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# ESTIMATING SEVERITY OF ILLNESS AND DISABILITY IN FRONTOTEMPORAL DEMENTIA: PRELIMINARY ANALYSIS OF THE DEMENTIA DISABILITY RATING (DDR)

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## Background

Current measures of severity and disability do not stage or track the progression of disability in frontotemporal dementia (FTD) well. We investigated the reliability of the newly developed Dementia Disability Rating (DDR) in the measurement and staging of illness severity in FTD and dementia of the Alzheimer type (DAT).

## Material/ Methods:

We studied 48 consecutive patients of the Johns Hopkins FTD and Young-Onset Dementias Clinic, with diagnoses of DAT, FTD, vascular dementia and “other” cognitive disorder (CDNOS). Cases were scored on the CDR and DDR by three trained raters, based on neuropsychiatric examinations performed at first visit and other assessments performed within the preceding year. Consensus ratings were assigned in conference.

## Results:

Inter-rater correlations of DDR sum of ranks scores for DAT ranged from 0.88 to 0.91, for FTD 0.89–0.96 and for CDNOS 0.85–0.97. Similar correlations were observed of the CDR sum of rank scores for DAT and FTD. Correlations of DDR summary scores for DAT were 0.67–0.91 and for FTD 0.79–0.91, as compared to CDR data: 0.87–0.92 ( $p < 0.0001$ ) and 0.80–0.93 ( $p < 0.0001$ ) for DAT and FTD respectively. In DAT patients the correlation between CDR and DDR summary scores was higher than in FTD patients, whereas correlations based on sum of ranks scores were high in both groups.

## Conclusions:

These preliminary data indicate the DDR measures disability in DAT and FTD, with reliability comparable to the CDR. Convergent validity was demonstrated for the DDR.

## SUMMARY

## INTRODUCTION

Frontotemporal dementia (FTD) is a focal neurodegenerative disorder with a modal age of onset in the mid-50s (Johnson et al., 2005; Ratnavalli, Brayne, Dawson & Hodges, 2002; Rosso et al., 2003) and median survival of 6–9 years from onset (Hodges, Davies, Xuereb, Kril & Halliday, 2003; Le Rhun, Richard & Pasquier, 2005; Xie et al., 2008). Its hallmarks are progressive decline in social functions: coarsening of temperament, dispositions, judgment, and comportment; dysregulation of emotions, drives and self-control; and disintegration of language and communication. Aphasia syndromes and motor syndromes are also well recognized (Boeve, 2007). Relative preservation of memory has been demonstrated (Harciarek & Jodzio, 2005; Hutchinson & Mathias, 2007; Kramer et al., 2003; Wittenberg et al., 2008). Measurable impairments in executive functions may be manifest early but are not consistent findings (Wittenberg et al., 2008). Moreover, executive dysfunction is not specific to FTD, as it is observed in dementia of the Alzheimer type, DAT (Collette et al., 2007; Hutchinson & Mathias, 2007), mild cognitive impairments (Lopez et al., 2005; Onyike et al., 2007) and other conditions. While FTD comprises heterogeneous syndromes and diagnosis is facilitated by formal criteria (McKhann et al., 2001; Neary et al., 1998), some longitudinal data indicate that early syndromes may evolve secondary and tertiary syndromes, leading to convergence on a common phenotype (Kertesz, Blair, McMonagle & Munoz, 2007; Kertesz, McMonagle, Blair, Davidson & Munoz, 2005). However, longitudinal data also suggest distinct pathways of decline (Libon et al., 2009).

Despite the early appearance of disability in FTD, the measurement of illness severity (i.e., in terms of progression and stage of illness) has proven difficult. Clinical practice has relied on synthesis of data from diverse sources – interview, examination, brain images, and measures of cognition, behavior and functional capacity) – while research has leaned heavily on instruments, such as Mini-Mental State Examination, MMSE (Folstein, Folstein & McHugh, 1975), and the Clinical Dementia Rating, CDR (Hughes, Berg, Danziger, Coben & Martin, 1982) developed for measurement and staging in DAT. Studies that base severity status on MMSE thresholds rely on critical assumptions: that decay of scores during FTD is linear, that MMSE distributions of different dementia phenotypes and clinical settings are similar, and that correspondence is high between scores, syndromes and disability. However, it is widely recognized that these assumptions are generally not well founded. For example, neither the asocial, behavioral aspects of the phenotype nor the early executive function impairments are well captured by the MMSE. As a result, the MMSE is insensitive to early impairment in FTD. Also, FTD patients show worse cognition and disability (based on CDR scores) than their counterparts with DAT who have the same MMSE score (Rosen et al., 2004). Furthermore, even though the decline follows a curvilinear trajectory of decay in MMSE scores similar to that observed in subjects with DAT (Grossman et al., 2008), some data show that the MMSE scores attained by FTD patients may decline faster than those of their counterparts with DAT (Chow,

Hynan & Lipton, 2006; Rascovsky et al., 2005). In the cognitive realm, decline in speech and language generally develops earlier in FTD than in DAT and progresses faster (Blair, Marczyński, Davis-Faroque & Kertesz, 2007). As a result, greater impairment on MMSE language items (Chow et al., 2006), rather than a faster progression of illness, likely explains the difference in rates of MMSE of FTD and DAT patients. Likewise, aphasia eventually undermines performance in other cognitive domains, resulting in scores that underestimate cognitive function. Considered together with the characteristics of the FTD phenotype, it is clear that correspondence between the MMSE and disease is neither strong nor linear. Nevertheless, the MMSE is still useful for estimating impairment, tracking decline, describing interval change and comparing populations, albeit in relative rather than absolute terms.

There are limitations to the use of the CDR in FTD research as well. The scoring algorithm (Morris, 1997; Morris, 1993), which also does not take into account language and behavioral dysfunction, is weighted to represent memory impairment more than other cognitive and disability factors. Since amnesia is usually not a prominent feature, it is not surprising that the CDR underestimates disability in early FTD (Mioshi, Hsieh, Savage, Hornberger & Hodges, 2010). A modified version developed three years ago, the Frontotemporal Lobar Dementia CDR (FTLD-CDR), adds two domains to capture behavioral and language impairments (Knopman et al., 2008), resulting in improved sensitivity for interval change. Nevertheless, its properties for staging FTD phenotypes are uncertain.

The Frontal Behaviour Inventory, FBI (Kertesz, Nadkarni, Davidson & Thomas, 2000) was developed specifically for measuring behavioral features, discriminating FTD from other dementia types and monitoring interval change. Thus it measures features that are central to the FTD phenotype. Furthermore, as the data are obtained from relatives or friends, rather than patients, measurement is not confounded by language impairments. However, the FBI does not measure the impairments in memory, orientation and praxis that emerge in advanced cases. The items pertain mainly to asocial behaviors, apathy, impulses and compulsions, all of which are highly variable in their frequency and timing and are subject to attenuation or disappearance as the illness advances. Thus one might observe 'improvement' in the scores during longitudinal studies. In fairness, the FBI was not, in conception or design, developed for the purpose of establishing severity or stage of illness, although it has shown utility in longitudinal studies (for example Knopman et al., 2008; Marczyński, Davidson & Kertesz, 2004).

More recently, the Frontotemporal dementia Rating Scale, FRS (Mioshi et al., 2010) was developed to measure rates of progression in the FTD phenotypes. Its 30 items were selected by item analysis of the pooled Cambridge Behavioural Inventory (Wedderburn et al., 2008) and Disability Assessment for Dementia (Gélinas, Gauthier, McIntyre & Gauthier, 1999). Cutpoints were derived statistically to establish categories of equal interval. These categories measured severity and interval change in subjects with different FTD phenotypes, and showed correlation with the MMSE and the CDR (but not with illness duration).

As this brief review illustrates, measuring severity and defining stages of FTD is difficult due to:

- heterogeneity of syndromes and presentations;
- variation in the frequency, timing, persistence and intensity of signal behavioral features;
- limited information on the natural history and rate of progression in FTD;
- relative preservation of memory, orientation and other cognitive faculties impaired early in DAT.

Furthermore, there remains the need for an instrument that measures disease progression and disability, rather than the intensity of suffering (a different goal that is undoubtedly important but readily served by instruments like the FBI and Neuropsychiatric Inventory (Cummings et al., 1994). We recently described the Dementia Disability Rating (DDR), an instrument developed to measure neurodegenerative disability in FTD and other dementia phenotypes in research (Sloane, Smyth, Appleby, Rabins & Onyike, 2010). The conceptual underpinning of the DDR is quantification of capacities immediately pertinent to everyday participation. This grounding in a disability or disablement perspective (Barberger-Gateau et al., 2004; Barberger-Gateau, Fabrigoule, Amieva, Helmer & Dartigues, 2002; Verbrugge & Jette, 1994) represents an “etiologically neutral” method to measure the impact of neurodegeneration and cognitive deficits on individuals. This approach offers potential for comparing severity and stage in frontotemporal dementia phenotypes to other neurodegenerative dementias. In this paper we report a preliminary analysis of some of the characteristics of the DDR. The objectives of the study were to estimate the reliability of the Dementia Disability Rating (DDR) in FTD and DAT, and its correlations with widely used indices of illness, such as the MMSE score, CDR ratings and illness duration.

## **METHODS**

The sample consisted of 48 consecutive patients evaluated at the Johns Hopkins FTD and Young-Onset Dementias Clinic from 2004–2006. A Johns Hopkins Institutional Review Board has approved the research. Patients were included in this study if they fulfilled criteria for the behavioral phenotype of FTD (Neary et al., 1998) or DAT (McKhann et al., 1984) or had other dementia or a cognitive disorder that did not fit either diagnosis and/or did not meet DSM-IV criteria (Diagnostic and statistical manual of mental disorders: DSM-IV, 4th ed., 1994) for dementia. Forty-eight consecutive patients who fit these criteria were identified: 21 FTD, 20 DAT, and 7 cognitive disorder (CDNOS) cases. Cases were scored on the CDR and DDR by CDR-trained raters (K.L.S., S.F.S., C.U.O.) on the basis of structured inspections of the following data:

- 1) neuropsychiatric examinations performed at the first visit;
- 2) clinical examinations, psychometric assessments and functional capacity tests (i.e., occupational or speech/language therapy evaluations) administered within three months before or after the visit;

3) psychometric tests and functional capacity tests administered in the year preceding the visit.

DDR case severity ratings derive from the median of domain rankings. Consensus ratings were assigned in conference. Demographic variables (gender, age at presentation, level of education, marital status), clinical variables (symptoms, functional deficits), cognitive test data (MMSE scores, neuropsychological test scores) and other elements of medical history were abstracted from the medical record.

## **INSTRUMENTS**

*DDR.* The development of the DDR began in 2007 and involved an iterative consensus process. Items were derived from formal diagnostic criteria (McKhann et al., 2001; Neary et al., 1998), clinical experience and literature review – with particular attention to studies describing phenotypes, and the natural history of disease evolution in FTD. For example, several studies describe the evolution of FTD features (Kertesz et al., 2007; Kertesz et al., 2005; Le Rhun et al., 2005; Libon et al., 2009; Pasquier, Lebert, Lavenu & Guillaume, 1999; Pasquier, Richard & Lebert, 2004), and some the evolution of disability (Mioshi et al., 2007; Wicklund, Johnson, Rademaker, Weitner & Weintraub, 2007). The items included behavioral and cognitive features that discriminate for the FTD phenotype, as well as others pertinent to dementia more generally (such as inattention, executive dysfunction, amnesia, disorientation, apraxia, apathy, irritability). The panel of neuropsychiatrists (C.U.O., B.S.A., D.M.B., and P.V.R.) grouped the items into grids defined by symptom domains on one axis and severity/phase of illness (i.e., early, middle or late) on the other. There have been many iterations (>10) of the DDR; early pilots showed that behavioral symptoms are not easily interpreted or classified, due to ambiguous phenomenological boundaries, large variety, and variability in frequencies and temporal occurrence. Subsequent pilots indicated the value of a disability-based approach, which offered: 1) intuitiveness and easy ascertainment, 2) broad application, and 3) unidirectional trajectories. Thus the iterative orientation of the DDR to functions immediately pertinent to everyday life, which were coalesced into five ordinal categories: awareness and orientation, speech and language, self-care and home maintenance, life skills and problem-solving, and compartment and socialization (Table 1). Scoring is based on the ranking of disability in each domain of functional capacity. Overall case severity ratings (i.e., the summary scores) are derived from the median of domain rankings, and two exception rules prevent underestimation of disability in the summary scores:

- 1) when the sum of domain ranks is  $\geq 2$ , the summary score will be  $\geq 1$ ;
- 2) when sum of domain ranks is  $\geq 6$ , the summary score will be  $\geq 2$ .

A score of zero indicates the absence of cognitive and functional impairments, and higher scores reflect greater disability.

**MMSE.** The MMSE was developed as a simple questionnaire to be used for rapid measurement of cognitive deficits during a clinical examination. It comprises 11 questions, covering the following cognitive domains: orientation, memory, attention, object naming, executing verbal and written commands, composing a sentence, and copying a complex polygon. Scoring is distributed unevenly among the domains, so that the orientation, memory and attention domains together account for 21 of the 30 points.

Table 1. Dementia Disability Rating

	IMPAIRMENT				
	None (0)	Slight (1)	Mild (2)	Moderate (3)	Severe (4)
<b>Awareness &amp; Orientation</b>	<i>Fully oriented to time, space, location and/or context</i>	<i>Modest/occasional disorientation to time, space, location and/or context</i>	<i>Significant disorientation to time space, location and/or context. Regularly reliant on cues</i>	<i>Marked disorientation to time, space, location and/or context. Generally needs active guidance</i>	<i>Complete disorientation to time, space, location and context; needs constant guidance; may be oriented to self</i>
<b>Speech &amp; communication</b>	<i>Normal speech fluency, and no impairment in comprehension or pragmatics (i.e., exchange)</i>	<i>Detectable abnormality of speech fluency, comprehension, or pragmatics, but no difficulty conversing</i>	<i>Obvious impairment of fluency, comprehension or pragmatics, but with effort and/or assistance is able to converse</i>	<i>Marked impairments, cannot converse, usually can provide responses and make simple requests or comments</i>	<i>Little or no communication; generally not able to provide responses, or to make requests or comments</i>
<b>Self care &amp; home maintenance</b>	<i>Normal, does not need any help with home maintenance and self-care tasks</i>	<i>Slight difficulty with home/self-care tasks; may need occasional reminders</i>	<i>Often needs reminders and prompting for home/self-care tasks; needs supervision with complex or multistep tasks</i>	<i>Needs supervision and practical assistance with most home/self-care tasks</i>	<i>Complete dependence on others for self-care</i>
<b>Life skills &amp; problem-solving</b>	<i>No difficulty with home or work skills, routines, or transactions, or in solving everyday problems</i>	<i>Modest/occasional difficulty with skills, routines, transactions or solving problems, performance is generally adequate</i>	<i>Significant difficulty with skills, routines, transactions or problem-solving; frequent judgment errors; performance is impaired, needs supervision</i>	<i>Marked difficulty; judgment very impaired; able to make simple decisions (e.g. what to wear or to eat) and/or able to do simple tasks (e.g. folding laundry)</i>	<i>Basic skills essentially lost. Cannot do any routines or transactions, or make any judgments; generally requires assistance with basic tasks</i>

Table 1. Dementia Disability Rating (cont.)

<p><b>Comportment &amp; socialization</b></p>	<p><i>Normal attitudes, habits, and social graces; sensitive to others; conforms to social rules and expectations. Maintains normal involvement in family life, and professional and community activities</i></p>	<p><i>Modest change in emotional or social involvement; sometimes appears disconnected. Lapses in empathy; Modest/occasional inertia, or transgressions, disinhibited or self-centered acts, or carelessness</i></p>	<p><i>Reduced involvement; frequent or moderate inertia; frequent disinhibited, self-centered or careless acts, or transgressions, or lack of empathy. Neglects interests; participation in activities may require coaxing</i></p>	<p><i>Little involvement. Everyday comportment is dominated by indifference and/or inertia; or by impulsive, intrusive acts, loss of graces, rigid routines or compulsions, etc. Interests abandoned; participation in activities is modest and usually requires direction</i></p>	<p><i>Profound loss of involvement; disconnected from immediate environment. Severe disruption of behavior: profound inertia, purposelessness, environment dependence or perseverative actions. Little or no interaction with others, cannot participate in activities</i></p>
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**CDR.** The CDR is an instrument for clinical staging of dementia that ranks cognitive and functional ability in each of six categories: *memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care*. Computation of the summary score is centered on the memory score. Experience with newly developed rules for interpreting CDR sum of ranks scores (O’Byrant et al., 2010) is still limited. Recently the CDR was adapted for FTD research, as the FTLD-CDR, by the addition of two new domains for *behavior/personality and language*. It retains essentially the scoring algorithm of the parent CDR. We do not present any data on the FTLD-CDR in this report.

**Statistical analysis.** STATA version 11.1 (Stata Corp., College Station, TX), was used to analyze the data. Descriptive analyses are based on proportions and medians, with differences analyzed with the Chi-square or Fisher’s exact test, for proportions, and t-tests or the median test, for continuous variables. Non-parametric correlation coefficients were used to estimate inter-rater and inter-variable correlations.

## RESULTS

The characteristics of the sample, including the distribution of CDR and DDR scores, are shown in Table 2. All 21 FTD patients had the behavioral phenotype. The FTD patients were younger than the patients in the other groups. They were comparable to both the other groups with respect to education, and MMSE and illness duration at the first visit, and to DAT patients in gender distribution. Clinical diagnoses were confirmed pathologically in the subjects who were deceased and had undergone autopsy (n = 4: frontotemporal lobar degeneration, FTLD = 2, Alzheimer disease, AD = 2).

Table 2. Sample characteristics

	<b>DAT (n=20)</b>	<b>FTD (n=21)</b>	<b>CDNOS (n=7)</b>
Male, %	55.0	52.4	42.9
Age at onset, years (IQR)	64.6 (60–74)	56.6 (52–70)	63.1 (40–73)
Education, years (IQR)	16 (14–18)	16 (14–18)	16 (14–18)
Married, %	100	76.2	85.7
Illness duration at first visit, years (IQR)	2.5 (1–5)	3.0 (2–5)	3.0 (2–13)
MMSE, score (IQR)	22.5 (16–25)	23 (21–25)	21 (19–28)
CDR, summary score (IQR)	1 (0.5–2)	1 (0.5–2)	1 (1–1)
CDR, sum of ranks score (IQR)	4.5 (3–11.5)	5 (4–9)	5 (4–6.5)
DDR, summary score (IQR)	2 (1–2.5)	2 (2–2)	2 (2–2)
DDR, sum of ranks score (IQR)	7.5 (5–11)	9 (6–12)	7 (7–9)

Data are presented as proportions or medians (interquartile range, IQR).

### **Characteristics of the DDR**

Estimates of the reliability of the CDR and DDR derive from inter-rater correlations of the sum of rank scores. The (non-parametric) Spearman rank correlation coefficients were computed, since the CDR sum of rank scores did not show normal distribution (the DDR scores approximated normal distribution). The data are shown in Table 3. Inter-rater correlations of DDR sum of ranks scores for DAT ranged from 0.88 to 0.91 ( $p < 0.0001$ ); for FTD, from 0.89 to 0.96 ( $p < 0.0001$ ); and for CDNOS, from 0.85 to 0.97 ( $p < 0.05$ ). Inter-rater correlations on the CDR sum of rank scores were similar for DAT and FTD. Correlations for the CDNOS group were lower. Inter-rater correlations of DDR summary scores were from 0.67 to 0.91 for DAT ( $p < 0.0001$ ), and for FTD, from 0.79 to 0.91 ( $p < 0.0001$ ), as compared to the correlations of the CDR summary scores, which were from 0.87 to 0.92 ( $p < 0.0001$ ) and from 0.80 to 0.93 ( $p < 0.0001$ ) for DAT and FTD respectively. Our sample of CDNOS patients was too small for reliable estimation of inter-rater correlations of DDR and CDR summary scores.

Table 3. Inter-rater correlation of CDR and DDR sum of ranks scores by dementia diagnosis

	<b>Clinical Dementia Rating, CDR</b>			<b>Dementia Disability Rating, DDR</b>		
	DAT	FTD	CDNOS	DAT	FTD	CDNOS
<b>Rater 1 v Rater 2</b>	0.85	0.94	0.37*	0.88	0.89	0.85
<b>Rater 1 v Rater 3</b>	0.88	0.96	0.84	0.97	0.96	0.90
<b>Rater 2 v Rater 3</b>	0.90	0.96	0.80	0.91	0.92	0.97

Inter-rater comparisons are based on Spearman's correlation coefficient.  
\* $p = 0.409$ ;  $p < 0.05$  for all other comparisons.



### **Relationships between DDR and CDR scores and other indices of disease progression**

In DAT patients the correlation between CDR and DDR summary scores was higher than was observed in FTD patients ( $\rho = 0.88$  versus  $0.68$ ), whereas correlations based on sum of ranks scores were high in both groups ( $\rho = 0.96$  and  $0.94$ ) – but not in CDNOS patients ( $\rho = 0.70$ ,  $p=0.081$ ). Correlations with the MMSE were very similar: for the DDR sum of ranks,  $\rho = -0.65$  in DAT and  $-0.69$  in FTD ( $p<0.005$  in both cases) and  $-0.84$  in CDNOS, and for the CDR sum of ranks,  $\rho = -0.64$  ( $p < 0.005$ ) in DAT and FTD, and  $-0.88$  in CDNOS. The DDR and CDR sum of ranks did not show any correlation with illness duration.

## **DISCUSSION**

This paper introduces the Dementia Disability Rating, DDR, and provides the first detailed description of its characteristics. Its development involved an iterative consensus process. The consensus approach facilitates bridging of knowledge and experience (which in this case included pilot trials) in order to achieve construct validity and optimal usability. Our data describes the DDR in DAT and behavioral-variant FTD samples. We have not yet examined its characteristics in other FTD phenotypes.

In this study we observed high inter-rater correlations of the DDR sum of ranks, in DAT and FTD, comparable to those obtained for the CDR. The DDR showed better results than the CDR in CDNOS – a heterogeneous group of seven patients who had mild cognitive disorder or other dementias. Inter-rater correlations of the DDR and CDR summary scores were similar in FTD, whereas inter-rater correlations of the DDR summary scores were lower and more variable than those of the CDR in DAT subjects. In our view these data demonstrate high inter-rater reliability for the DDR *item* ratings in the three phenotypes that are at least equivalent to those obtained for the CDR – for which there exists a formalized training protocol (Morris, 1997). The DDR summary scores showed reliability equivalent to the CDR when applied to the FTD cases, but not when applied to the DAT cases. There are two possible explanations for this observation:

- 1) the CDR algorithm for the summary scores may be better suited to DAT than the simpler method of the DDR;
- 2) it is an artifact of the retrospective design, since the CDR algorithm centers on memory function, whose rating may be comparatively straightforward, since it is generally tested during clinical assessments.

Prospective observations are required to resolve this issue.

Preliminary evidence that the DDR possesses convergent validity is provided by the similarly high correlations between the DDR and CDR sum of ranks scores in DAT and FTD patients. There was substantial difference between DAT and FTD patients in the level of correlation between the DDR and the CDR summary scores, which was not unexpected in light of the relative preservation of memory in patients with FTD, the CDR scoring algorithm and the absence of a DDR mem-

ory domain. The negative correlations between the DDR and the MMSE provide further indications of convergent validity. The DDR and the CDR sum of ranks scores showed nearly identical negative correlation with the MMSE. Contrary to our expectation, the DDR showed poor correlation with illness duration, while the CDR showed modest correlation. Illness duration is difficult to ascertain accurately and diagnostic delay is longer for FTD (Pasquier et al., 2004; Passant, Elfgrén, Englund & Gustafson, 2005), suggesting that FTD onset is more difficult to recognize than DAT onset. Furthermore, in FTD rates of disease progression are both more variable and rapid in comparison to DAT (Borroni et al., 2009; Hodges et al., 2003; Hu et al., 2009; Rascovsky, Salmon, Hansen & Galasko, 2008; Rascovsky et al., 2005; Xie et al., 2008), due to factors such as Parkinsonism and concurrent motor neuron disease.

Measurement of disease severity and staging of illness are important functions for practice and research, in terms of application to clinical prognostication, treatment monitoring and long-term planning, and in descriptive studies, clinic-pathologic correlations and clinical trials. In some contexts, such as treatment trials, it suffices to measure interval change in relative terms (i.e., emphasizing sensitivity and reproducibility). Studies focused on rates and extent of disease progression, patterns of evolution, and stages of disability, may require measurement in more absolute terms (i.e., emphasizing scope, depth and validity). For the latter type of measurements, in particular, there are few instruments – all but one developed in the last three years. The CDR is well established in DAT research, and has been widely used in FTD research. Lately it has been shown to underestimate severity in the early stages of FTD (Mioshi et al., 2010). The FTLD-CDR and the FRS have been demonstrated sensitivity to interval change in the behavioral, primary non-fluent aphasia and semantic dementia phenotypes of FTD (Knopman et al., 2008; Mioshi et al., 2010). Given the origins of the FTLD-CDR, utility for clinical staging would be expected but has not been demonstrated. Its inclusion in the National Alzheimer's Coordinating Centers protocols (Beekly et al., 2007) suggests additional characterization will be forthcoming. The utility of the FRS for measuring severity in different FTD phenotypes has been described (Mioshi et al., 2010), but its statistically defined severity thresholds need to be verified in other samples. The DDR differs from these measures in its emphasis on disability, and the observations reported here indicate that this approach fully registers the dementia-related disability – whether this derives from cognitive or behavioral impairments. The DDR shows reliability at least comparable to the CDR in DAT and FTD, and may have promise for estimation and staging of dementia severity in other phenotypes, such as cerebrovascular disease and head trauma, where amnesia and disorientation are not prominent features.

There are some caveats to consider in relation to our observations in this study. The samples are not large, the ratings were retrospective, the diagnoses of DAT and FTD have not been confirmed by pathological examination or genetic analysis, and the study did not examine DDR characteristics in other FTD phenotypes. Since this study did not analyze longitudinal observations, we cannot

yet evaluate the utility of the instrument for measuring interval change. Thus these data are preliminary, but indicate that the DDR measures severity of decline and disability in DAT and FTD with reliability comparable to the CDR. These data also demonstrate convergent validity for the DDR. This is the first report of a DDR characterization study that is in progress, and the next steps will include development of training protocols, implementation of a prospective design in order to facilitate replication, and expansion of these analyses to larger samples.

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