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Modified Cued Recall test for the diagnosis of Alzheimer's disease in a Greek sample of adults with Down syndrome: A preliminary study

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Abstract:	Diagnosing Alzheimer’s disease (AD) in adults with Down syndrome remains challenging due to pre-existing intellectual disabilities (ID) and lack of specialized assessments. This was a cross-sectional multi-center study examining the capability of the Greek version of the modified Cued Recall Test (mCRT) to identify AD in DS adults. Analysis showed statistically significant negative correlations between age and scores on all mCRT measures. Statistically significant differences were detected between ID levels and all mCRT main scores and between the two diagnostic groups and performance at immediate and delayed recall. ROC analysis revealed an optimal cut-off score of 26.5 (0-36). In conclusion, mCRT is a highly sensitive tool for detecting AD in adults with DS.

Abstract

Diagnosing Alzheimer's disease (AD) in adults with Down syndrome remains challenging due to pre-existing intellectual disabilities (ID) and lack of specialized assessments. This was a cross-sectional multi-center study examining the capability of the Greek version of the modified Cued Recall Test (mCRT) to identify AD in DS adults. Analysis showed statistically significant negative correlations between age and scores on all mCRT measures. Statistically significant differences were detected between ID levels and all mCRT main scores and between the two diagnostic groups and performance at immediate and delayed recall. ROC analysis revealed an optimal cut-off score of 26.5 (0-36). In conclusion, mCRT is a highly sensitive tool for detecting AD in adults with DS.

Keywords: Alzheimer's disease; cognitive impairment; dementia; Down syndrome; intellectual disability; modified Cued Recall Test; neuropsychological assessment validation study

Introduction

The relationship between Down syndrome (DS) and Alzheimer's disease (AD) has been well established. DS is a genetic disorder resulting from trisomy in chromosome 21. Typical manifestations include issues with growth, intellectual disability, and unique facial features (Akhtar & Bokhar., 2023). The syndrome has been linked to various disorders and conditions, among others, to AD (Fortea et al., 2021). AD is the most common form of dementia, characterized by progressive cognitive decline affecting thinking, language, orientation, attention, memory, and behavior, ultimately impairing daily activities. (Monteiro et al., 2023).

DS individuals live now longer than ever. Medical and technological advances have significantly increased their life expectancy from 40 - 45 to around 60 years (McCarron et al., 2017). Nonetheless, aging brings its challenges and pathological changes. More than fifty years of research (Iulita et al., 2022) indicate that around the age of fifty, a significant number of DS individuals will display symptoms of AD. The risk increases gradually with age (Ballard et al., 2016), starting from 23% in individuals around the age of fifty and exceeding 80% in individuals approximately at 65 (McCarron et al., 2017).

The high prevalence of AD in this specific population is mainly due to genetic factors and, more specifically, due to an additional copy of the amyloid precursor protein gene located in chromosome 21. This protein-coding gene is responsible for the overproduction of the amyloid beta protein (Aβ) which drives to senile plaques on the brain (Wiseman et al., 2018), constituting one of the two AD hallmarks. According to research data, by the age of 40, AD-related pathological alterations are already present in DS individuals at a universal level (Fortea et al., 2020).

Nevertheless, diagnosis of AD has been proven challenging, mainly due to pre-existing cognitive deficits in DS individuals (Benejam et al., 2020; Sacco et al., 2022). In other words, typical symptoms in the general population, such as a decline in the ability to perform activities of daily living reported by the patient and/or their caregiver(s), may be overlooked when assessing the cognitive status of DS individuals, because of the ID which is already present as a lifelong characteristic of DS and affects their

everyday functionality (Benejam et al., 2020). In the same way, traditional diagnostic assessments are of poor use when attempting to evaluate memory performance in individuals with IDs (Camoih et al., 2013). For this reason, over the last years, there has been an increasing focus on the development and use of appropriate assessment tools to detect prodromal AD and full-blown AD Dementia (ADD) in individuals with DS, which up to this point are significantly less in number in contrast to those used in the general population.

AD patients in the typical population and AD patients with DS often exhibit deficits in episodic memory (Benejam et al., 2022; Devenny, 2002). However, even though a decline in episodic memory is part of normal aging (Craik, 1994; Tromp et al., 2015), in the case of AD, when assessed using appropriate diagnostic tools, recall is not facilitated after providing semantic cueing (Benejam et al., 2015; Grober et al., 2008; Vogel et al., 2007) Therefore, tools assessing episodic memory that include the assistive use of cues, such as semantic images or categories, can be of great help when attempting to differentiate AD symptomatology from other conditions.

The Cued Recall Test (CRT) and its modified version (mCRT), which was specifically developed to be used in individuals with IDs, is designed based on the standards mentioned above and is considered a useful as well as a valid instrument to assess DS individuals and to differentiate healthy from AD patients (Devenny et al., 2002). Similar research studies have been conducted in Spain (Benejam et al., 2020; 2015), France (Sacco et al., 2022), and the US (Krisky et al., 2022), indicating that the mCRT is sensitive in detecting AD symptomatology in DS adults. More specifically, in the Devenny et al. study (2002), 160 US participants (66 non-DS with ID and 75 DS participants, both of which did not present any observable cognitive decline, and 19 DS individuals with early-stage AD) were assessed using the mCRT and scores among the three groups were compared. Although the research team admitted that the sample was relatively small and that the followed procedure for determining participants' clinical status was imperfect, the obtained results affirmed that the specific diagnostic tool presented a high degree of sensitivity and specificity (>90%) for scores lower than 23 (maximum possible score =36) and was,

therefore, able to detect DS individuals with and without AD reliably (Devenny et al., 2002). Despite its limitations, the study set a good knowledge base and led the way for further research.

Later attempts to validate the instrument are limited in number. Benejam and her colleagues (2020; 2015) explored the mCRT's properties in Spanish populations, while Krisky and colleagues (Krisky et al., 2022) and Sacco and colleagues (Sacco et al., 2022) examined the validity of the tool in a US and French population-based cohort, respectively. In each case, the assessment could discriminate cognitively stable from AD-affected participants with DS. However, the proposed cut-off scores varied greatly, probably due to methodological differences in the study design, such as how diagnostic categories were divided and how participants were assigned. More specifically, results from Benejam et al. (2015) indicated that all cognitively stable participants obtained a total score of at least 30 on immediate recall, and only one DS individual with AD scored higher than 23 points. Cut-off scores from their later research (Benejam et al., 2020) were higher (i.e., 29 and 28 for the mild and moderate ID levels, respectively) than those reported in the Devenny et al. study (2002). Sacco and his colleagues (2022) found that all DS participants with AD obtained scores lower than 22 (in contrast to cognitively stable DS adults whose scores were higher) except in one case where the participant's score was 22. Finally, according to Krisky et al. (2022), given the fact that they could not find a perfect balance between sensitivity and specificity, DS adults scoring higher than 33 were highly unlikely to present AD symptoms compared to those scoring lower than 20. Nevertheless, even if it has been suggested (Benejam et al., 2020) that more strict cut-off scores should be established, all studies found that the tool is sensitive in detecting AD symptomatology in DS individuals.

Early and accurate detection of prodromal and dementia symptomatology in the specific population is critical. However, premorbid intellectual disability raises the need to utilize specialized assessment tools adapted to the abilities of the specific population. The mCRT has been, so far, proven to accurately discriminate cognitively intact individuals from those affected by AD in the early or later stages of the disease. Setting specific cut-off scores to distinguish between diagnostic groups is of equal importance.

An attempt to validate the instrument using participant samples from different cultures and different cohort populations will offer the potential to generalize results. The primary goal of this study was to assess the validity of the mCRT in a Greek sample of DS individuals. A secondary aim was to propose cut-off scores that could be able to distinguish between DS individuals with and without cognitive impairment related to AD symptomatology.

Methods

Study Design

This was a multicentre cross-sectional study. Ethical standards of medical research were followed to ensure good clinical practice and data protection. Participation in the study was voluntary, and written informed consent was signed by each parent or legal guardian, following the Declaration of Helsinki. The study was approved by the Greek Association of Alzheimer's Disease and Related Disorders (Alzheimer Hellas) ethics committee (82/19-10-2022). Data was collected as part of the Horizon 21 consortium.

Participants

Seventy-five (75) individuals with DS (37 males and 38 females) participated in the study aged 18 to 65. They were recruited through several contexts (i.e., Down syndrome Associations, Special Schools, Centres of Creative Activities, or the researchers' contacts). They came from different Greek regions, both urban and suburban, as well as rural places:therefore, they could represent the DS population in Greece. All participants were over 18, spoke Greek as their primary language, had the visual and hearing abilities to understand the task, and had not completed the assessment in the last 6 months to avoid potential learning effects. Seven participants exhibiting hearing and vision issues could not complete the assessment and were excluded from the study. Table 1 summarises the main characteristics of the assessed population (n= 68).

Data collection and AD diagnosis

Data collection included detailed recording of participants' demographic characteristics, family and personal medical history, and medication use. Their caregivers provided information on their ID level based on past formal examinations of the participant's level of functioning. In case there was no pre-existent AD diagnosis, participants' clinical status was determined upon consensus among the research team members (psychiatrist/neurologist and neuropsychologists) and based on information received by participants' caregivers through structured interviews. Participants who met the criteria for prodromal and definite AD as reported in the ICD-11 diagnostic criteria for dementia and the DSM-5 criteria for mild/major cognitive impairment and mild major cognitive impairment due to AD and whose cognitive decline could not be explained by another medical and/or psychiatric condition or major life change were considered cognitively impaired due to AD. Thus, after careful examination of the participants' current clinical profiles, and the change from a previous status, three main diagnostic groups were formed: healthy, prodromal AD/AD (those with prodromal and definite AD), and uncertain diagnosis due to non-neurodegenerative causes.

Modified Cued Recall Test (mCRT)

The Cued Recall Test (CRT) is an assessment tool used to evaluate episodic memory and was developed by Grober and Buschke (1987) who found it to be a helpful instrument for the detection of individuals in the preclinical stage of dementia and who are in an increased risk to develop the disease (Grober et al., 2008). It was modified by Devenny et al. (2002) to be used in adults with DS, who found that the tool exhibited a high degree of sensitivity and specificity (0.947 and 0.939, respectively) for total scores lower than 23 in all three trials on immediate recall (maximum possible score 36). The mCRT has not so far been validated in Greek. For the translation of the mCRT into the Greek language by Tsolaki and colleagues, the International Test Commission (ITC) guidelines (www.intestcom.org) were followed. The back translation procedure was also followed to eliminate any inconsistencies that would disrupt the

accuracy of the results. Overall, the translation process did not present any challenges or required any changes to the items.

mCRT procedure

The mCRT consists of three stages. During the first stage (i.e., the learning phase), 12 visual stimuli are presented to the participant, divided into three sets of four images. In this stage, the examiner presents one of the cards and asks the participant questions to encourage encoding and naming, therefore learning (i.e., There is a fruit in this paper. Can you please point it out and give me its name?). When the participant identifies all the stimuli presented in the card, the researcher turns the card over and asks the participant to recall the four items previously presented. This procedure continues until the participant successfully recalls all four items in each card a maximum of three times.

The next stage follows immediately after the learning phase and constitutes the evaluation process. During this phase, the participant is asked to recall as many of the 12 items presented as possible. The participant is given a minute to answer and then is provided with a cue to facilitate retrieval (i.e., "What kind of fruit did we see?"). The testing phase consists of three trials. At the end of the second phase, participants and researchers spend 20 minutes making short conversations before the third and final stage, which attempts to record scores on delayed recall. Thus, the participant is asked one more time to recall as many items as possible and is given a cue as in the previous stage.

Correct answers score one point on the free and cued recall score categories. Scoring was done according to the paradigm by Devenny et al. (2002), whose performance measures were based on the combination of scores of both free and cued recalls. Hence, scores on the mCRT included: a) one total score on each of the three trials on immediate recall (range 0-12). In this case, total scores included answers given both at free and cued recall. Furthermore, there was b) a score on immediate free recall, and c) a score on immediate recall (this measurement combined freed and cued recall responses). Both ranged from 0 to 36 and included performance on all three trials. Finally, there was d) a score on delayed

free recall (range 0-12) and e) a score on delayed recall (range 0-12). Intrusion errors (i.e., answers with items not included in the three cards) were also recorded.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences version 29.0.1.0 (IBM Corp. Armonk, NY). Categorical data were summarised as the number of participants and the corresponding percentages, and continuous data were summarised using means and standard deviation. All continuous data were checked for the normality of their distribution. The Pearson and Spearman correlation coefficient assessed the relationship between age and the mCRT's scores. Independent sample t-test, or the non-parametric Mann-Whitney U-test (in case of non-normal distribution), were performed to explore potential differences between gender, level of ID, cognitive status, and performance on the assessment. Regression analysis served to explore the effects of age on performance in each of the task conditions. ROC curve analysis served to evaluate the tool's sensitivity and specificity and to set cut-off scores. Only one of the participants with severe ID (n = 6) could complete the task, achieving a total score of 9 on immediate recall. For this reason, the specific sub-population was excluded from the analyses. Individuals whose status was deemed uncertain due to non-neurodegenerative causes (n = 3) were excluded from further analysis as well. The significance level was set at $p \leq 0.05$.

Results

Results demonstrated statistically significant negative correlations between age and scores on immediate free recall (rs= -.297, p= .02), on immediate recall (rs = -.298, p < .02), on delayed free recall (rs= -.310, p= .01) and on delayed recall (rs= –.263, p= .04). Regression analysis revealed that age influences significantly performance on the test, explaining more than 45% of the variance: R^2= .47, F= (2, 56) = 8,021, p < .001 for performance on scores on immediate recall, R^2= .47, F= (3, 55) = 5,313, p < .003 for scores on delayed free recall and R^2= .51, F= (4, 54) = 4,825, p < .002. Statistically significant differences were detected between the mild and moderate ID levels and performance on all the mCRT main scores: u = 236, z = -2.58, p < .010 for scores on immediate free recall, u = 258.5, z = -2.24, p < .025) for

scores on immediate recall, $u = 234$, $z = -2.66$, $p < .008$) for scores on delayed free recall and $u = 232$, $z = -2.73$, $p < .006$ for scores on delayed recall. No differences were detected between gender and performance. Probability values are presented in Table 3.

Cognitively stable vs Prodromal AD/AD. A Mann-Whitney U test analysis (probability values can be found in Table 3) yielded significant differences between the two diagnostic groups and their scores on immediate free recall ($u = 97.5$, $z = -4.20$, $p < .001$), immediate recall ($u = 47$, $z = -5.11$, $p < .001$) as well as their scores on delayed free recall ($u = 124$, $z = -3.82$, $p < .001$) and delayed recall ($u = 96.5$, $z = -4.37$, $p < .001$). No significant differences were detected between the two groups and the intrusion errors they produced. Table 2 includes details regarding the performance of each group in each of the task conditions. ROC analysis results yield an AUC of .932 (standard error = 0.031, 95% confidence interval= 0.87-0.99), indicating that the mCRT is highly sensitive in detecting individuals with AD symptomatology. As shown in Table 4, the optimal cut-off score was 26.5, with a good balance between sensitivity and specificity (87.5% and 86%, respectively).

Secondary analyses. Correlations among the three trials and scores on immediate recall were also explored and were all highly significant ($p < .001$), indicating that performance is unlikely to improve from trial to trial. In addition, the strong correlation between trial one and the score on immediate recall ($r = .945$, $p > .001$) suggests that administering the test once might be equally informative. The correlational analysis also showed a strong relationship between scores on free and immediate recall for cognitively impaired individuals ($r = .889$, $p < .001$) and a moderate correlation for healthy participants ($r = .597$, $p < .001$), suggesting that performance for the former does not improve upon cueing.

Discussion

The life span of the DS population has dramatically increased over the last decades due to advances in the medical and technological domains. However, genetic factors render DS individuals particularly vulnerable to developing AD symptomatology as they age. For this reason, research is focusing more and

more on the detection, prevention, and treatment of AD in the specific population to improve DS individuals' quality of life.

The present study aimed to examine the performance patterns of individuals with DS in Greece on the mCRT and the ability of this assessment tool to distinguish cognitively healthy participants from those exhibiting symptoms of prodromal AD/AD. Although there are some studies on the subject in other countries, this was the first time a study was conducted in a Greek sample with DS.

In line with previous research (Benejam et al., 2015; Sacco et al., 2022), the present analysis results showed that younger individuals achieved better scores on the assessment, and intellectual disability played a role in performance. Individuals with severe and profound ID were not included in the analyses as they could not complete the assessment due to difficulty understanding the task. Only one of the participants with severe ID could not complete the assessment, supporting Benejam et al. 2015's suggestion that the test is only valuable for evaluating DS individuals in the upper levels of the ID scale. This fact also highlights the need to develop diagnostic tools adapted to the abilities of this unique subgroup so that data obtained by the assessment can be used in conjunction with information received by the caregiver to evaluate the cognitive status of the person under examination.

In addition, data analysis of this study revealed significant differences between the performance of the two diagnostic groups, indicating that the mCRT can discriminate between cognitively stable and cognitively impaired individuals due to prodromal AD/AD. In line with this finding, ROC analysis showed that the tool is highly sensitive in detecting AD symptomatology, and the trade-off between sensitivity and specificity indicated that the optimal cut-off score for immediate recall is 26.5. The specific cut-off score differs from those suggested in previous research studies on the topic, probably due to methodological differences between the design of the present research study and those conducted in the past. Differences can be observed in the sample size and the diagnostic categories in which participants were divided. More specifically, while in some studies (Benejam et al., 2020; Krinsky et al., 2022) participants were divided into three clinical groups (i.e., healthy vs, prodromal AD vs with dementia AD),

in this study, participants with both prodromal and full-blown AD symptomatology were included in the same group (i.e., prodromal AD/AD) due to the small sample size.

Moreover, significant correlations in scores among the three trials indicate stability in performance as the assessment progresses. A significant correlation between each trial (trial one presenting the highest association) and scores on immediate recall suggests that the administration of just the first trial might be equally informative and less time-consuming, as proposed previously (Krisky et al., 2022). Finally, the strong positive correlation between scores on free and immediate recall in prodromal AD/AD participants, in contrast to only moderate in healthy participants, supports the finding that the performance of individuals experiencing symptoms of AD does not improve when provided cues (Grober et al., 2008). Therefore, free recall scores are not equally informative as total scores on the task when screening for AD, and lower total scores on free recall might indicate the presence of another psychiatric or physical condition (e.g., depression, vascular dementia, and similar conditions). Finally, results highlighted once more that DS individuals in the lower levels of ID are implausible to understand the task and be able to complete it (Benejam et al., 2015; Krinsky et al., 2022).

The most important strength of this study is the generality of the findings. Participants were recruited from different centres around Greece; therefore, it is reasonable to assume that results are likely to be replicated in different DS cohorts of the country. However, the study presents two main limitations that should be addressed in future research attempts. First and foremost, the sample was rather small. Given the relatively small population in Greece and the families' reluctance to participate in research studies, finding an appropriate sample size has been a challenge. Nevertheless, more participants would enable further analysis to obtain more robust results. Moreover, the present study used a cross-sectional design. For this reason, it is difficult to conclude about the change in individual performance over time.

AD detection is essential in DS since it leads to early interventions that improve the quality of life for affected individuals and their families. Appropriate instruments adjusted to the specific population and their cognitive profile are indispensable. In summary, the mCRT was found to be able to distinguish DS

participants with and without cognitive impairment due to AD. Despite the study's limitations, the results were informative, and to a significant extent, consistent with previous research. Future research studies should aim to recruit more participants and to use longitudinal designs. They should also include a variety of factors that may influence the neurological profile of DS individuals that, in turn, may lead to better interventions, both pharmacological as well as psychological, and/or nutritional. Finally, more focus should be placed developing appropriate assessment tools adjusted to the cognitive profile and abilities of individuals with severe and profound ID. Nevertheless, the study set the first step towards validating the mCRT in the Greek population with DS.

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Table 1

Participants' Main Characteristics

Characteristics	n	(%)	Age (m/range)
Gender			
Male	34	50%	32.34 (18-59)
Female	34	50%	35.24 (19-65)
ID			
Mild	24	36.9%	35.63 (18-59)
Moderate	38	53.8%	33.11 (19-65)
Severe	6	9.2%	30.67(21-49)
CS			
Cognitively stable	46	67.7%	30.18 (18-55)
Prodromal AD/AD	19	27.7%	42.89(30-65)
Uncertain due to non-neurodegenerative causes	3	4.6%	32.67(28-37)

Note. ID= Intellectual Disability; CS= Cognitive Status

Table 2

Performance of cognitively intact and impaired groups on the mCRT

		Total Score Immediate Free Recall	Total Score Immediate Recall	Total Score Delayed Free Recall	Total Score Delayed Recall
Cognitively Stable	Mean	17.56	32.09	5.16	9.28
	SD	8.302	5.887	3.538	4.256
	Maximum	36	36	12	12
	Minimum	3	9	0	0
Prodromal AD/AD	Mean	6.88	16.06	1.25	3.38
	SD	5.667	10.312	1.732	3.845
	Maximum	16	30	4	10
	Minimum	0	0	0	0

Note. SD=Standard Deviation

Table 3.

Probability values on correlation between performance and age and differences between performance and ID level and cognitive status.

	Total Score Immediate Free Recall	Total Score Immediate Recall	Total Score Delayed Free Recall	Total Score Delayed Recall
Age	.022	.022	.017	.044
Mild vs moderate ID	.010	.025	.008	.006
Cognitively stable vs Prodromal AD/AD	<.001	<.001	<.001	<.001

Note. ID= Intellectual Disability

Table 4.

Sensitivity and specificity of the mCRT's scores (>17) on immediate recall based on comparisons between performances of cognitively stable participants and participants with prodromal AD/AD.

Positive if less than or equal to	Sensitivity	Specificity
17.50	0.500	0.977
19.50	0.500	0.953
20.50	0.625	0.953
22.00	0.625	0.907
23.50	0.625	0.884
25.00	0.688	0.860
26.50	0.875	0.860
27.50	0.875	0.814
28.50	0.938	0.795
29.50	0.938	0.791
30.50	1.000	0.791
31.50	1.000	0.767
32.50	1.000	0.698
33.50	1.000	0.581
34.50	1.000	0.512
35.50	1.000	0.349
37	1.000	0.000