy might be interpreted differently in the context of marital strife
24 or divorce proceedings.

25
26 A pressing issue for both the ALS and FTD communities to address is whether the criteria
27 for MCI and MBI should be "relaxed" when evaluating individuals who are known to carry a
28 pathogenic variant that dramatically increases their risk for developing FTD, or when
29 evaluating an individual who has already developed clinically manifest ALS. Indeed, at
30 least one set of proposed criteria has endorsed this approach¹⁵. An obvious challenge,
31 however, arises from the fact that FTD/ALS kindreds have a higher prevalence of psychiatric
32 and neurodevelopmental conditions (an endophenotype with a genetic basis⁶⁷), and that
33 stressors associated with lifetime risk of disease and having multiple affected relatives
34 may produce reactive states such as anxiety or depression that are not genetically
35 determined. Additionally, the non-specific nature of many early cognitive and behavioral
36 symptoms that might emerge along the frontotemporal axis raises the real possibility that

relaxed criteria might dramatically undermine specificity. This could lead to incorrect classification of many pathogenic variant carriers as having a prodromal syndrome. Indeed, it is essential to note that most clinical designations of MCI and MBI, for example, are simply clinical descriptions that are, to some extent, non-specific. Once better developed, biomarker evidence of underlying pathobiology (e.g. TDP-43) of disease will be critical in helping to differentiate those in whom MCI/MBI is a prodromal manifestation of disease from those in whom it is not. Here the analogy to MCI in Alzheimer's disease, with or without biomarker evidence of amyloid and tau, is apt.

As criteria for MCI and MBI evolve, it is worth reflecting on the goal that criteria aim to achieve. Emphasizing sensitivity at the expense of specificity may be appropriate if the evaluative measures used to determine MCI/MBI are designed for screening, to be followed by detailed assessments that will identify the true positive cases. If, however, the ascertainment of MCI/MBI is intended to be definitive, then high specificity would be preferred. Optimizing specificity (i.e. low false positive rate) provides the necessary confidence in the "diagnosis" and the designation of a prodromal stage in a pathogenic variant carrier. One obvious approach to improving specificity is to distinguish those deemed to have *mild* cognitive or behavioral impairment from those in whom there is *uncertainty* about the presence of MCI or MBI. Indeed, this is the approach adopted by the ALS community, while the FTD community has relied heavily on a CDR plus NACC-FTLD score of 0.5 to capture both instances of *mild* and *uncertain*. Even with a distinction between mild and uncertain categories, however, there are likely to be "wobblers" – those who vary over time between being considered 'normal' and a designation of MCI/MBI^{4, 68} or a CDR plus NACC-FTLD score of 0.5⁶⁹.

Any effort to refine criteria for MCI/MBI is hindered by the lack of a gold standard for being confident in the presence of a prodromal clinical syndrome. One valuable approach to "validating" that the MCI/MBI construct captures a relevant clinical state, would be to examine whether the presence of MCI/MBI is predictive of the short-term risk of phenoconversion to a clinically manifest state – akin to how proposed criteria for mild motor impairment (MMI) have been found to meaningfully predict time to ALS phenoconversion⁶, recognizing that prodromal states may sometimes arrest and not progress to being fully clinically manifest. Such an approach might also inform the question of whether criteria for MCI/MBI should be "relaxed" in the presence of a known pathogenic variant. Understanding the extent to which a designation of MCI/MBI based on relaxed vs. non-relaxed criteria is predictive of the future risk of phenoconversion to a clinically

1 manifest state would help inform whether prodromal designation based on relaxed criteria
2 is a useful construct. It might also be hypothesized that those with persistent MCI/MBI
3 have the highest short-term risk of phenoconversion to FTD, while those with fluctuating
4 MCI/MBI have intermediate risk, and those without MCI/MBI have the lowest risk.

5
6 Irrespective of the criteria proposed, a potential challenge is that MBI (and a mild
7 dysexecutive syndrome) in a pathogenic variant carrier might reasonably be expected to
8 predict the risk of phenoconversion to bvFTD (or perhaps ALS), but it is less clear that mild
9 language impairment (MLI), for example, should do the same. As such and given that the
10 dominant clinically manifest frontotemporal axis syndromes are bvFTD and PPA, it might be
11 argued that MBI and MLI⁷⁰ would be a more meaningful way to parse different prodromal
12 syndromes, with the expectation that MLI would predict the short term risk of
13 phenoconversion to PPA. It is recognized that there is an ontological issue – some may view
14 MLI as a form of non-amnesic MCI, while others might consider it a mild form of PPA
15 despite not meeting criteria for a fully manifest syndrome.

16
17 In considering revisions to existing criteria for prodromal MCI/MBI and clinically manifest
18 frontotemporal syndromes, there would be value in explicitly considering the extent to
19 which cross-sectional evidence of cognitive decline or behavioral change is sufficient
20 versus the need for evidence of longitudinal cognitive or behavioral change. The advantage
21 of incorporating cross-sectional measures in isolation is that cognitive/behavioral
22 designations can be made based on a single assessment, relying on *history* (i.e. the clinical
23 interview) to have confidence that cognitive decline and aberrant behaviors do indeed
24 represent a meaningful *change* from pre-morbid state. The challenge, however, is that there
25 are few robust tools for quantifying behavioral change or subjective cognitive decline along
26 the frontotemporal spectrum – hence the importance of the clinical interview. While a
27 requirement for longitudinal assessments would, of necessity, delay diagnostic
28 designation, this approach would likely improve confidence that cognitive and behavioral
29 impairment do indeed represent a change, thereby improving specificity.

30
31 A final issue to consider is the approach to determining that changes in cognition and
32 behavior are functionally relevant. To some extent this is captured by the CDR plus NACC
33 FTLD (e.g. in the items related to community affairs, and homes & hobbies). Which factors
34 contribute to functional impairment captured by the CDR plus NACC FTLD, however, is
35 often difficult to disentangle. While interviewers and respondents are asked to set aside

functional impairment due to motor disability, respondents find it difficult to recognize when functional effects are not solely due to cognitive or behavioral symptoms. Two expansions of this instrument to capture motor dysfunction have been developed – the CDR plus NACC FTLD-motor (FTLD-M)⁷¹ and the Multi-Impairment Rating Scale (MIR)⁷² – but both collapse subcortical motor (extrapyramidal) and motor neuron dysfunction into a single domain. The Amsterdam Instrumental Activities of Daily Living (IADL) scale^{73, 74}, by contrast, captures whether functional impairment is secondary to cognitive or physical limitations, but omits the impact of behavioral disturbance and limitations due to physical disability are excluded from scoring. Ultimately, there is currently an urgent need for a functional scale that captures the impact of all relevant phenotypic elements – cognitive, behavioral, motor neuron and extrapyramidal. Also, while functional impairment is traditionally considered a core requirement for the diagnosis of dementia⁷⁵, current diagnostic criteria for possible bvFTD do not explicitly require evidence of functional impairment. More formally requiring evidence of functional impairment might help to serve as a relative sharp boundary between prodromal MCI/MBI and a clinically manifest syndrome such as bvFTD.

Conclusions

With increasing recognition of the need to define diseases based on their underlying pathobiology, it is relevant to note that most forms of ALS and ~50% of cases of FTD share the same underlying biology in the form of TDP-43 pathology. Viewed from this perspective, the clinical syndromes of ALS and FTD might be regarded simply as different phenotypic manifestations of the same disease⁷⁶. The study of cognition and behavior in these TDP-43 proteinopathies (and indeed in tauopathies and ALS associated with SOD1 or FET protein aggregates), therefore, is somewhat reminiscent of the ancient parable of the blind men and an elephant. Each group perceives a different aspect of the phenotype based on their clinical training and perspective as well as the tools used to characterize cognition and behavior. Meaningful progress will require direct engagement with the at-risk community as well as active efforts to break down existing silos between the ALS and FTD communities, and within each community, among those studying the presymptomatic and clinically manifest stages of disease (Table 3).

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CM reports no competing interests

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MSB reports no competing interests

SA reports no competing interests

JdV reports no competing interests

ER reports no competing interests

YAP reports no competing interests

MRT is on the Clinical Advisory Board for Biogen ATLAS study, the Scientific Advisory Board for Novartis ASTRALS study. He has undertaken consultancies on ALS diagnosis and

biomarkers for AviadoBio & uniQure . He is Associate Editor for Practical Neurology. He is names on patents filed by University of Oxford for 1. A peptide sequence for the identification of TDP-43 proteinopathies and 2. Methods for Diagnosing Motor Neuron Diseases.

PvD reports participation in advisory boards for Biogen, CSL Behring, Alexion Pharmaceuticals, Ferrer, QurAlis, Cytokinetics, argenx, UCB, Muna Therapeutics, Alector, Augustine Therapeutics, VectorY, Zambon, Amylyx, Novartis, Prilenia, Verge Genomics, Sapreme Technologies, Trace Neuroscience, NRG Therapeutics, Crucible Therapeutics (paid to institution). PVD has received speaker fees from Biogen and Amylyx (paid to institution). EBL reports consulting fees from Eli Lilly.

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Appendix 1

Phenotype and Biology of ALS Frontotemporal Spectrum Disorders Workshop Attendees

Samir Abu Rumeileh, Ammar Al-Chalabi, Sharon Abrahams, Megan Barker, Michael Benatar, Alberto Benussi, Bradley F Boeve, Robert Bowser, Danae Campos-Melo, Sharon Coleman, Johnathon Cooper-Knock, Kathryn Cousins, Mari DeMarco, Joke De Vocht, Neil Donison, Cristian Droppelmann, Elizabeth Finger, Leah Forsberg, Nicole Harris, Lee

Freiburger, Jenna Gregory, Henne Holstege, Edward Huey, Clifford R. Jack, Murray Junop, Sanjay Kalra, Brianna Kaplanis, Raffaella Klima, Edward B. Lee, David Lester, Irene Litvan, Alessandra Longo, Sarah Marzi, Caroline McHutchison, Crystal McLellan, Roisin McMackin, Corey McMillan, Christopher M. Morrow, Indu Navar Bingham, Veronica Noches, Panteleimon Oikonomou, Nicholas Olney, Bjorn Oskarsson, Chiadi Onyike, Markus Otto, Federica Palacino, Francesca Paron, Dung Pham, Yolande Pijnenburg, Barbara Poletti, Kathleen Poston, Mercedes Prudencio, Emma Rhodes, Janice Robertson, Angela Roberts, Alex Salazar, Niyatee Samudra, Christen Shoesmith, Vincenzo Silani, Isis So, Tomas Solomon, Michael Strong, Maria Carmela Tartaglia, David Taylor, Martin Turner, Michael Van Es, Juan-Camilo Vargas-Gonzalez, David A. Wolk.

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Figure legend

Figure 1 The relationship between motor and cognitive/behavioral manifestations of ALS and FTD are illustrated through the motor neuron and frontotemporal axes of the Miami Framework. Within each axis, there is a phenotypic continuum from clinically silent, to prodromal, to clinically manifest disease, with independent timelines for progression within each axis. The term mild motor impairment (MMI) captures the prodromal stage of disease along the motor neuron axis. The terms mild cognitive impairment (MCI) and mild behavioral impairment (MBI) capture the prodromal stage of disease along the frontotemporal axis. Key phenotypic manifestations of disease along each axis are also summarized.

1

Table 1 Classifying behavioral and neuropsychiatric dysfunction in FTD, ALS and related disorders

Diminution of customary behaviors ^a		Emergence of behaviors that are ordinarily absent (Behavioral dysregulation) ^a		Neuropsychiatric ^a		
Volition	Social	Repetitive behaviors (including compulsions)	Behaviors that breach social norms (including impulsions)	Affective	Perceptual	Ideational
Apathy (absence of will or drive) Poverty of speech Diminished self-initiated activity that is not related to physical limitations (inertia)	Reduced personal warmth ^b Disregard for needs / feelings of others ^b Loss of insight (anosognosia, anosodiaphoria) Loss of social interest	Hyperorality Uncharacteristic habits (e.g. new food preferences, new smoking, new list making) Repetitive speech Behavioral rigidity Hoarding Collecting Checking Strumming Tapping	Blurting out or interrupting Grabbing Excessive or inappropriate jocularity Aggression Rash or high-risk actions (e.g. excessive spending, reckless driving) Loss of tact Rule-breaking or criminality Undue familiarity with strangers Hypersexuality Hyper-religiosity Utilization behavior Rule breaking or criminality Poor personal hygiene or impolite physical behaviors (e.g. spitting, flatulence)	Dysphoria Anhedonia Blunting Anxiety Irritability Agitation Euphoria Suicidality	Hallucinations Illusions	Delusions Somatizations Obsessions

^aThese should all reflect a change from baseline or premorbid state.^bThese represent a loss of sympathy/empathy.2
3
4
5

1 **Table 2 Probing for cognitive and behavioral changes during the clinical interview: a primer for ALS neurologists**

Executive Functioning
Trouble planning ahead or making future arrangements (e.g., packing for a trip, scheduling appointments)
Trouble solving everyday problems or handling a household emergency (e.g., small fire, plumbing leak)
Trouble managing business or financial transactions
Trouble completing or staying focused on a task
Trouble performing multi-step tasks (e.g., using a computer or smartphone, cooking a meal)
Difficulty filling out paperwork or online forms (not due to language impairment, e.g., tax returns, medical forms)
Problems organizing personal belongings (e.g., increased clutter, messiness)
Poor judgment or decision-making (e.g., falling victim to financial scams, dressing inappropriately for the weather)
Language
Trouble coming up with the names of objects or people
Mispronouncing words or trouble with grammar
Trouble understanding the meaning of words
Sometimes speech does not make sense (e.g., empty, off topic, not organized, not logical)
Trouble understanding what someone else is saying (not due to hearing loss)
Trouble communicating by writing, or trouble with spelling words
Trouble understanding explanations or plans (e.g., in the doctors' office, or at work)
Apraxia of Speech
Trouble manipulating the lips and tongue to articulate words and sentences in a smooth manner, in the absence of bulbar dysfunction
Memory and Orientation
Forgets about upcoming appointments or events
Forgets details of recent conversations or events
Losing or misplacing personal items (e.g., phone, keys, credit cards, documents)
Trouble remembering short lists of items (e.g. grocery shopping list)
Repeats questions, comments, or stories
Episodes of confusion or disorientation (e.g., unsure of where they are, what day/month/year it is, or what they are supposed to be doing)
Behavioral and Neuropsychiatric
Has an urge to do something over and over again (e.g., hum, tap, count, check, eat certain foods or non-food objects)
Excessively outgoing or cheerful, especially when inappropriate for the context (e.g., laughing at a funeral, approaching strangers)
Displays behaviors that are not socially acceptable (e.g., offensive jokes or comments, chewing with mouth open)
Performs private behaviors in public without embarrassment (e.g., self-stimulation, flatulence, nose picking)
Engages in risky behavior without considering potential consequences (e.g., gambling with large sums of money, reckless driving)
Behavioral rigidity (e.g. strict adherence to a schedule, eating only certain foods)
Change in personality or personal style (e.g., more gregarious, more outlandish clothing/hair/makeup)
Poor insight into symptoms (e.g., denies behavioral changes that are readily apparent to others, unconcerned about future progression or loss of function)
Sad mood, feeling down or depressed (more than difficulty adjusting to diagnosis)
Tendency to be more irritable or angry
Seems emotionally flat or less expressive (e.g., less affectionate, cries or laughs less often, diminished reaction to good or bad news)
Excessively worried or anxious (e.g., increase in reassurance seeking, more easily overwhelmed, difficulty relaxing or sleeping)
False beliefs (e.g. feeling like someone is trying to cause them harm, feeling like the police or FBI are monitoring their thoughts)
Sees something or someone that others do not see (e.g., people, animals, shapes, shadows)
Hearing something or someone that others do not hear (e.g., voices of people whispering or talking, sirens)

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3
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Table 3 Research Priorities

For the ALS community	
Incorporate the use of structured clinical interviews with both study participant/patient and partner to ascertain the presence, severity, and functional impact of cognitive and behavioral symptoms	
Clarify the frequency of subthreshold cognitive performance on tests of executive function, verbal fluency (phonemic and semantic), and memory among pre-symptomatic pathogenic variant carriers at elevated risk for ALS, and among those with clinically manifest ALS. This will entail development of robust normative data.	
Harmonize criteria for MCI/MBI to ensure consistency across the phenotypic continuum of the motor neuron axis. This will entail deciding whether to consider cognitive and behavioral domains jointly or separately.	
Empirically evaluate the sensitivity/specificity of the ECAS (alone) against a full NP battery that includes the ECAS, as a tool for evaluating cognition and behavior among pathogenic variant carriers at elevated risk for ALS	
For the FTD community	
Harmonize criteria for cognitive and behavioral dysfunction to ensure ‘continuity’ between the criteria for MCI/MBI and those for bvFTD/PPA	
Explore the utility of developing a conceptual framework for mild language impairment (MLI)	
Develop better tools for quantifying changes in behavior over time	
Address unanswered questions about the CDR plus NACC FTLD. What is the relationship (e.g. agreement) between CDR of 0.5 (defined by FTD community) and MCI/MBI (defined by the ALS community)? Consider using a CDR plus NACC-FTLD score of 0.25 to designate an uncertain prodromal state, and a score of 0.5 to designate mild but definitive prodromal disease	
For the ALS and FTD communities together	
Develop culturally appropriate tools for measuring cognitive and behavioral changes and establish appropriate normative data to define “impairment” relative to unimpaired populations.	
Undertake a factor analysis of behaviors and neuropsychiatric symptoms from a large dataset to evaluate the utility of the tripartite model proposed in Table 1.	
Establish mutually agreed upon definitions of MCI and MBI (as well as the assessments and tools required to make such designations) along the clinical continuum of the motor neuron and frontotemporal axes.	
Using a common dataset, explore the agreement (and factors that drive disagreement) between designations of MCI/MBI (using current definitions proposed by the ALS community) and a CDR plus NACC FTLD global score of 0.5.	
Evaluate the prognostic utility of different definitions of prodromal states on the frontotemporal axis, for predicting phenotypic conversion to a clinically manifest syndrome. For example, is a prodromal state with predominant executive dysfunction more likely to evolve into ALS, while one with more behavioral dysfunction more likely to develop bvFTD?	
Develop and validate a functional impairment measure that considers the collective impact of cognitive, behavioral, and motor changes on functioning.	
Integrate measures of functional impairment into clinical assessments to help differentiate those with prodromal frontotemporal dysfunction from those with a clinically manifest syndrome.	

ALS = amyotrophic lateral sclerosis; MCI = mild cognitive impairment; MBI = mild behavioral impairment; ECAS = Edinburgh Cognitive and Behavioural ALS Screen; NP = neuropsychological; FTD = frontotemporal dementia; bvFTD = behavioural variant frontotemporal dementia; PPA = primary progressive aphasia; MLI = mild language impairment; CDR plus NACC FTLD = Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration Behaviour and Language Domains.

Miami Framework, Axes I and II



Phenotypic Manifestations

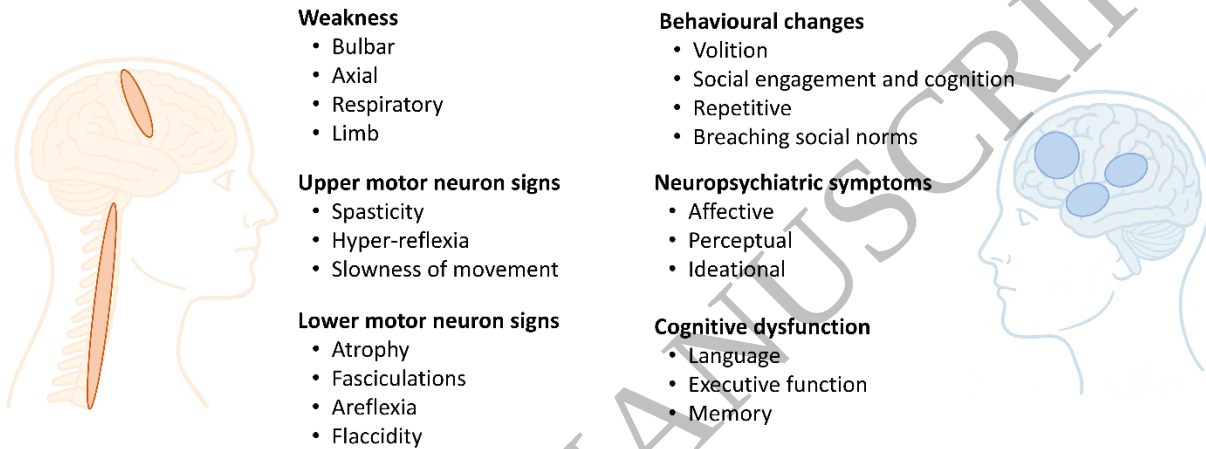


Figure 1
165x104 mm (x DPI)