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Primitive Reflexes and Dementia in Adults With Down Syndrome

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Abstract

Background and Objectives
To determine whether primitive reflexes serve as an indicator of dementia in adults with Down syndrome (DS), we collected neurologic examination data, cognitive and behavioral assessments, and clinical consensus diagnoses of dementia from 92 adults with DS.

Methods
In a cross-sectional, observational study of a regional cohort, χ^2 and Fisher exact tests examined individual reflexes across the diagnostic group (no, possible, or probable dementia). In 64 participants with all 8 reflexes assessed, the number of primitive reflexes was assessed as a predictor of diagnosis using age-controlled multinomial logistic regression and of performance on clinical assessments (Brief Praxis Test [BPT], Severe Impairment Battery [SIB], and the Dementia Questionnaire for People with Learning Disabilities [DLD]) using age-adjusted linear regression.

Results
Primitive palmomental, grasp, snout, and suck reflexes were more frequent in individuals with probable dementia, but all participants showed at least 1 primitive reflex. Multiple primitive reflexes in combination served as a better indicator of dementia, with each additional abnormal reflex tripling probability of the probable dementia group membership controlling for age. Abnormal reflex count was not associated with direct assessment of cognition and praxis (SIB and BPT) but associated with informant ratings of cognitive and behavioral functioning (DLD).

Discussion
The presence of multiple reflexes serves as an indicator of dementia status in DS as a supplement to direct assessment of cognition and praxis. The reflex examination may serve as a tool in the multimethod evaluation for dementia in DS, as it appears unaffected by intellectual disability and language mastery.

Individuals with Down syndrome (DS) have an increased likelihood of developing dementia, especially Alzheimer disease (AD), with a much younger age at onset than typically aging peers. This is due to neuropathologic changes such as amyloid plaques and neurofibrillary tangles[1] that often accumulate in the mid-30s in the DS population, as well as high rate of other AD risk factors.[1-3]

With improved technology and medical care, individuals with DS are living longer than ever.[4] As such, attempts to detect and diagnose symptoms related to prodromal dementia have increased in an effort to preserve quality of life. Varying penetrance of trisomy 21 in affecting cognitive state, complex medical comorbidities, challenges with identifying and tracking cognitive decline, and variability in cognitive test performance between medical visits make early detection of prodromal dementia symptoms quite challenging. As such, methods using sound neurocognitive and behavioral measures[5-7] in conjunction with physical or physiologic findings are especially appealing. Here, we report the prevalence of primitive reflexes in a cohort of adults with DS and examine the associations of abnormal reflexes with clinical dementia diagnosis and measures of cognitive and social functioning. Individual primitive reflexes were hypothesized to have varied and limited associations with dementia diagnosis due to a high prevalence at baseline,[8,9] whereas the number of primitive reflexes found in combination was hypothesized to be associated with dementia diagnosis, cognitive test performance, and caregiver-informant ratings of functioning.

Methods

Parent Study

The aging in Down syndrome (ADS) study follows a cohort of adults with DS and their caregiver-informants in Kentucky and surrounding states. Participants complete yearly visits that include a neurologic examination, brain imaging (MRI), and a battery of cognitive tests and informant questionnaires.

Participants

Between 2011 and 2018 participants with DS over the age of 25 years were recruited into the study. The current analysis uses each participant's most recent study visit from an ongoing longitudinal study of aging in DS. Participants were excluded from the current analysis if they had ongoing, untreated medical conditions (e.g., thyroid dysfunction or cardiovascular complications).

Standard Protocol Approvals, Registrations, and Patient Consents

All informed consent and study procedures were approved for use with human subjects through the local institutional review board. All participants (or their guardians) provided written consent to participate in the study.

Data Availability

Any data not published within the article will be shared in anonymized form on request from any qualified investigator.

Reflexes

During the study visit, participants completed a neurologic examination with study neurologists (G.J., W.R., and D.L., all with 1–3 decades of experience) using a standard assessment form that guided the examination features. Our behavioral neurologist (G.J.) cross-trained our 2 other study neurologists (W.R. and D.L.) to ensure standardized approaches to the examination to minimize variability among examiners. During the neurologic examination, plantar grasp, hand grasp, palmomental, gegenhalten, snout, glabellar, suck, and jaw jerk reflexes were assessed. The examining neurologists recorded whether the abnormal reflex was absent or present and where indicated also recorded laterality (palmomental and grasp).

Cognitive Assessments

Participants completed an assessment battery to measure cognitive functioning. The 2 primary cognitive measures used were the Severe Impairment Battery (SIB)[10] and Brief Praxis Test (BPT).[11] In addition, the Dementia Questionnaire for People with Learning Disabilities (DLD)[12] was used as an informant measure of social and cognitive impairment. These measures were selected to serve as the core battery at inception of the parent cohort study because they have low floors, are relatively quick to administer, and provide sufficient coverage of relevant domains. Major motivations for establishing such a core battery included (1) a need to keep study visit demands reasonable for the participants and family, as many traveled from hours away, and visits include the clinical measures as well as extensive neuroimaging, and (2) a need to follow participants through the course of dementia until death, with the assumption that later in the course, only limited cognitive data would be obtainable. Supplemental measures of cognition were included in the parent cohort study, but because participants were so often unable to tolerate the extended battery, the present analyses are restricted to the core battery.

The SIB, BPT, and DLD total scores are the 3 measures of impairment used in the current analysis. Certain cognitive measures were reflected over the mean so that all shared the same directionality of impairment. Standard linear transformations ($\log_{10}$ and square root) were used to correct negative and positive skew to meet the normality assumption of the linear models used in the analysis while maintaining all the variability information obtained with the original measures. Specifically, the SIB and the BPT were negatively skewed and were reflected by subtracting each score by the maximum score on each test, plus 1. Then, the reflected scores were transformed using $\log_{10}$. The DLD was positively skewed and was transformed by adding 1 point to the DLD total score and then taking the square root. All statistical tests were performed on the transformed cognitive assessment scores, but raw values are presented in tables and plots for east of interpretation.

Consensus Diagnosis

Dementia diagnosis was determined through a consensus review of each participant's neurologic examination findings and neuropsychological assessment results. Medical records were also reviewed to identify medical conditions and level of

intellectual disability. The expert panel consisted of 2 or 3 neurologists and 2 psychologists using the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for dementia.[13] Assignment to the possible dementia group included individuals rated as "possible dementia (dementia criteria are met yet additional evidence for progression is needed)," "uncertainty regarding dementia status; functional and cognitive decline may both be present," or "likely impaired (some cognitive declines are detectable—mild cognitive impairment)." Assignment to the probable dementia group included individuals rated as "probable dementia (criteria are met with convincing evidence of substantial and progressive decline)."

Statistical Analysis

The Pearson χ^2 test was used to assess the relationships between categorical variables (sex, diagnosis, intellectual disability, and abnormal reflex). The Fisher exact test was used instead in cases in which cells had fewer than 5 observations. Pairwise comparisons with the Fisher exact test and Bonferroni correction for multiple comparisons were used to compare frequency of abnormal reflexes across diagnosis groups. One-way analysis of variance (ANOVA) was used to evaluate the relationship between continuous variables (age, SIB, BPT, and DLD) and diagnostic status. Post hoc t tests corrected with the Tukey procedure assessed pairwise differences when the ANOVA was significant.

A multinomial logistic regression was used to estimate the relationship between abnormal reflexes and diagnosis group. The main effects of age and abnormal reflex count were evaluated along with the second-order interaction. Two models with and without the interaction term were compared using the Akaike information criterion (AIC) and Bayesian information criterion (BIC), and the model with the lowest AIC and BIC was considered the model with superior fit. All statistical tests were 2 tailed, and the alpha level was set at 0.05. All analyses were completed in R 3.6.1 using Table 1,[14] gmodels,[15] rstatix,[16] emmeans,[17] nnet,[18] rcompanion,[19] performance,[20] ggpubr,[21] tidyverse,[22] and sjPlot[23] packages.

Results

Between 2011 and 2018, 92 participants completed a study visit with primitive reflex examination, cognitive assessment, and consensus diagnosis. Full participant characteristics are provided in Table 1. A total of 64 participants had all reflexes assessed during the visit, and 28 participants had at least 1 positive primitive reflex. All participants were included in the analysis of association between individual reflexes and diagnosis group. Only the 64 participants with complete reflex assessments were used in the multinomial logistic regressions examining the associations among number of abnormal reflexes, individual reflexes, and diagnosis group.

Age differed across diagnosis groups (F(2,87) = 65.92; $p < 0.001$), with the no dementia group being younger than

Table 1 Participant Characteristics

	No Dementia (n = 50)	Possible Dementia (n = 14)	Probable Dementia (n = 28)	Total (N = 92)
Female sex	52.00% (26)	71.43% (10)	67.86% (19)	59.78% (55)
Intellectual disability				
Borderline/mild	57.14% (28)	50.00% (7)	39.29% (11)	50.55% (46)
Moderate to profound	42.86% (21)	50.00% (7)	60.71% (17)	50.55% (45)
Age	37.71 (7.46)	50.29 (4.6)[a]	55.57 (6.38)[c]	45.08 (10.66)
	36.31 (32.57–43.27)	49.47 (48.66–50.67)	54.86 (51.42–59.87)	46.57 (36.06–53.61)
BPT total	70.33 (7.21)	70.54 (9.36)	51.57 (17.68)[b,c]	65.18 (14.06)
	72 (67–76)	74 (67–78)	59 (41–66)	70 (60–74)
SIB total	86.25 (12.39)	81.92 (17.04)	58.25 (21.9)[b,c]	77.26 (20.50)
	91 (77.5–94.5)	87 (79–92)	60.5 (49–73)	84 (64–92)
DLD total	9.88 (9.83)	21.07 (12.15)[a]	45.59 (14.39)[b,c]	22.47 (19.63)
	8 (3–13.5)	23 (12–29)	47 (35–52)	16 (5–36)
DLD cognitive	4.69 (6.72)	12.29 (8.65)[a]	25 (7.92)[b,c]	12.04 (11.61)
	2 (0–6)	11 (6–17)	26 (19–31)	7 (1–21)
DLD social	5.19 (4.65)	8.79 (5.07)[a]	20.59 (8.24)[b,c]	10.43 (9.08)
	4 (1–9)	9.5 (5–13)	19 (16–24)	9 (3–16)

Note: The table depicts the percentages (n), mean and (SDs), and medians with (quartile 1–quartile 3).
For the Brief Praxis Test and Severe Impairment Battery Totals, lower scores indicate greater impairment. For the Dementia Questionnaire for People with Learning Disabilities Total and subscales, higher scores indicate greater impairment.
[a] Possible differed from no dementia, $p < 0.05$.
[b] Probable differed from possible, $p < 0.05$.
[c] Probable differed from no dementia, $p < 0.05$.

Table 2 Associations Between Individual Reflexes and Diagnosis Group

	No Dementia (n = 50)	Possible (n = 14)	Probable (n = 28)	χ^2 Test and p Value	Cramer V
Glabellar					
Normal	39.58% (19)	28.57% (4)	21.43% (6)	$X^2(2) = 2.77$; $p = 0.23$ Ψ	0.18
Abnormal	60.42% (29)	71.43% (10)	78.57% (22)		—
Palmomental					
Normal	56.52% (26)	28.57% (4)	28.57% (8)	$X^2(2) = 6.99$; $p = 0.03$ Ψ	0.28
Abnormal	43.48% (20)	71.43% (10)	71.43% (20)		—
Snout					
Normal	68.89% (31)	50.00% (7)	32.14% (9)[b]	$X^2(2) = 9.49$; $p = 0.009$	0.33
Abnormal	31.11% (14)	50.00% (7)	67.86% (19)		—
Jaw					
Normal	91.67% (44)	100% (14)	92.59% (25)	$X^2(2) = 1.22$; $p = 0.73$ Ψ	0.12
Abnormal	8.33% (4)	0% (0)	7.41% (2)		—
Palmar grasp					
Normal	93.18% (41)	100% (14)	60.72% (17)[a,b]	$X^2(2) = 16.49$; $p < 0.001$ Ψ	0.44
Abnormal	6.82% (3)	0% (0)	39.29% (11)		—
Gegenhalten					
Normal	96.67% (29)	91.67% (11)	76.00% (19)	$X^2(2) = 5.72$; $p = 0.06$ Ψ	0.29
Abnormal	3.33% (1)	8.33% (1)	24.00% (6)		—
Suck					
Normal	97.73% (43)	75.00% (9)	62.96% (17)[b]	$X^2(2) = 15.08$; $p < 0.001$ Ψ	0.43
Abnormal	2.27% (1)	25.00% (3)	37.04% (10)		—
Plantar grasp					
Normal	100% (29)	100% (11)	100% (25)	—	—
Abnormal	0% (0)	0% (0)	0% (0)		—

Note: The table depicts the percentages and (n) of each diagnostic subgroup evincing a normal or abnormal reflex.
Ψ Fisher exact p value correction.
[a] Probable differed from possible, $p < 0.05$.
[b] Probable differed from no dementia, $p < 0.05$.

the possible (t = −5.93; $p < 0.001$) and probable groups (t = −11.08; $p < 0.001$). There was no difference in age between the possible and probable groups ($p > 0.05$). Both BPT (F(2,73) = 15.30; $p < 0.001$) and SIB (F(2,78) = 16.47; $p < 0.001$) total scores were associated with diagnosis group such that the probable dementia group had lower performance compared to possible (BPT: t = −4.91; $p < 0.001$; SIB: t = −5.69; $p < 0.001$) and no dementia (BPT: t = −4.67; $p < 0.001$; SIB: t = −3.34; $p = 0.004$) groups. There was no difference between no dementia and possible groups on either the BPT or SIB ($p > 0.05$ for both). DLD total scores also differed by diagnosis group (F(2,86) = 65.14; $p < 0.001$). All 3 groups differed from one another, with the probable group having the highest DLD total score, followed by

possible, then no dementia groups (all p values <0.001). Similarly, all 3 groups differed from one another for the cognitive (all p values <0.001) and social (all p values <0.05) subscales of the DLD.

Individual Reflexes

The χ^2 and Fisher exact tests evaluated whether individual reflexes were associated with diagnosis group. All participants demonstrated at least 1 abnormal reflex when assessed. Grasp, palmomental, snout, and suck abnormal reflexes were associated with the diagnosis group (Table 2). Abnormal snout was more frequently observed within the probable dementia group compared with the no dementia group ($p = 0.010$). Abnormal suck was more frequently observed within the probable dementia

group compared with the no dementia group ($p < 0.001$). Abnormal palmar grasp was more frequently observed within the probable dementia group compared with the no dementia ($p = 0.004$) or possible ($p = 0.023$) groups. Glabellar reflex and the presence of gegenhalten were not associated with the diagnostic group.

Number of Abnormal Reflexes

Participants with complete reflex assessment (n = 64) were analyzed to determine whether there was an association between the number of abnormal reflexes and diagnosis group. Participants had 1–6 abnormal reflexes. Multinomial logistic regression, controlling for age, revealed an association between the number of abnormal reflexes and diagnosis group ($X^2(2) = 8.92$; $p = 0.012$). With each additional abnormal reflex, the odds (OR = 3.95; 95% CI: 1.35–11.57) of being in the probable vs no dementia diagnosis group increased 295% ($Z = 2.51$; $p = 0.01$). There was no difference in odds of possible vs no dementia ($Z = 1.20$; $p = 0.23$) nor in odds of probable vs possible dementia ($Z = 1.81$; $p = 0.07$). Figure 1 depicts the relationships between number of abnormal reflexes and probability of diagnostic group membership. Among participants without dementia (n = 28), Poisson regression found no association between age and abnormal reflect count ($t = 0.99$; $p = 0.33$).

Linear regression was used to test the association between count of abnormal reflexes and cognitive measures. All models controlled for age. Count of abnormal reflexes was not associated with BPT ($F(1,50) = 3.65$; $p = 0.06$) or SIB total scores ($F(1,55) = 1.10$; $p = 0.30$). There was an association between count of abnormal reflexes ($F(1,59) = 4.68$; $p = 0.03$) and DLD total score, controlling for age (see Figure 2).

Discussion

One of the first suggestions that persons with DS show pathologic aging-related neurobehavioral changes resulting in increased or changed primitive reflexes much like non-DS individuals with dementia, rather than simply early-life developmental differences, was an early cross-sectional study of 123 patients with DS, which found baseline primitive reflexes to be prevalent in youth with DS and to increase in number with age.[8] Numerous cross-sectional studies published in the following 2 decades reported similar findings and further found that the number of abnormal reflexes present increases more quickly in advanced age, starting around the age of 50 years.[24-27] One study that reported reflex data showed that with increasing age, individuals with DS show more reduced cognitive ability on neuropsychological tests than do age-matched non-DS controls.[27] That study, however, did not directly associate the presence of abnormal reflexes with cognitive functioning. Two slightly more recent longitudinal studies of individuals with DS reported only cross-sectional reflex data and did not analyze those data in relation to cognitive functioning.[28,29] Overall, primitive reflexes have not received much direct consideration as an indicator of dementia in the DS and aging literature.

The present data demonstrate that primitive reflexes, albeit present in all individuals in our DS cohort regardless of the dementia diagnosis group, increased in number in association with both diagnostic categorization as well as subjective informant-based measures of cognition and social functioning (DLD scores).

These data support previous observations that the presence of singular abnormal reflexes is not a useful indicator of dementia in DS, much as it is not useful in typically developing individuals.[30-32] As in previous studies of both DS[25,26] and typically developing groups,[33-35] the palmomental sign was highly prevalent even in individuals without dementia, although the prevalence in our DS cohort is considerably higher than in reports of non-DS groups. The glabellar sign (present in 60%) was more prevalent in individuals without dementia than the palmomental (present in 43%), which is unlike previous findings in typically developing individuals.[31,34-36]

The present data also suggest that the accumulation of multiple primitive reflexes in this population may represent classic frontal release signs, as frontal pathology is associated with behavioral and cognitive changes in the aging DS population.[37,38] Overall, primitive snout, suck, palmomental, and palmar grasp reflexes increased along with severity of

Figure 1 Estimated Probability of the Dementia Group by Number of Abnormal Reflexes
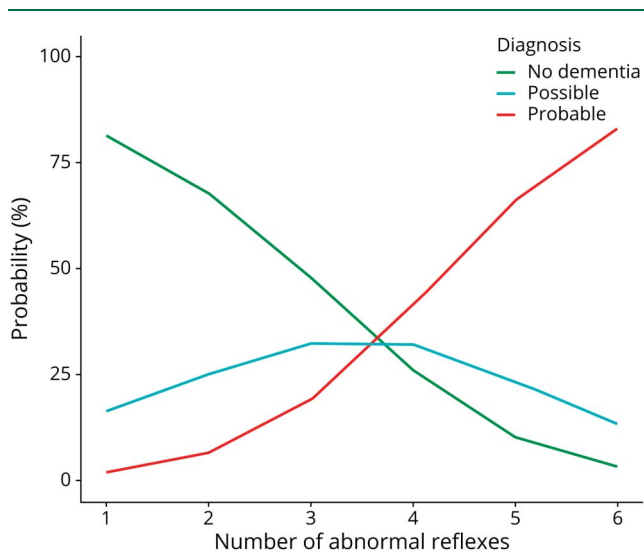
Note: probability of having no dementia, possible dementia, or probable dementia as the number of abnormal reflexes increases. As the number of abnormal reflexes increased, the probability of probable dementia increased and the probability of no dementia decreased. The probability of possible dementia group memberships was maximal between 3 and 4 concurrent abnormal reflexes, as any fewer increased the probability of no dementia status and any more increased probability of probable dementia status.

Figure 2 Association Between Abnormal Reflexes and DLD Total Score
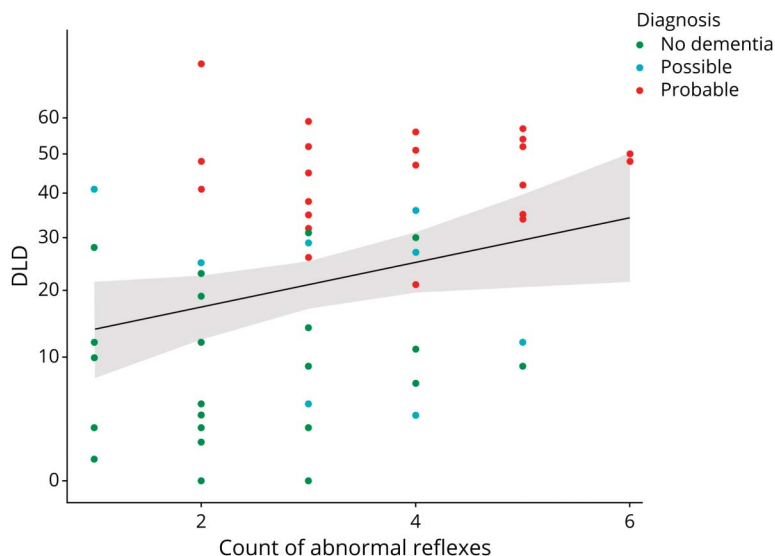
As the number of abnormal reflexes increased, DLD total score increased. DLD total score is presented in raw values, but the model analyzed transformed DLD total score. DLD = Dementia Questionnaire for People with Learning Disabilities.

dementia diagnosis, but only the suck and palmar grasp signs were relatively rare in individuals without dementia and thus somewhat diagnostically specific. These findings are in line with data from the Maastricht Aging Study[31] of non-DS individuals, which showed that between the ages of 25 and 82 years, no one exhibited the palmar grasp or rooting reflex. Furthermore, the suck reflex was only seen in 2% of individuals across this age range (mostly in persons aged 65+ years).

A major finding of the present study is that a higher number of primitive reflexes present in combination were associated with clinical dementia diagnosis. This effect remained when controlling for age. Specifically, although all individuals exhibited at least 1 primitive reflex of the 8 assessed, each additional abnormal reflex decreased the probability of being nondemented by roughly 20% for up to 5 comorbid reflexes. Each additional reflex similarly increased the likelihood of probable dementia. The maximum probability of being in the possible dementia group was just over 30%, associated with the presence of 3–4 primitive reflexes of the 8 assessed. Previous reports have varied in the number and types of reflexes assessed, so rates of reflexes found in combination are not directly comparable. However, our findings support previous reports that higher numbers of primitive reflexes in combination may reflect dementia and illustrate such a relationship using a more comprehensive reflex assessment than has been reported previously.

Finally, the number of concurrent primitive reflexes was not related to objective measures of cognitive ability but was related to caregiver-informant ratings of social and cognitive functioning on the DLD. Specifically, each additional abnormal reflex was associated with a 5–10-point increase in the DLD score, with that increase more pronounced at higher numbers of primitive reflexes. That the number of abnormal reflexes was strongly related to both dementia diagnostic status and caregiver-informant ratings of impairment but not to neurocognitive tests known to be sensitive to dementia in this population[39] is in line with findings of the Maastricht Aging Study of non-DS individuals, which notes: "Primitive reflexes were not systematically related to cognitive function…. This was observed in both the cross-sectional and longitudinal analyses, for all cognitive measures, and for all types of reflexes…. When age by [primitive reflex] prevalence interaction terms were included in the models, no age dependency of the relationships between [primitive reflex] and cognitive variables was revealed…. Similar results were found when evaluating the outcome in terms of cognitive impairment, no dementia (CIND), when analysing the presence or absence of any reflex, or when analysing the total number of reflexes present."[31]

Overall, these findings are in line with previous literature associating primitive reflexes with neurodegenerative disease and represent an update to the DS and dementia literature by contributing results from a long-followed cohort surviving to older age, applying more recent criteria for clinical dementia diagnosis, and using a clinical consensus diagnostic process. Moreover, the present study extends prior work associating reflex examination results with both neuropsychological test scores and caregiver-information ratings,[9] in particular by assessing multiple domains of neuropsychological performance. Perhaps most salient is that the observed associations are robust to effects of age and level of intellectual disability.

These findings suggest that primitive reflexes may yet play a role in clinical evaluation in the aging DS population. Whereas in non-DS dementia cases, cognitive decline may be

detected earliest by formal neuropsychological testing or by subjective memory complaint of the individual, verbal expressive limitations and intellectual disability often preclude adequate measurement and detection of AD-related decline in individuals with DS until later in the disease process. Given this clinical course, the appearance of multiple primitive reflexes in combination would supplement cognitive and informant-based questionnaires in identifying dementia in DS. Given the cross-sectional nature of the present data, we would not conclude that primitive reflexes are a predictive marker of future dementia, but rather that primitive reflexes, while common in individuals without dementia with DS, are associated with dementia when several are present concurrently.

Still, the present study has several limitations. First, 30% of the initial sample of 92 participants did not have all reflexes assessed. Despite initial cross-training and use of standard assessment forms, the circumstances under which individual reflexes were not assessed in a particular case likely varied by examining clinician and the participant's ability to engage in the examination. Second, there is potential variation in preferences in technique when rating primitive reflexes as abnormal (e.g., the number of trials to an abnormal rating of glabellar). Intensity of the applied stimulus was also left to the preference of the clinician, although as has been noted,[40] a forceful enough stimulus may elicit certain primitive reflexes in just about anyone. Cross-training was intended to mitigate such variability from the outset. Finally, the final consensus diagnosis is based in part on the clinical assessment and neurologic examination findings under study, which as in all similar clinical dementia research raises concern in regard to the weighting placed on such primitive reflexes by the examining clinicians and consensus teams when reviewing each case. Regarding this latter concern, we note that these are objective examination findings collected before diagnosis in a uniform manner. As such, although the presence/absence of primitive reflexes may influence the neurologist's initial diagnostic impression and later consensus diagnosis, the other direction is controlled for. Diagnosis does not influence the objective examination findings.

Baseline presence of primitive reflexes due to atypical CNS development must be accounted for when studying aging and dementia in a DS population. Although monitoring for frontal release signs has been largely supplanted in dementia surveillance by measures with sensitivity earlier in the disease process, such as neurocognitive assessment and neuroimaging, such monitoring remains relevant particularly in the DS population with its attendant assessment difficulties. Given the present findings, new appearance of primitive reflexes in combination may indicate appropriateness of additional medical examinations to determine the presence or absence of AD neuropathology based on PET or lumbar puncture for pathologic tau and amyloid-beta protein levels, especially when family or caregivers report cognitive and/or functional changes.

Open questions persist, including the mechanism for development of frontal release signs and developmental vs disease characteristics that contribute to the observed differences in primitive reflex onset between aging individuals with DS and those without. As the ADS cohort grows, longitudinal survival analysis of reflex onset in combination with serial neuroimaging and eventual pathology findings on autopsy will allow further examination of these issues.

Disclosure
The authors report no disclosures relevant to the manuscript. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Appendix Authors

Name	Location	Contribution
Jordan Harp, PhD	University of Kentucky, Lexington	Design and concept of the study; interpreted the data; and drafted and revised the majority of the manuscript
Lisa Koehl, PhD	University of Kentucky, Lexington	Design and concept of the study and drafted a significant portion of the manuscript
Kathryn Van Pelt, PhD	University of Kentucky, Lexington	Design and concept of the study; analyzed the data; prepared tables and figures; and drafted a significant portion of the manuscript
Elizabeth Head, PhD	University of California, Irvine	Design and concept of the study; design and concept of the parent cohort study; and provided comments and revisions to the manuscript
Gregory Jicha, MD, PhD	University of Kentucky, Lexington	Major role in data acquisition and provided comments and revisions to the manuscript
William Robertson, MD	University of Kentucky, Lexington	Major role in data acquisition
Donita Lightner, MD	University of Kentucky, Lexington	Major role in data acquisition
Ira Lott, MD	University of California, Irvine	Design and concept of the study and provided comments on manuscript and data presentation
Frederick Schmitt, PhD	University of Kentucky, Lexington	Design and concept of the study; design and concept of the parent cohort study; and provided comments and revisions to the manuscript

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