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Cognitive outcome measures for tracking Alzheimer's disease in Down syndrome

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Abstract

Down syndrome (DS) is now viewed as a genetic type of Alzheimer's disease (AD), given the near-universal presence of AD pathology in middle adulthood and the elevated risk for developing clinical AD in DS. As the field of DS prepares for AD clinical intervention trials, there is a strong need to identify cognitive measures that are specific and sensitive to the transition from being cognitively stable to the prodromal (e.g., Mild Cognitive Impairment—Down syndrome) and clinical AD (e.g., Dementia) stages of the disease in DS. It is also important to determine cognitive measures that map onto biomarkers of early AD pathology during the transition from the preclinical to the prodromal stage of the disease, as this transition period is likely to be targeted and tracked in AD clinical trials. The present chapter discusses the current state of research on cognitive measures that could be used to screen/select study participants and as potential outcome measures in future AD clinical trials with adults with DS. In this chapter, we also identify key challenges that need to be overcome and questions that need to be addressed by the DS field as it prepares for AD clinical trials in the coming years.

1. Introduction

Down syndrome (DS) is a developmental disability caused by a full or partial extra copy of chromosome 21 (Korenberg et al., 1994). Complete triplication of chromosome 21 occurs in approximately 95% of DS cases. Other less common forms of DS include translocation (4% of DS cases), in which the extra copy of chromosome 21 attaches to another chromosome, and mosaicism (1% of DS cases), which involves only some cells containing three copies of chromosome 21 and other cells being euploid (Irum et al., 2021). DS is the most common known genetic cause of intellectual disability and has an estimated incidence of 1 in 691 live births in the US (Mai et al., 2019) and 1 in 1000 to 1100 worldwide (World Health

Organization, 2018). Individuals with DS have a physical phenotype consisting of shortened extremities, poor muscle tone, flat nasal bridge, and a large tongue (Bhattacharyya, Sanyal, & Bhattacharyya, 2018). Individuals with DS also share a behavioral phenotype consisting of intellectual disability, language impairments especially in expressive language (Abbeduto, Warren, & Conners, 2007), and mental health problems and maladaptive behaviors including restlessness, inattention, and anxiety (Hodapp & Fidler, 2021).

Adults with DS are also at increased risk for Alzheimer's disease (AD) and experience an earlier age of AD onset than adults without DS (e.g., Zigman & Lott, 2007). The early hallmark features of AD brain pathology, including the accumulation of amyloid-beta (Aβ), are near-universally present in DS by age 40 years (Fortea et al., 2021; Head, Powell, Gold, & Schmitt, 2012; Lao et al., 2017). It is estimated that over half of adults with DS exhibit AD dementia by 55 years of age (Rubenstein, Hartley, & Bishop, 2020) and this rises to 88–100% after age 65 years (Mann & Esiri, 1989). AD has been identified as the proximate cause of death in 70% of cases of adults with DS (Hithersay et al., 2019; McCarron et al., 2017). These findings have led researchers to view DS as a genetically-determined form of AD, similar to the autosomal dominant form of AD (Fortea et al., 2020).

The high risk of AD in DS is posited to be due to the triplication of the amyloid precursor protein (APP) gene located on chromosome 21 (e.g., Prasher et al., 1998; Wiseman et al., 2015). There is excess production of Aβ due to increased APP expression and proteolytic processing. With age, Aβ accumulates into intracellular plaques, which is an early event in the cascade of AD pathology (Jack et al., 2013). Thus, the triplication of the APP gene is considered to be sufficient to cause the elevated rate of AD in DS. Indeed, in a recent case report, an adult with DS who had partial trisomy of chromosome 21 that did not involve the triplication of the APP gene, did not exhibit elevated AD pathology (Doran et al., 2017). Other genes located on chromosome 21 are posited to modify and/or contribute to the effects of increased APP expression through mechanisms such as oxidative stress and inflammation (Fortea et al., 2021). Genes on chromosomes other than 21, including those shown to alter the risk of AD in non-DS populations (e.g., Giri, Zhang, & Lü, 2016; Rossini et al., 2020), may also alter the timing of AD in DS. Although findings are mixed (Kim, Basak, & Holtzman, 2009; Yamazaki, Zhao, Caulfield, Liu, & Bu, 2019), the apoliprotein E (APOE) gene has been associated with an earlier age of AD-related cognitive decline and increased Aβ deposition in DS (e.g., Prasher et al., 2008; Vilaplana et al., 2020).

2. Unfolding of AD pathology and symptomology in DS

The unfolding of AD pathology in DS occurs over many decades (Fig. 1). Aβ and synaptojanin 1 begin accumulating within enlarged endosomes and lysosomes as early as the embryonic stage (e.g., Flores-Aguilar et al., 2020; Martini et al., 2020). Intracellular Aβ, within endosomes, can lead to mitochondrial dysfunction and oxidative damage throughout the developmental period (Benejam et al., 2020). By early adulthood, individuals with DS evidence decreased cerebral spinal fluid (CSF) Aβ concentrations (Dekker, Fortea, Blesa, & De Deyn, 2017; Fortea et al., 2020), that correspond to fibrilized Aβ plaques in the brain (Jennings et al., 2015; Montoliu-Gaya, Strydom, Blennow, Zetterberg, & Ashton, 2021). Elevated levels of tau protein are evident as individual with DS age into their mid-30s

(Fortea et al., 2020). By the mid-40s, tau is hyperphosphorylated, leading to neurofibrillary tangles (Schöll et al., 2019; Startin et al., 2019), increased plasma neurofilament light protein (NfL), an indication of neuroinflammation (Fortea et al., 2018), and decreased brain glucose metabolism and hippocampal volume (e.g., Teipel & Hampel, 2006; Wisniewski, Wisniewski, & Wen, 1985). White matter degeneration has been linked to other AD pathology and observed in individuals with DS in their 40s and 50s (e.g., Bazydlo et al., 2021; Lin et al., 2016). Overall, the pattern of unfolding AD pathology observed in DS has overlap with what has been theorized using the Aβ cascade hypothesis (e.g., Karran, Mercken, & De Strooper, 2011) and modeled using the amyloid, tau, neurodegeneration (AT[N])biomarker framework (Jack et al., 2016) with the autosomal dominant AD population (e.g., Fortea et al., 2021; Lott & Head, 2019; Rafii, 2020).

Similar to autosomal dominant and late onset AD, there is a long preclinical phase in DS, where AD-related pathological changes have occurred but clinical AD symptomology is not present (e.g., Fortea et al., 2020; Head & Ances, 2020; Lott & Head, 2019). During this preclinical stage, adults with DS continue to be “cognitively stable,” meaning that their cognitive functioning remains intact with no more than normative aging-related changes. The cognitively stable stage is then followed by the transition into a “prodromal” stage, where initially mild and subtle declines in cognition and functioning occur at a level beyond normative aging. The term mild cognitive impairment (MCI) has been used to describe this intermediate stage between being cognitively stable and clinically-significant AD dementia in the DS population and in other AD populations. Finally, the ‘AD dementia’ stage involves marked impairments in cognitive and functional ability.

Studies indicate a median age of clinical status of AD dementia ranging from approximately 50 to 58 years in adults with DS (e.g. Knox et al., 2021; Rubenstein et al., 2020; Sinai et al., 2018) with transition to the prodromal stage reported to occur around age 50 to 53 years (Fortea et al., 2020). However, there is considerable variability in the age of onset of the prodromal stage and clinical AD dementia in DS. Some studies report that up to 55% of adults with DS exhibit clinical AD dementia by age 49 years, while other studies indicate that 15% to 77% may not exhibit clinical AD dementia until their 60s (Holland, Hon, Huppert, & Stevens, 2000; Lai & Williams, 1989; Tyrrell et al., 2001). A variety of factors are thought to drive this variability including genes such as APOE (Fortea et al., 2020), co-occurring physical health conditions (Lao et al., 2020), and lifestyle (e.g., Mihaila et al., 2019). As for survival, the median survival time from clinical AD dementia to death in adults with DS has been reported to be 3.8 years, which is half as long as what has been reported for late onset and autosomal dominant forms of AD (Sinai et al., 2018). However, there is a need for more longitudinal studies to fully understand the course of prodromal AD in DS.

Given the high risk for AD in DS, developing interventions that can delay or prevent the onset of AD-related pathology and cognitive decline is of high importance to the field of DS. Due to this critical need, the National Institutes of Health have funded several studies aimed at establishing biomarkers of AD pathology in DS and understanding their association with AD-related cognitive decline and dementia. Funded studies include the Alzheimer’s Biomarkers Consortium of Down syndrome (ABC-DS), which involves a collaboration

between eight primary research sites located across the United States and one in the United Kingdom. Inherent in this effort is the aim of establishing feasible, reliable, and valid measures that can track AD-related cognitive declines in adults with DS. Similar large-scale efforts aimed at identifying valid measures of cognitive declines occurring in the progression of AD in DS are underway both in the United States and other countries, including, the LuMIND-International Down Syndrome Community (LuMIND-IDSC)led Longitudinal Investigation for Enhancing Down Syndrome Research (LIFE-DSR) Study and Down Syndrome—Clinical Trial Network (DS-CTN), London Down Syndrome Consortium (LonDownS) and the Down Alzheimer Barcelona Neuroimaging Initiative. Recent efforts to launch large data management and portals (e.g., NIH-funded Data Coordinating Center for INCLUDE projects) are also underway and will allow DS researchers to combine and analyze data on common cognitive measures across studies.

With the identification of feasible, valid, and sensitive measures for tracking AD-related cognitive decline in adults with DS, the field will be primed to support clinical AD trials, such as the efforts that are underway in the Trial-Ready-Down Syndrome (TRC-DS; https://clinicaltrials.gov/ct2/show/NCT04165109) study. These future AD clinical trials in DS are likely to be aimed at early AD pathology, including Aβ or tau accumulation, and are likely to focus on individuals in the “cognitively stable” and/or “preclinical” stage. Thus, having established measures of early cognitive decline that align with biomarkers of AD during the preclinical stage may be especially important for screening and identifying participants for these clinical trials and for monitoring intervention effectiveness across time.

3. Challenges in assessing cognition and dementia in DS

Direct assessments of cognitive decline and dementia symptoms, however, can be challenging with adults with DS. Otherwise healthy adults with DS (i.e., prior to the onset of AD-related cognitive decline) generally score on standardized measures of IQ in the mild (IQ: 50–69) to moderate (IQ: 35–49) intellectual range and evidence adaptive functioning impairments in-line with this severity level (Hamburg et al., 2019). This means that measures developed to assess AD-related cognitive decline in neurotypical populations (i.e., adults from the general population of similar age) are typically too difficult for adults with DS. As a result, the DS field often uses cognitive measures designed for younger populations (e.g., children), who are of matched mental age to adults with DS, and/or modified versions of measures originally created for the neurotypical adult population.

While the majority of adults with DS score in the mild to moderate range of intellectual functioning (based on cognitive measures and adaptive skill measures) prior to AD-related decline, a subset of adults with DS have cognitive and functional ability levels that are more severely affected and require extensive to pervasive support in everyday life (Karmiloff-Smith et al., 2016). The large heterogeneity in intellectual functioning across the DS population, creates further challenges for cognitive assessment. Among research samples of adults with DS, IQ scores have been reported to range from 8 to 67, with mental age equivalents ranging from ≤2 years to 12 years across IQ tests and samples (e.g., Carr, 1988; Dykens, Hodapp, & Evans, 2006; Godfrey & Lee, 2018). Expressive vocabulary on standardized tests has also ranged from ≤2 years to 12 years in adults with DS (e.g.,

Finestack & Abbeduto, 2010; Kristensen et al., 2022; Pennington, Moon, Edgin, Stedron, & Nadel, 2003). Most traditionally used cognitive measures are not designed for such a wide range of functioning.

Many of the existing cognitive measures relevant to the early progression of AD in DS have poor sensitivity and specificity in adults with DS with a mental age equivalent of ≤4 years or IQ <30 to 40 (Pezzuti et al., 2018). Heterogeneity in intellectual functioning level and expressive language ability across the DS population also means that single indicators (i.e., cutoff score) on measures of cognition are not relevant for tracking AD. Focusing on within-person change in scores on a measure overtime can help address this problem. However, to date, little is known about how much decline on a specific test is clinically relevant and indicative of AD-related change. This issue is complicated by the possibility that the amount of change on a specific test that signals clinically meaningful decline could vary as a function of premorbid level of intellectual disability.

3.1 Floor effects

One frequently encountered problem with cognitive measures for the DS population is floor effects (i.e., scores clustered at or near the lowest possible score). Floor effects occur when tests or parts of tests are too difficult for all or for a marked portion of the individuals assessed. Floor effects lead to skewing in the mean and in the distribution of scores, making it impossible to detect a reduction in the score over time. In order to minimize floor effects, many studies examining AD in DS have study inclusion criteria that involve an IQ cut off score that excludes adults with DS who have more severe intellectual impairments (e.g., IQ <50 and requiring extensive to pervasive support in everyday life) (e.g., Breia et al., 2014; Hamburg et al., 2019).

In recent years, z-scores, or approaches that derive true deviations from population norms, have been used in populations with intellectual disability including DS. These alternative approaches attempt to capture performance near the floor of the test by increasing the range of scores (e.g., Hessl et al., 2009; Pezzuti et al., 2018). Other researchers have recommended the use of raw scores, rather than standard scores (Hamburg et al., 2019). Creating measurement standards and understanding which scoring methods are most sensitive to AD-related changes for adults with DS, given their widely varying premorbid level of intellectual disability, is an important step for the field in the coming years. Indeed, these efforts are particularly important for establishing tests that have few floor effects in lower functioning adults with DS (i.e., those with severe/profound premorbid levels of intellectual disability based on cognitive and adaptive living skill support needs). Until the field has identified cognitive measures that are reliable and valid for capturing AD-related decline in adults with DS with severe or profound premorbid levels of intellectual disability, this subgroup will not be able to be included in clinical AD trials.

3.2 Co-occurring conditions

Another challenge to capturing AD-related cognitive decline in adults with DS is the high rate of co-occurring mental and physical health conditions. Many of these conditions can impair cognitive performance in ways that mirror what is seen early on in the progression

to AD in adults with DS, leading to over- or under-diagnosis of clinical AD. In terms of physical health, adults with DS are at a higher risk for hypothyroidism than the general population (e.g., Guaraldi et al., 2017), which has been shown to impact learning and memory (Lai et al., 2021). Adults with DS are also at risk for vision (e.g., cataracts, strabismus, and keratoconus) (Hashemi, Mehravaran, Asgari, & Dehghanian Nasrabadi, 2021; Krinsky-McHale et al., 2014) and hearing problems (Bent, McShea, & Brennan, 2015) that may affect visual processing, comprehension of instructions, and performance on visual or verbal memory tests in ways that mimic AD-related cognitive decline. Adults with DS are also at risk for disrupted sleep (Giménez et al., 2018) and sleep disordered breathing problems (e.g., Trois et al., 2009), which are linked to memory and executive functioning difficulties in DS (Cody et al., 2020; Gandy et al., 2020) which can also mimic AD-related cognitive declines. Vitamin B2 and folate deficiency are also elevated in the DS populations and their effects on cognition can overlap with those seen in AD dementia (Prasher, 2005). Finally, adults with DS are at risk for late-onset epilepsy (De Simone, Puig, Gélisse, Crespel, & Genton, 2010; Sharma et al., 2018), and this condition can cause diagnostic uncertainty, as it also contributes to cognitive decline and disrupts the performance of activities of daily living (Lott et al., 2012). More recently, late-onset epilepsy has been seen as an indicator of AD dementia (Altuna, Giménez, & Fortea, 2021).

Mental health problems also complicate the assessment of AD-related cognitive declines in DS, particularly if information about prior cognitive functioning is not available. Relative to their neurotypical peers, individuals with DS have a heightened prevalence of autism spectrum disorder (Moss, Richards, Nelson, & Oliver, 2013) and attention-deficit/hyperactivity disorder (Del Hoyo Soriano et al., 2020), which are both associated with their own profiles of cognitive strengths and weaknesses and variability in testing performance. As a result, these conditions can make it difficult to determine if AD-related cognitive declines are occurring. In a study by Tassé et al. (2016), depression and anxiety were found to be common mental health problems in adults with DS, and the rate of these problems increased across adulthood. Obsessive compulsive disorder, and ordering and tidiness in particular, also have an elevated prevalence in adults with DS relative to the neurotypical population (Prasher & Day, 1995; Vicari, Pontillo, & Armando, 2013). These mental health conditions can affect attention, motivation, working memory, processing speed, perseveration, and task completion and performance of everyday living skills (e.g., Culpepper, Lam, & McIntyre, 2017)—all of which may result in declines in testing performance that mirror what would be seen in the early stages of AD-dementia in DS.

3.3 Regression

The phenomenon of behavioral regression can also complicate the assessment of AD-related cognitive decline in DS. Regression involves the sudden onset or progressive “regression” (known by other names, including “DS disintegrative disorder” or “idiopathic regression in DS”) that occurs in a subset of individuals with DS in late adolescence to early adulthood. Regression has been reported to involve a wide range of symptoms including the loss of daily living skills, language skills, and motor functions, changes in personality such as disinterest/withdrawal, and sleep disorders (see Rosso et al., 2020; Walpert, Zaman, & Holland, 2021).

It is now widely agreed that regression is not part of the early unfolding of AD pathology in DS. Indeed, treatment of regression, which most often involves anti-depressants or anti-psychotics, normally leads to at least partial recovery of cognitive and functional abilities with time. However, only a minority of adults with DS (about one-third; Walpert et al., 2021) who experience regression return to their baseline level of cognitive and functional abilities. Regression can thus complicate efforts to capture baseline levels of cognitive functioning prior to AD pathology. It can also be mistaken for early AD-related symptomology. While regression is not considered to be part of AD pathology, it remains unclear if it shares etiological mechanisms with AD and/or if regression at earlier life stages accelerates AD pathology or cognitive decline. In a recent small study (Handen et al., 2021), there was evidence that there may be subtle differences in AD-related proteomic biomarkers (i.e., tau and NfL) between adults with DS in their 20s through 40s that were reported to have experienced regression compared those who did not.

4. Cognitive measures and AT(N) biomarkers

Despite the challenges to assessing cognitive decline and in differentiating AD dementia from other co-occurring conditions in DS, a body of research has emerged on cognitive measures that appear to be promising for tracking AD-related progression in DS. A subset of this research has been aimed at identifying cognitive measures that are sensitive to early AD biomarkers of pathology, as has been done in the autosominal dominant AD population. In particular, a growing body of research has identified cognitive measures that are sensitive to AD biomarkers, drawing on the AT(N) framework. The AT(N) framework is an AD biomarker descriptive classification scheme used in non-DS populations to map the progression of AD pathology (Jack et al., 2016). The ‘A’ refers to biomarkers of Aβ (e.g., PET Aβ or CSF $A\beta_{42}$). The ‘T’ refers to biomarkers of tau (e.g., tau PET or CSF phospho tau). The ‘(N)’ refers to biomarkers of neurodegeneration or neuronal injury (e.g., [^{18}F] fluorodeoxyglucose-positron emission tomography [FDG–PET], structural MRI, or CSF total tau).

Table 1 identifies some of the cognitive measures that have been associated with AT(N) biomarkers in the DS population. Much of the research around cognitive measures and the AT(N) model has been cross-sectional and focused on PET Aβ (i.e., ‘A’ in the AT(N) model (e.g., Annus et al., 2016; Hartley et al., 2014; Nelson et al., 2011). Among the handful of longitudinal studies (e.g., Hartley et al., 2017, 2020), there is evidence of an association between PET Aβ and early AD cognitive decline (e.g., transition to the prodromal stage). Using the PET imaging agent [^{11}C]PiB, Hartley et al. (2020) reported that non-demented adults with DS with marked Aβ accumulation (Aβ+group) performed worse on measures of memory, visual attention, executive function, and visuospatial ability than those without marked accumulation (Aβ−group). These cognitive domains were assessed using the Cued Recall Test (Zimmerli & Devenny, 1995), cancelation subtest of the Developmental Neuropsychological Assessment (NEPSY; Korkman, Kirk, & Kemp, 2007), Stroop Cats and Dogs Task (Ball, Holland, Treppner, Watson, & Huppert, 2008), and Block Design items from the Weschler Intelligence Scales for Children (WISC-IV; Wechsler, 2004) and Haxby extension (Haxby, 1989). Moreover, across time, the Aβ+ group had greater decline in memory, visual attention, and visuospatial ability than the Aβ− group. However, only

the Cued Recall Test differentiated the Aβ+ group from the subset of adults with DS who converted from Aβ− to Aβ+ during the study (spanning 2–8 years). Thus, episodic memory was the cognitive domain affected earliest in the transition from preclinical to prodromal AD in DS (i.e., it was the only measure to differentiate those who recently converted from Aβ− to Aβ+ from those who were Aβ−). These early episodic memory declines appeared to be followed by declines in visual attention, executive functioning, and visuospatial abilities, with these non-memory domains differentiating the Aβ− group from the Aβ+ group. Episodic memory is similarly the earliest cognitive domain impacted by AD pathology (e.g., PET Aβ and PET tau) in the autosomal dominant and late-onset AD populations (Gagliardi et al., 2019; Tromp, Dufour, Lithfous, Pebayle, & Després, 2015). Recent DS research (Hom, Taylor, et al., 2021; Hom, Walsh, et al., 2021) suggests that PET Aβ accumulation in the frontal lobe specifically, may lead to early impairments in memory and other cognitive domains as assessed by the Rapid Assessment of Developmental Disabilities (RADD; Walsh et al., 2007), WISC-IV Digit Span Forward, and Stroop Cats and Dogs Task.

There is also evidence of an association between CSF biomarkers of the “A” in AT(N) and clinical ratings of AD based on a battery of cognitive measures (e.g., Fortea et al., 2018), including the Cambridge Examination for Mental Disorders of Older People with Down Syndrome and others with Intellectual Disabilities (CAMDEX-DS; Ball et al., 2004) and the Cambridge Cognition Examination (CAMCOG; Roth et al., 1986). Mixed evidence has been reported for an association between biomarkers of plasma Aβ (e.g., Aβ 1–40 and Aβ 1–42 and their ratio) and AD-related cognitive decline (Fortea et al., 2018; Iulita et al., 2016) and AD clinical status (Petersen et al., 2021).

Cognitive measures have also been found to correlate with biomarkers of PET tau (i.e., ‘T’ in the AT(N) model) prior to AD dementia in DS. In a small sample (n = 12), Rafii et al. (2017) found that PET tau measured via 18F-AV-1451 was negatively associated with performance on the Observer Memory Questionnaire (OMQ; O’Shea, 1996), Vineland-II (Sparrow & Cicchetti, 1989), recent memory items of the CAMCOG, and the Repeatable Battery for the Assessment of Neuropsychological Status Total score (RBANS; Randolph, Tierney, Mohr, & Chase, 1998). In a sample of 92 non-demented adults with DS, Tudorascu et al. (2021) found that higher tau PET 18F-AV-1451 was associated with lower episodic memory scores (on the Cued Recall Test), motor control and planning (on the Purdue Pegboard (Vega, 1969), and dementia symptoms on the Down Syndrome Mental Status Examination (DSMSE; Haxby, 1989).

In a follow-up study on the same sample of non-demented adults with DS analyzed by Tudorascu et al. (2021), elevated PET tau predicted lower episodic memory performance in models that controlled for Aβ. Thus, early declines in episodic memory on the Cued Recall Test were most closely associated with the presence of PET tau than Aβ accumulation alone (Hartley et al., 2022). Research by Fortea et al. (2018) also found that biomarkers of CSF (e.g., 181-phosphorylated tau and total tau) differentiated adults with DS deemed to be symptomatic for AD dementia (i.e., in prodromal stage) versus those deemed to be asymptomatic based on the CAMOG and CAMDEX-DS. Plasma biomarkers of total tau have also been found to be sensitive to AD-related cognitive decline in DS, both in terms

of differentiating those in the cognitively stable stage from the prodromal stage of AD and from AD dementia (e.g., Fortea et al., 2018; Petersen et al., 2021).

Less has been published on cognitive measures sensitive to biomarkers of (N) in the AT(N) model in the DS population, and there appears to be little consensus on what the optimal biomarkers of (N) are for DS within or across various domains of biomarkers (e.g., imaging, plasma, and CSF). PET FDG studies of adults with DS have shown an association with AD dementia status (Haier, Head, Head, & Lott, 2008; Neale, Padilla, Fonseca, Holland, & Zaman, 2017; Rafii et al., 2015), as well as cognitive impairments on the DSMSE (Dani et al., 1996) and Dementia Questionnaire for Mentally Retarded Persons (Evenhuis, 1992, 1996; Haier et al., 2008). Structural MRI changes (e.g., T1-weighted indices) have been associated with a status of AD dementia in DS (Matthews et al., 2016; Rafii et al., 2015). Diffusion tensor imaging biomarkers of white matter degeneration have also been associated with cognitive declines (including specifically in memory) prior to AD dementia in DS (Bazydlo et al., 2021; Rosas et al., 2020), and have been associated with AD dementia status (Lin et al., 2016; Powell et al., 2014). Finally, plasma and CSF biomarkers of neuroinflammation, and specifically NfL, have been reported to be an indicator of both prodromal and AD dementia status in DS (Fortea et al., 2018; Petersen et al., 2021) and associated with scores on the CAMOG, Cambridge Neuropsychological Test Automated Battery (CANTAB®, 2016) Paired Associates Learning subtest, and OMQ (Rafii et al., 2019).

In summary, a growing body of research has identified cognitive correlates of biomarkers (imaging, CSF, and plasma) of AD pathology in DS drawing on the AT(N) framework. These studies have found associations between biomarkers of Aβ and tau and early and subtle memory declines, with the presence of elevated Aβ and tau being most sensitive to memory impairments in PET imaging studies. These early cognitive declines were closely followed by associations between biomarkers and declines in attention and executive functioning and then declines in other cognitive domains, as show in Fig. 2. Biomarkers of (N) have also been linked to AD-related cognitive decline. Going forward, it will be important for the field to examine profiles (A+/T+/(N)− vs A+/T+/(N)+) of biomarkers of A, T, and (N) in adults with DS in order to better understand the time-ordered sequence of AD pathology in relation to changes in cognition.

5. Measures sensitive to AD-related decline and dementia symptoms

5.1 Prodromal stage

Another line of DS research has been aimed at identifying measures sensitive to cognitive decline indicative of the prodromal stage, which is often when an MCI clinical status is given. Much of this research has focused on identifying cognitive measures that can capture subtle cognitive declines that occur prior to the onset of AD dementia and understanding which cognitive domains decline first (i.e., their sequence of decline). This work has leveraged data-driven methods and pooled data across studies to estimate long-term trends from cross-sectional and short-term longitudinal studies of adults with DS (e.g., Aschenbrenner et al., 2021; Firth et al., 2018; Silverman et al., 2021). In general, research studies on cognitive measures of the prodromal stage of AD in DS have found that directly-administered

measures of cognition are more sensitive to early decline than informant-based measures (Firth et al., 2018; Prasher, 2018).

Findings from two large-scale efforts have largely converged in terms of the cognitive domains affected in the transition to prodromal AD (Aschenbrenner et al., 2021; Firth et al., 2018; Krinsky-McHale, Zigman, Lee, et al., 2020). Firth et al. (2018) explored the sequence of cognitive decline prior to clinical dementia, drawing on a cross-sectional sample of 283 young (16–35 years) and middle-aged (36+ years) adults with DS. Using an event-based model, the earliest decline occurred in memory, attention, visuomotor ability, and verbal fluency; this decline was assessed based on the first trial memory score from the CANTAB paired associates learning task, NEPSY-II car and motorbike score (Hatton et al., 2001) and a semantic verbal fluency task.

Aschenbrenner et al. (2021) compiled data from five large longitudinal studies to identify measures sensitive to the early indicators of transition to the prodromal stage of AD in DS. A machine-learning approach was used to examine the items and measures, which differed across the five studies. Their sample included 312 adults with DS, all without a diagnosis of clinical AD dementia, with at least two cycles of data. After adjusting for age and baseline level of intellectual functioning, their models showed that declines in memory and attention occurred early on, and that these declines were followed by declines in measures of executive function. The authors concluded that that the Cued Recall Test and CANTAB paired associate learning test were promising directly-administered measures of memory for consideration in AD clinical trials in DS (see Aschenbrenner et al., 2021 for full list of recommended measures).

A third large-scale recent study has also focused on cognitive measures of the prodromal stage in adults with DS. In this study, researchers examined cognitive measures that could differentiate adults with DS with a clinical status of MCI from those deemed to be cognitively stable (Silverman et al., 2021). It is important to note that the MCI stage continues to be debated within other AD populations (Dubois & Albert, 2004; Petersen, 2009), and is difficult to diagnose within the DS population. In the Silverman et al. (2021) study, a clinical status of MCI was based on within-person change (to the extent possible) and the individual's overall profile of performance on directly-administered cognitive measures as well as informant-report measures. Drawing on a large (n ¼ 269) longitudinal study, Silverman et al. (2021) examined cognitive measures that differentiated the 67 adults with DS who developed MCI from those who remained cognitively stable. They found that adults with DS who developed MCI had greater declines in memory, mental status, visuospatial ability, and adaptive behavior relative to those who remained cognitively stable. These cognitive domains were measured using the Selective Reminding Test (Buschke, 1973), Modified Mini Mental Status Evaluation–Down syndrome (Wisniewski & Hill, 1985), DSMSE; Test for Severe Impairment (Albert & Cohen, 1992), Block Design subtests of WISC-Revised (Wechsler, 1974), and adaptive behavior on the American Association on Mental Deficient Adaptive Behavior Scale, Part I (ABSI; Nihira, 1976). In this study, performances on a measure of verbal fluency (McCarthy Category Fluency Test: McCarthy, 1972) and on the Beery-Buktenica Test of Visuomotor Integration (Beery, Buktenica, &

Beery, 2004) did not differentiate those who developed MCI-DS from those who remained cognitively stable, but these measures were associated with transition to AD dementia.

Overall, recent data-driven and large sample efforts are remarkably consistent in identifying memory and attention as the domains impacted early on in the transition to prodromal AD in DS, with subsequent changes in visuospatial ability, executive functioning, verbal fluency, motor control and planning, and mental status, all prior to AD dementia (Fig. 2). This sequence is well-aligned with studies examining the cognitive correlates of AD biomarkers of Aβ and tau reviewed earlier (e.g., Hartley et al., 2017; Tudorascu et al., 2020) which also suggest that declines in memory, followed by declines in attention and executive functioning, are associated with biomarkers of early AD pathology in DS. These findings also align with other recent studies that have reported that measures that assess a range of cognitive domains, including memory, attention, and executive functioning, differentiate adults with DS clinically deemed to be in the prodromal stage (or have MCI) from those who were cognitively stable (e.g., Benejam et al., 2020; Fortea et al., 2018; Hom, Taylor, et al., 2021; Hom, Walsh, et al., 2021; Krinsky-McHale et al., 2020). Table 1 displays cognitive measures that have been found to be associated with cognitive changes associated with the prodromal stage of AD, including a clinical status of MCI, in DS.

5.2 AD dementia

Identifying feasible, valid, and sensitive cognitive measures of the AD dementia stage is also critical for the longitudinal evaluation of the effectiveness of AD clinical trials in DS. Insight into how to track change during the dementia stage can also yield information to help caregivers and health providers anticipate care needs and the course of progression following clinical dementia diagnosis (Jozsvai, Hewitt, & Gedye, 2018). Direct measures of cognition can become increasingly difficult for individuals with AD dementia, due to their reduced level of cognitive functioning (which exacerbates floor effects), and because lengthy testing batteries can be taxing. The late onset of seizures, which is linked to AD dementia in DS (e.g., De Simone et al., 2010; Möller, Hamer, Oertel, & Rosenow, 2001), can also make direct testing difficult (Lott et al., 2012).

In DS, AD dementia is characterized by cognitive, physical, and behavioral deterioration, including memory loss, communication problems, loss of mobility, change in eating, weight loss, and problems with continence (McCarron et al., 2018). It has also been associated with night-time confusion, agitation, wandering, and visual hallucinations (Urv, Zigman, & Silverman, 2010). There is also evidence that the rate of cognitive decline in adults with DS accelerates after the transition to AD dementia (Keator et al., 2020) and that men and women with DS may decline at different rates; specifically, women decline faster than men following AD dementia (e.g., Keator et al., 2020), which is also true in non-DS populations (see Ferreira, Ferreira Santos-Galduróz, Ferri, & Fernandes Galduróz, 2014).

5.3 Direct measures

Table 1 highlights some of the direct measures that have shown promise for detecting AD dementia in DS. The RADD measures overall cognition using selected items from tests that were designed for neurotypical populations. On the RADD, a total score of <20 had a

sensitivity of 0.89 and a specificity of 0.75 for detecting AD dementia in adults with DS with severe ID, and a total score of <60 had a sensitivity of 0.95 and specificity of 0.79 for classifying AD dementia in those with mild ID (Hom, Walsh, Doran, & Lott, 2018). The CAMCOG-DS has also been shown to differentiate individuals with DS who are cognitively stable from those with AD dementia (Fonseca, Ball, & Holland, 2018), with a sensitivity of 0.75 and specificity of 0.88 for people with mild ID and a sensitivity of 0.84 and specificity of 0.84 for people with moderate ID (Benejam et al., 2020). The CAMCOG-DS also has limited floor effects in adults with DS with mild and moderate premorbid ID levels (Hon, Huppert, Holland, & Watson, 1998). The Severe Impairment Battery (SIB; Saxton et al., 2005), which measures nine domains of cognitive functioning has also been shown to be effective in differentiating between early-stage and late-stage AD dementia in adults with DS (Koehl, Harp, Van Pelt, Head, & Schmitt, 2020), with a sensitivity of 0.63 and specificity of 0.59 (Wallace et al., 2021). The Test for Severe Impairment (TSI) covers a range of cognitive functions and was found to have few floor effects in adults with DS with premorbid ID in the moderate to severe range (Tyrrell et al., 2001). The TSI has been found to differentiate adults with DS with versus without AD dementia (Tyrrell et al., 2001), but there are no published rates of sensitivity or specificity for the DS population. The DSMSE has also been found to differentiate adults with DS with versus without AD dementia, although some researchers have noted that this measure was better suited for adults with DS with mild to moderate premorbid ID (McCarron, McCallion, Reilly, & Mulryan, 2014). Using a Total score (Free + Cued), the Cued Recall Test was recently found to have a sensitivity of 0.84 and specificity of 0.81 for distinguishing cognitively stable adults with DS from those with AD dementia (Krinsky-McHale, Silverman, Lee, et al., 2022, and a sensitivity of 0.91 and specificity of 0.75 in a previous study (Devenny, Krinsky-McHale, & Kittler, 2006).

5.4 Informant measures

Informant reports aimed at capturing cognitive and functional decline have also been found to be sensitive to clinical AD in DS. The Dementia Questionnaire for People with Learning Disabilities (DLD; Evenhuis, 2018) is an informant-report of cognitive and behavioral changes. The criterion for clinical AD is an increase in the Sum of Cognitive Scores of ≥7 points and/or an increase of the Sum of Social Scores of ≥5 points in comparison to baseline (premorbid) functioning. The standardization study using these criteria found the DLD to have a sensitivity of 1.00 and a specificity of 0.75 for classifying AD dementia in DS (Deb & Braganza, 1999; Evenhuis, 2018), whereas Shultz et al. (2004) found the DLD to have a sensitivity of 0.65 and specificity of 0.93 among their sample of DS participants with and without AD dementia. Additionally, McCarron et al. (2014) found the DLD to be sensitive to change across time and Harp et al. (2021) demonstrated that the DLD Sum of Cognitive Scores combined with the Vineland-II Community subdomain score had a sensitivity of 1.00 and a specificity of 0.81 for detecting clinical AD in a sample of adults with DS, in which 31% had profound ID. In other studies, however, the DLD was reported to be plagued by floor effects in adults with profound ID (McKenzie, Metcalfe, & Murray, 2018). Regardless of premorbid ID level, a single assessment cut-off score was found to be less sensitive and specific to AD dementia compared to longitudinal changes in scores (Evenhuis, 1996, 2018).

The Dementia Scale for Down Syndrome scale (DSDS; Gedye, 1995) was designed to measure cognitive decline in adults with DS, especially those with severe or profound ID. In the standardization study 76% had severe or profound ID, and the DSDS had a sensitivity of 0.85 and specificity of 0.89 for AD dementia. By comparison, the DLD had a sensitivity and specificity of 0.92 for the same sample. In a subsequent study by Shultz et al. (2004), the DSDS had a sensitivity of 0.65 and specificity of 1.00, whereas the DLD's corresponding values were 0.65 and 0.93, respectively. For adults with DS with mild to moderate ID, the DSDS was found to be better at detecting individuals with middle or late stages of dementia relative to those in the early stage of dementia (Prasher, 2018).

The CAMDEX-DS includes an informant interview and is available in English, Portuguese, Spanish, and German. Using cohorts from the United Kingdom, the CAMDEX-DS had a sensitivity of 0.88 to1.00 and specificity of 0.94 for classifying the clinical AD in DS samples (Ball et al., 2004; Beresford-Webb et al., 2021). The CAMDEX-DS also successfully differentiated between adults with AD dementia from those with co-occurring mental conditions and without dementia (Beresford-Webb et al., 2021). In Brazil, the Portuguese version was reported to have a sensitivity of 1.00 and specificity of 0.98 (Fonseca et al., 2019). The CAMDEX-DS has recently been updated and is now the CAMDEX-II (Beresford-Webb et al., 2021). The Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID; Deb, Hare, Prior, & Bhaumik, 2007) is also effective for classifying AD dementia in DS, with a published sensitivity of 0.92 and specificity of 0.97. However, it has been noted that the DSQIID may not be as useful for adults with severe or premorbid ID or advanced dementia if using the fixed cut-off score of 20 (O'Caoimh, Clune, & Molloy, 2013).

The National Task Group-Early Detection Screen for Dementia (NTG-EDSD) is a freely available measure (Esralew, Janicki, DiSipio, Jokinen, & Keller, 2013; Esralew, Janicki, & Keller, 2018) that has been translated into at least 18 languages and was designed for use in adults with DS with varying premorbid ID levels. A recent study by Silverman and colleges (2021), however, highlighted limitations of the measure in terms of screening for MCI-DS. Using a criterion of one or more total concerns on the NTG-EDSD, in a sample of 185 adults with DS, sensitivity was 0.89 and specificity was 0.52. When using a more severely affected criterion of two or more total concerns, sensitivity dropped to 0.83 but specificity increased to 0.64. Among the domains, sensitivity was highest within the Memory and Language domain and specificity was highest in the Language and Communication domain.

In terms of informant-report of adaptive behavior, the *Adaptive Behavior Assessment System* (ABAS; Harrison & Oakland, 2000) has been used in AD research in DS (e.g., Strydom, Dickinson, Shende, Pratico, & Walker, 2009), but little has been published about its ability to detect AD dementia. The *Adaptive Behavior Scale* (ABS; Nihira, Foster, Shellhaas, & Leland, 1975) and its abbreviated version (short ABS; Hatton et al., 2001) has been found to be a valid and reliable measure with few ceiling or floor effects in the DS population (Kay et al., 2003; Startin et al., 2016). Margallo-Lana et al. (2007) followed a cohort of 92 institutionalized adults with DS over a period of 15 years and <10% of their participants had ABS total scores that deteriorated by more than one standard deviation. However, a limitation of that study was that none of the participants resided in a home,

where there would likely be more opportunities and variability in daily responsibilities and community experiences. In contrast, Zigman, Krinsky-McHale, Schupf, Urv, and Silverman (2018) followed 133 adults with DS at 18-month intervals for at least five cycles. The ABS Part I scores changed more for those converting to AD dementia compared to those who were cognitively stable at each time point, both before and after the onset of AD dementia.

The *Vineland Adaptive Behavior Scales* is the most commonly used adaptive living skills instrument in AD research in DS (e.g., Hamburg et al., 2019; Keeling et al., 2017). When considered in combination with other measures, the Vineland shows promise in detecting AD dementia in DS. In a study of 141 adults with DS (51% with AD dementia and 38% had severe to profound ID), the Vineland-II Community subdomain score was particularly effective at classifying those with versus without AD dementia (Harp et al., 2021). Meanwhile, in a study of 168 adults with DS (20% with AD dementia, all with mild or moderate ID), the Vineland-III Communication domain score was the only composite score that differentiated those with and without AD dementia (Pulsifer et al., 2020). Hence, the Vineland Communication score appears to be the best indicator of clinical AD in higher functioning individuals with DS, whereas the Vineland Community score may be the best indicator for lower functioning individuals at baseline.

6. Conclusions and next steps

DS is now recognized as a genetic type of AD, given the near universal presence of AD pathology by age 40 years (Lott & Head, 2019) and 90% lifetime risk of clinical AD dementia in DS (McCarron et al., 2014). Over the past decade, a growing body of DS research has been aimed at identifying measures of cognition that correspond to AD biomarkers and are sensitive to early declines and progressive stages of AD. The driving goal of this research is to prepare the field for AD-DS clinical trials. The research that explores the progression of AD is complicated by the challenges of assessing cognition in the DS population. Research in DS has begun to identify associations between AD biomarkers and transition to the prodromal stage and the AD clinical status including a variety of PET imaging, CSF, and plasma biomarkers that map onto the AT(N) model. Overall, research to-date has generally been consistent in revealing a pattern of AD-related cognitive decline in DS that is similar to that of autosomal dominant and late-onset AD. Specifically, research suggests a sequence of decline that starts with changes in memory and attention, and has found that measures of these domains correlate with PET biomarkers of A and T in the AT(N) model. These early cognitive changes are then followed by changes in executive functioning, visuospatial and visuomotor ability, and verbal fluency.

In this chapter, we highlighted several direct and caregiver-reported measures (Table 1) that have shown promise for detecting adults with DS in the prodromal stage (including a clinical rating of MCI-DS) and/or who have AD dementia. Many are also good candidates for inclusion in AD intervention trials that are focused on the transition from the preclinical to prodromal stage of AD in DS. Some of these measures, however, work better for those with mild to moderate premorbid intellectual disability and when used longitudinally to track change in performance over time. It should be noted that in some studies, there was circularity in that the measure evaluated for sensitivity or specificity in detecting MCI or AD

dementia was also used in making the clinical rating of MCI or AD dementia. Thus, there remains a strong need for more work aimed at understanding the reliability and validity of these cognitive measures in isolation and when used across samples and clinicians.

Looking forward, there are several important next steps for DS research on cognitive measures in order to prepare for clinical AD intervention trials. While varying levels of premorbid intellectual disability may preclude reliance on a single cut-point on many cognitive measures, guidelines should be developed that are focused on within-person change when possible and that reference premorbid level of functioning. It is also important for the field to establish best practices on specific measures in terms of using raw (vs standard scores) and true deviation approaches to maximize variability in measures at both the between-person and within-person across time level. It is possible that the amount of decline on specific measures that are clinically relevant will differ as a function of premorbid intellectual and functional ability level. Guidelines for differentiating AD-related decline from the effect of co-occurring physical and mental health would also be valuable in clinical and research settings. Finally, there is a critical need for more research to identify more reliable and valid measures for individuals with DS with severe and profound levels of premorbid intellectual disability, as many of the promising cognitive measures are prone to floor effects.

To-date, research on cognitive measures of AD-related decline in DS have predominantly involved individuals who identify as white, non-Hispanic. Moreover, most studies have limited participation to adults with DS who are fluent in the dominant language of that country (e.g., English for studies in the U.S.). There is a critical need for DS researchers to focus on recruiting more racially/ethnically diverse samples and to work to ensure that research opportunities are available for individuals who speak multiple languages, as important subgroups of adults with DS are being left out of science.

Finally, in the coming years there is also a need to understand how genetic factors such as mosaicism, translocation, and APOE status impact the trajectory of AD-related cognitive decline in DS. For example, it is possible that the cognitive domains and/or timeline for cognitive decline differs as a function of these genetic factors. If so, screening recommendations and clinical trial planning may need to differ based on these genetic considerations. Indeed, there is evidence that cognitive declines may occur 2 years earlier in adults with DS who have the APOE e4 gene (Fortea et al., 2020). Genetic factors may have an important role in the progression of AD within the DS population. Similarly, it is possible that lifestyle factors such as physical activity and leisure activities (Fleming et al., 2021; Mihaila et al., 2019) and co-occurring conditions such as sleep disruptions and sleep disordered breathing (Chen, Spanò, & Edgin, 2013; Cody et al., 2020) also alter the rate of cognitive decline associated with AD in DS; the potential role of these environmental and health factors on profiles of cognitive decline need to be explored in the coming years.

As the DS field nears its first large-scale AD prevention trials, there is critical need for research that continues to focus on identifying feasible, reliable, valid, and sensitive measures of cognitive decline and dementia symptoms in full array of adults with DS. It is important that this research consider measures that are suitable for the wide array of

premorbid intellectual levels and support needs. It is also critical that this research focus on identifying cognitive measures that are sensitive to the transition from preclinical to prodromal AD in DS, including measures that correlate with AD biomarkers during these stages. These measures will play a key role in participant screening/recruitment for selection into AD clinical trials, tracking intervention efficacy, and characterizing the progression of AD in DS.

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Abbreviations

DS	Down syndrome
AD	Alzheimer's disease
Aβ	amyloid beta
APP	amyloid precursor protein
AT[N]	amyloid, tau, neurodegeneration

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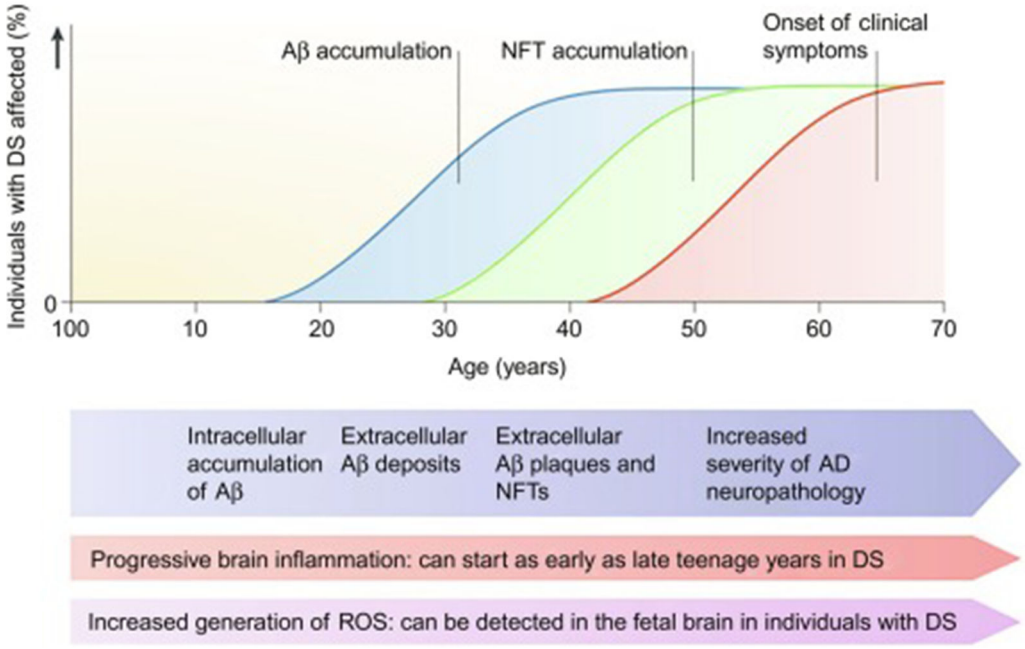

Fig. 1.

Hypothetical model of Alzheimer's disease from birth to 70 years in Down syndrome from Lott and Head (2019).

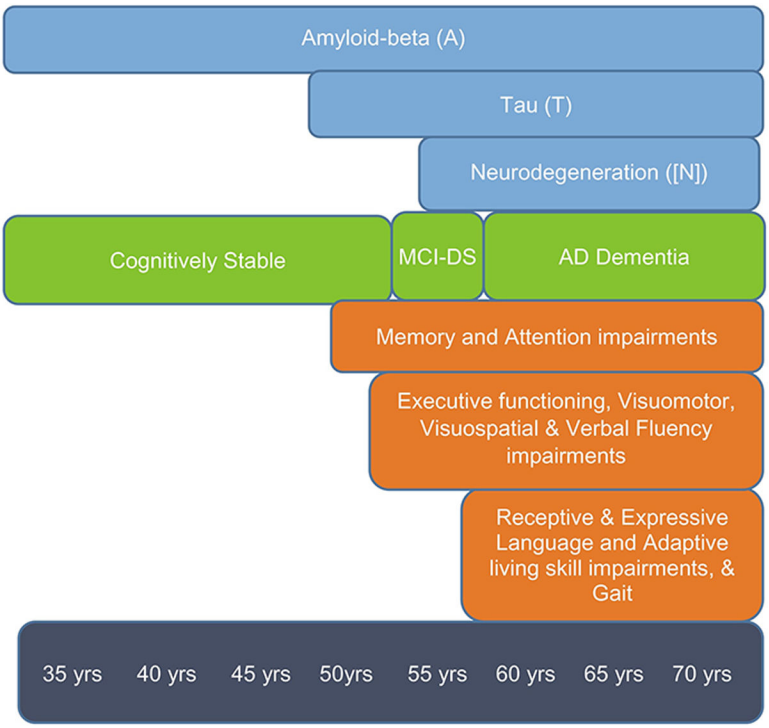

Fig. 2.

Mapping of Alzheimer's biomarkers (blue), clinical Alzheimer's disease status (green), cognitive and functional declines (orange) and chronological age in the progression of Alzheimer's disease in Down syndrome.

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Table 1

Summary of cognitive measures highlighted in the current chapter and the Alzheimer's disease (AD) stage or variable domain that they have been associated with in Down syndrome.

				AD stage/variable domain		
Domain	**Measure**	**Measure citation**	**Type of measure**	**AT(N) biomarkers**	**Prodromal**	**AD dementia**
Adaptive behavior	American association for mental deficiency, adaptive behavior scale (AAMD-ABS)/Part I	Nihira et al. (1975), Nihira, Leland, and Lambert (1993); Hatton et al. (2001)	Informant		X	X
	Vineland adaptive behavior scale	Sparrow and Cicchetti (1989); Sparrow, Cicchetti, and Balla (2005); Sparrow, Cicchetti, and Saulnier (2016)	Informant	X	X	X
	Cambridge neuropsychological test automated battery (CANTAB)	CANTAB® (2016)	Direct		X	X
Overall cognitive functioning	Cambridge examination for mental disorders of older people with Down syndrome and others with disabilities (CAMDEX)	Ball et al. (2004)Beresford-Webb et al. (2021)	Informant		X	X
	Rapid assessment of developmental disabilities (RADD)	Walsh et al. (2007)	Direct			X
	Repeatable battery for the assessment of neuropsychological status total score (RBANS)	Randolph et al. (1998)	Direct	X		
	Down syndrome mental status examination (DSMSE)	Haxby (1989)	Direct	X	X	X
Dementia symptoms	Dementia questionnaire for mentally retarded persons	Evenhuis (1992, 1996)	Informant	X		
	Dementia questionnaire for people with learning disabilities (DLD)	Evenhuis, Kengen, and Eurlings (1998, 2006)	Informant			X
	Dementia scale for Down syndrome (DSDS)	Gedye (1995)	Informant			X
	Dementia screening questionnaire for individuals with intellectual disabilities (DSQIDD)	Deb et al. (2007)	Informant			X
	National task group-early detection screen for dementia (NTG-EDSD)	Esralew et al. (2013)	Informant		X	X
	McCarthy category fluency test	McCarthy (1972)	Direct			X
Executive Functioning	Neuropsychological (NEPSY) word generation	Korkman et al. (2007)	Direct	X		
	NEPSY cancelation	Korkman et al. (2007)	Direct	X	X	X
	Stroop cats and dogs task	Ball et al. (2008)	Direct	X		
	Cued recall test	Zimmerli and Devenny (1995)	Direct	X	X	X
Memory	Observer memory questionnaire (OMQ)	O'Shea (1996)	Informant	X		
	Cambridge cognition examination (CAMCOG)	Roth et al. (1986)	Direct	X	X	X

Domain	Measure	Measure citation	Type of measure	AD stage/variable domain		
				AT(N) biomarkers	Prodromal	AD dementia
	Selective reminding test	Buschke (1973)	Direct		X	
	WISC-IV digit span forward	Wechsler (2004)	Direct	X		
Mental Status	Modified Mini Mental Status Evaluation - DS	Wisniewski and Hill (1985)	Direct		X	
	Severe Impairment Battery (SIB)	Saxton et al. (2005)	Direct	X	X	X
	Test for Severe Impairment (TSI)	Albert and Cohen (1992)	Direct		X	X
Visuomotor Control and Planning	Developmental Test of Visuomotor Integration (VMI)	Beery et al. (2004)	Direct	X	X	X
	Purdue pegboard	Vega (1969)	Direct	X	X	X
	NEPSY-II car and motorbike score	Hatton et al. (2001)	Direct		X	
Visuospatial ability	Weschler intelligence scale for children-IV (WISC-IV) block design and haxby extension	Wechsler (2004); Haxby (1989)	Direct	X	X	X