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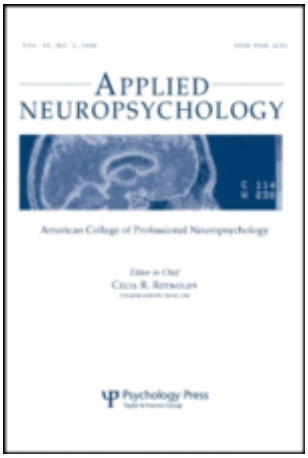

Normative data for COGITAB: an Italian tablet-based test battery conceived for the preclinical phase of Alzheimer's disease

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Complete List of Authors:	beltrami, daniela; Reggio Emilia Local Agency - IRCCS Advanced Technologies and Care Models in Oncology, Clinical Neuropsychology, Cognitive Disorders and Dyslexia Unit, Neurology, Department of Neuro-Motor Diseases Barletta-Rodolfi, Caterina; Reggio Emilia Local Agency - IRCCS Advanced Technologies and Care Models in Oncology, Clinical Neuropsychology, Cognitive Disorders and Dyslexia Unit, Neurology, Department of Neuro-Motor Diseases Bertini, Flavio; University of Parma, Department of Mathematical, Physical and Computer Sciences Braglia, Luca; Reggio Emilia Local Agency - IRCCS Advanced Technologies and Care Models in Oncology, Research and Statistics Infrastructure Calzà, Laura; Università di Bologna, Interdepartmental Centre for Industrial Research in Health Sciences and Technologies Corbo, Massimo; Casa Cura Igea (CCI), Department of Neurorheabilitation Sciences Gasparini, Federico; Reggio Emilia Local Agency - IRCCS Advanced Technologies and Care Models in Oncology, Clinical Neuropsychology, Cognitive Disorders and Dyslexia Unit, Neurology, Department of Neuro-Motor Diseases Marti, Alessandro; Reggio Emilia Local Agency - IRCCS Advanced Technologies and Care Models in Oncology, Clinical Neuropsychology, Cognitive Disorders and Dyslexia Unit, Neurology, Department of Neuro-Motor Diseases Montesi, Danilo; University of Bologna, Department of Computer Science and Engineering

	Pisano, Marta; Reggio Emilia Local Agency - IRCCS Advanced Technologies and Care Models in Oncology, Clinical Neuropsychology, Cognitive Disorders and Dyslexia Unit, Neurology, Department of Neuro-Motor Diseases Rusconi, Maria Luisa; University of Bergamo, Department of Human and Social Sciences Sozzi, Matteo; ASST "A. Manzoni", Department of Neuroscience Tonon, Cecilia; Reggio Emilia Local Agency - IRCCS Advanced Technologies and Care Models in Oncology, Clinical Neuropsychology, Cognitive Disorders and Dyslexia Unit, Neurology, Department of Neuro-Motor Diseases Ghidoni, Enrico; Reggio Emilia Local Agency - IRCCS Advanced Technologies and Care Models in Oncology, Clinical Neuropsychology, Cognitive Disorders and Dyslexia Unit, Neurology, Department of Neuro-Motor Diseases
Keywords:	Digital cognitive assessment tool, Alzheimer's disease, Preclinical AD, Cognitive screening

Abstract

The number of people with dementia is increasing worldwide. Two main approaches have been adopted to identify subjects with Alzheimer's disease (AD): the neuropsychological evaluation and the identification of biomarkers of AD. The first method is less invasive and easier to perform. This study assesses the psychometric properties of COGITAB, a novel web application designed to be sensitive to the subtle cognitive changes distinctive of the early Mild Cognitive Impairment (MCI) and the preclinical phase of AD. We enrolled 518 healthy controls, classified according to several risk factors and the presence of a family history of dementia. The participants were given COGITAB after a neuropsychological screening. The COGITAB Total Score (TS) was significantly affected by age and years of education. Acquired risk factors and family history of dementia significantly impacted only the COGITAB total execution time (TET), not the TS. This study provides normative data for a newly developed web application. Control subjects with acquired risk factors performed slower, giving an important role to the TET recording. Further studies should examine the ability of this new technology to discriminate between healthy subjects and subjects with initial cognitive decline, even when not detected by standard neuropsychological assessments.

Keywords: Digital cognitive assessment tool; Alzheimer's disease; Preclinical AD; cognitive screening

Introduction

As a result of the aging of the population, dementia is emerging as a major health problem. It is estimated that more than 44 million people worldwide are affected by Alzheimer's disease (AD) or a related form of dementia, and it is believed that this number will reach approximately 150 million in 2050, as reported by the U.S. National Institute of Aging. The costs for dementia are also significant, at approximately US$1 trillion per year, rising to 2 trillion over the next 10 years (Patterson, 2018).

The development of disease-modifying drugs represents a promising chance for individuals suffering of AD, especially at the preclinical or prodromal stages of AD (Mild Cognitive Impairment, MCI, due to AD). An early diagnosis is also important for nonpharmacological interventions, to globally improve physical and cognitive functions, ADL skills, and behavioral and psychological symptoms (Lowrani et al., 2020). In fact, although much of the risk of developing AD can be attributed to genetics, some acquired factors may predispose an individual to a cognitive decline: vascular diseases (Mayeux & Stern, 2012; Imtiaz et al., 2014), excessive alcohol consumption (Kim et al., 2012; Piazza-Gardner et al., 2013; Panza et al., 2013), depression (Byers & Yaffe, 2011; Vilalta-Franch et al., 2013; Zverova et al., 2013; Wu et al., 2018) and insomnia (Shi et al., 2018); smoking cessation is highly recommended to reduce the incidence of dementia (Durazzo et al., 2014).

Therefore, an early diagnosis could be the best way to promptly access medical and support services, increasing the chances of early interventions to maintain a good quality of life for as long as possible, thus reducing the cost of care, and permitting more time to deal with legal, financial and care decisions (Bondi et al., 2008; Rentz et al., 2013; Sperling et al., 2014).

It is known that neuropathological process of AD may begin many years before the onset of clinical symptoms (Dubois et al. 2014) and that the preclinical or prodromal phase is

characterized by the alteration of AD biomarkers, including amyloid **β** 42 (A**β**42) and tau in the cerebrospinal fluid (CSF), amyloid deposition, magnetic resonance imaging alterations, fluoro-2-deoxyglucose (FDG)-PET abnormalities and cognitive changes (Han et al., 2017; Schindler et al., 2017; Alzheimer's Association, 2020).

Despite the importance of biomarkers for the diagnosis of AD, neuropsychological evaluation plays a significant role in early diagnosis offering advantages to the high costs and invasiveness of organic biomarker analysis (Tarnanas et al., 2014).

A recent review about cognitive changes in preclinical AD (Mortamais et al., 2017) shows that the earliest variations involve episodic and semantic memory, as well as executive functions. A decline in episodic memory is typically the earliest and most robust symptom of MCI and dementia, and it can arise 6-10 years before the onset of the symptomatic phase (Bäckman et al., 2001; Bondi et al., 2008; Sperling et al., 2011; Mortamais et al., 2017;). Because it is not clear whether immediate or delayed measures are the most sensitive for early dementia, the analysis of both is recommended. Associative memory is especially sensitive to early AD (Parra et al., 2010, Della Sala et al., 2012) and older adults with deficits in this cognitive area are at increased risk for dementia (Buschke et al., 2017; Mowrey et al., 2018); moreover, there is evidence of deficits in short-term associative memory in older adults with AD, familial AD and asymptomatic carriers of the E280A single presenilin-1 mutation (Parra, Abrahams, Fabi et al., 2009; Parra, Abrahams, Logie et al., 2010). The assessment of executive functioning is often missed in short cognitive screening, especially regarding the so-called “hot” components (Allain et al., 2013), which involve “emotional”, “belief” or “desires”, such as experiences of reward and punishment, regulation of social behavior and decision making. “Cold” components, such as the coordination mechanism of the central executive, inhibition and shifting, can be affected many years before the clinical phase and the decline seems to accelerate two or three years before (Grober et al., 2008; Allain et al., 2013).

Meta-analysis (Wild et al., 2008; Ismail et al., 2010; Zygouris et al., 2014; Tsoi et al., 2015) indicated cognitive screening as an excellent tool in terms of accuracy, availability and cost, to discriminate between cognitively healthy participants and people affected by MCI or dementia. In the past few years, research focused on automated tests, which can be administered via a tablet/smartphone or computer (for a review, see Thabtah et al., 2020), and differed for various properties from the traditional paper and pencil screening.

Most of the existing tests focus on discrimination among subjects with MCI or dementia and cognitively healthy subjects (Wild et al., 2008; Ismail et al., 2010; Tsoi et al., 2015; Zygouris et al., 2014; Mortamais et al., 2017;). Despite being very accurate in detecting early or mild cognitive decline, these tests do not seem to register the slight changes that are distinctive of a preclinical phase (Mortamais et al., 2017). This is why a more cognitively demanding and sensitive tool is needed.

We have developed a new web application named COGITAB which is conceived to be almost self-administered via a tablet in a general practitioner's (GP) office in approximately 30 minutes. Primary care is an ideal place to early identify people with cognitive concerns, but also to manage the risk of developing dementia after the patient is screened. COGITAB was designed to be quick to administer and easy to score. It is run, scored, and processed by software and it will provide an immediate non-numerical outcome of a subject's performance compared with the normative sample.

In the present study (phase one), we preliminarily analyzed the Italian normative data of this new cognitive battery, and we examined its user-friendliness and feasibility, underlying possible weaknesses or problems. These aspects are indispensable for future validation and dissemination phases. Moreover, we explored the possible differences related to the presence of a family history of dementia (genetic factors) and of some acquired risk factors for AD

development (e.g. vascular diseases, smoking, depression, anxiety, etc.) that can negatively impact cognitive efficiency.

The aim of a second ongoing study (phase two) was to investigate the validity of COGITAB for cognitive screening of subjects with objective and subjective cognitive impairment. For the first group we recruited patients diagnosed with early dementia and Mild Cognitive Disorder (MCI). The second sample was composed of patients diagnosed with Subjective Cognitive Disorder (SCD), claiming a persistent decline in cognitive capacities despite a normal performance on standard neuropsychological tests. In the case of a positive outcome in terms of diagnostic accuracy, a third "dissemination" step (phase three) will take place. GPs and other specialists will be exhaustively instructed about how to correctly manage the tool (for further details, see COGITAB Battery and Discussion).

Materials and Methods

Participants

We enrolled 537 participants aged between 45 and 75 years, with varied levels of education (5-18 years) from two regions of northern Italy (Emilia Romagna, Lombardia). The inclusion criteria were having Italian as one's native language, absence of current or previous disabling neurological pathologies, blindness, deafness or other serious sensory impairment, intellectual or cognitive disability, and serious psychiatric diseases.

Nineteen participants were discarded because of the incompleteness of the anamnestic interview or COGITAB procedure because of technical issues (e.g. inadequate internet connection).

The final sample was composed of 518 subjects (231 males; 287 females) aged between 45 and 75 years (mean=59.26; SD=8.22) with varied years of education (range: 5-18; mean=12.63; SD=3.88). A description of age and years of education can be found in Table 1.

Each participant was classified according to two categories: acquired risk factors (high vs. low) and family history of dementia (yes vs. no). High risk was determined if at least two of the following conditions were detected: health risk factors (at least two between hypertension, diabetes, minor cardiovascular disease, thyroid dysfunction, dyslipidemia and other internal pathologies), lifestyle risk factors (smoking, drinking or drug addiction) or psychological risk factors (subclinical anxiety or depression, and the feeling of a physiological memory decline without any previous request for clinical assessment). The most common recurring risk factors were dyslipidemia and hypertension (both in pharmacological treatment), subclinical anxiety/depression and smoking habit. None of the participants reported alcohol or drug addiction. A family history of the disease was based on the presence of first-third degree relatives with a neurodegenerative pathology. In fact, even in the absence of a first degree family history, a second or third-degree family history can be indicative of an elevated risk (Cannon-Albright et al., 2019). Participants were divided into four groups: 271 low risk without a family history, 71 high risk without a family history, 129 low risk with a family history and 47 high risk with a family history. The age distribution among the four cohorts is reported in Table 2.

Procedure

Each session lasted approximately 60 minutes. The procedure was approved by the local research ethics committees and fully explained to the subjects, informed written consent was obtained.

All participants were first requested to complete a clinical interview conducted by a neuropsychologist (anagraphic data and clinical information; occupation/retirement; family history of dementia; lifestyle habits, psychosocial and physiopathological factors). After the anamnestic phase, the participants were assessed using the Mini-mental State Examination

(MMSE) and Montreal Cognitive Assessment (MoCA), which are two 30-point screening tests widely used in clinical practice to detect cognitive decline.

After this cognitive screening, the examiner manually entered information regarding the subject code, the presence of subclinical anxiety/depression and family history of dementia, on a tablet which was then placed on the table about 15 cm in front of the subject. COGITAB was introduced as follows: "Now, you'll be asked to follow the instructions that will appear on the screen. The same instructions will be audible by tapping the speaker icon that you'll see on the screen". The first three requests (date, month and year of birth) allowed the subject to become familiar with the instrument, possibly receiving suggestions on the correct way to tap the screen (e.g., "wait a while before tapping again", "press the screen more slightly", etc.).

After this first phase, the examiner was exclusively available for technical support, such as internet connection issues. The examiner was previously instructed on how to use COGITAB and on how to answer to the subject's possible questions. The COGITAB evaluation lasted for about 30 minutes.

To assess possible variations in COGITAB performance over time, we scheduled a second complete evaluation after approximately 16 months (mean=16.20; SD=4.86). Unfortunately, because of the Covid-19 pandemic, only a small sample of 45 participants accepted the follow-up (Table 3).

COGITAB battery

COGITAB was designed as a web application that implemented a client server architectural pattern. A web application is a program that uses a browser and web technologies to perform tasks over the internet, while a client-server pattern allows us to partition workloads between two modules, the service requester (i.e., the client, a computer or a tablet) and the provider of a service (i.e., the server). In COGITAB, the client module includes the user interfaces and

logic of the tasks and runs in a web browser, while the server module provides the cognitive tests, safely stores the results and provides authorized users with a report of the outcomes for each subject. These design solutions provide the following advantages: COGITAB runs on multiple platforms (browsers and devices) regardless of the operating system and underlying hardware; all users access the same version, and updates can be performed easily just by updating the server; all the results are stored in a centralized server and are protected using high-level solutions. This makes it possible to conduct comparative analyses over time for the same patient and to pursue advanced epidemiological studies.

The two modules use state-of-the-art open-source web technologies; in particular, the client module was developed using the Angular JS framework and the following front-end technologies: HTML version 5, CSS version 3, and JavaScript version 5. The server module was developed using the framework Django the following back-end technologies: Python version 2.7 and PostgreSQL version 9. COGITAB can be administered through any browser using a tablet or computer; however, it was optimized for Google Chrome and Mozilla Firefox browsers running on a 10-inch tablet or greater.

COGITAB is composed of ten subtests (see Table 4 for a summary) conceived to assess those cognitive domains found to be compromised early in MCI and preclinical dementia. Temporal orientation, episodic and semantic memory, and visuo-constructive and visuo-spatial abilities are examined. Executive functions such as divided attention, shifting, verbal fluency, perceptual speed, and inhibition/switching are also analyzed. Moreover, the subjects were asked to self-evaluate their own performance, thus testing meta-cognitive skills, which have predictive value regarding their progression to dementia in MCI patients (Vogel, Stokholm et al., 2004; Vogel, Hasselbalch et al., 2005; Galeone et al., 2011; Wolfsgruber et al., 2014), even though levels of awareness are heterogeneous among them (Roberts et al., 2009). Instructions were made available as text and via audio. Most of the subtests were inspired by existing

cognitive tests, such as the Trail Making Test (Reitan, 1958), object recognition and lexical access tasks (Sartori & Job, 1988), the Stroop Test (Stroop, 1935), the Judgment of Line Orientation Test (Benton, 1978), the Multiple Features Target Cancellation Test or the Bell Test (Marra et al., 2013; Gauthier et al., 1989) and the Rivermead Behavioral Memory Test (Wilson et al, 1985). The exposure time was reduced and different cognitive functions were examined in parallel to create more cognitively demanding tasks. The most articulated, challenging and ecological task of COGITAB is the third one. The subject was requested to remember a character (face, name and surname), a shopping itinerary and all the purchased items, in terms of categories and quantities. The same questions were submitted right after the exposure and after 20 minutes. This task examined visual and verbal immediate and delayed memory, associative memory, recall and recognition processes, and implicit memory.

At the end of the test, data were automatically sent to a central server, and the examiner has access to an easy and immediate total score (TS), which was computed considering correct answers, errors and reaction times (Table 4, last column). The total execution time (TET), which reflects the overall activity duration, was also registered. The outcome datasheet was enriched with different quantitative (single scores, number of errors, latencies, reaction times, etc. for every single task) and qualitative details (type of errors, visual reproduction of the single tasks, etc.). After the tool validation, these details will be available to neuropsychologists, neurologists, and geriatricians in case of GP prescriptions for further diagnostic assessment. For a screening use (GP office), we designed an easier and more intuitive non-numerical outcome report that is still underway (see Discussion).

Statistical Analysis

The present study is descriptive in nature and aimed at describing the normative data of a sample of healthy subjects. The sample size was not determined according to a prespecified target/outcome. We analyzed data from 518 patients, a method that was judged to be both

adequate for the linear regression model used for equivalent score determination and feasible from a logistic/organizational standpoint.

The performed tests were considered to show statistically significant results if the *p*-values were < 0.05; confidence intervals of estimates were two tailed and calculated considering a 0.95 confidence level. Statistical analyses were performed using R version 4.0.4.

The primary aim was to describe the distribution of TSs. We estimated the mean and confidence interval, median and (bootstrap) confidence interval, distribution quantiles, asymmetry index, kurtosis index and Shapiro–Wilk test *p* value to assess the normality of the sample.

Furthermore, we computed the equivalent scores (ESs) following the Capitani and Laiacona procedure (2017). The analysis entailed outer and inner tolerance limit calculations, regression equation estimation and correction factor determination, and equivalent score table derivation. The analysis consisted of estimating the relationship between the score (dependent variable) and sex, age and education (independent variables) by a linear regression model; this model is then used to estimate correction factors applied to the raw score obtained by an individual to produce an adjusted score (corrected given age and education) comparable with those produced by other individuals. Finally, the adjusted scores can be classified into different levels or equivalent scores, given the table of the equivalent scores, where the ES is on the 0-4 scale. An ES score of 0 indicates an adjusted score under the outer tolerance limit (suggesting an abnormal situation), an ES of 4 is for the patient with an adjusted score above the median of adjusted scores, and ES scores of 1-3 suggest an increasing level of performance.

TS and TET were analyzed with ANOVA and ANCOVA-style linear regression models: the first used the presence of a family history, risk group and their interaction as main covariates; the latter adjusted estimates by sex, age, and years of education. We also measured the correlation between TSs and self-evaluations. MMSE and MoCA adjusted scores were also analyzed across the four cohorts by the Kruskal–Wallis test.

Finally we assessed the variation between test and retest scores. The retest assessment was conducted approximately 16 months later (Bartels et al., 2010).

Results

All the subjects performed normally at the traditional cognitive screening tests (MMSE adjusted score mean=29, SD=1.24; MoCA adjusted score mean=25.23, SD=2.46) according to the respective standardization studies (Measso et al., 1993 and Conti et al., 2014). MMSE and MoCA performances were positively correlated (rho 0.29, [0.21, 0.37], p<0.001). Table 5 shows mean and confidence interval, median and (bootstrap) confidence interval, asymmetry, kurtosis and p value from the Shapiro–Wilk test for each cohort, all corroborating the approximately normal shape of the distribution.

A linear regression model was used to assess the influences of age, education and sex on the TS ($F(3.514)=44.134$, $p<0.0001$). Because only age and education (respectively $t(514)=-10.03$, $p<0.0001$; $t(514)=4.50$, $p<0.0001$) were significantly associated with the TS, the final estimated model was $y=80.13–0.64(age–59.26)–0.02(age–59.26)^2+0.60(education-12.63)$, where 59.26 was the average age of the normative sample and 12.63 was the average years of education. We derived the correction grid accordingly with raw score adjustments (for some education/age values; see Table 6 and the appendix for full reference of adjustments). The adjustment had to be added to the raw score to obtain the adjusted score (adjusted score = raw score + y).

The adjusted scores of the normative samples were used to develop rules to classify adjusted scores into five ES by using the outer tolerance limit (59, the 18the ordered adjusted score of the normative sample), adjusted scores median (79.9) and z values of the normal distribution. The criteria used to categorize individuals' adjusted scores can be found in Table 7. The scores of group 0 were lower than the outer tolerance limits; scores of group 4 were higher than the

median value of the sample; those of groups 1, 2, and 3 were intermediate between the central value and the pathology threshold on a quasi-interval scale.

To explore possible differences related to the family history of dementia and acquired risk factors, the COGITAB TS was compared between the four cohorts (Table 8). Only the high-risk group was associated with a diminished mean score (-6.2 points, CI: -9.656 to -2.791, p<0.001). However, once controlled for sex, age and education, the high-risk group effect was no longer significant (p=0.128). Therefore, neither the family history nor the risk factors showed a significant impact on TS.

The TSs positively correlated with self-observations (p<0.001). The subjective perception of a good cognitive performance was actually related to a higher TS, suggestive of good meta-cognitive skills (Table 9).

We analyzed the TET similarly to the TS. The high-risk group was slower than the lower-risk group (approximately +2.1 minutes; CI: 1.17 to 3.01, p <0.001); when controlling for sex, age and education the difference was 1.3 minutes (CI 0.4 to 2.2); the family history group showed no association at all (p value = 0.514) (Table 10).

As previously described, a small sample of 45 participants underwent COGITAB a second time after about 16 months to analyze the practice effect and test-retest correlation. We observed a nonsignificant slight enhancement in the retest (+3.5 points, CI=-0.23 to 8.30, p=0.065; r=0.25, CI -0.05 to 0.51, p=0.098, Table 11).

Finally, despite being somewhat limited by the small sample of test/retest observation, we estimated the linear model useful for Reliable Change Index estimation, using the retest score as explained variable, baseline score and age as covariate, following Duff (2012). The estimated model was retest = 121.733 + 0.124 · score − 0.816 · age, with reasonably normally distributed residuals (Shapiro Wilks test p=0.147) and a standard error of 9.16. In this

framework a physician interested in judging a change to be clinically significant could apply the equation (retest − (121.733 + 0.124 · score − 0.816 · age))/9.16 and compare this score with the standard normal distribution cutoffs (e. g. accepting a 5% false positive rate, a value below -1.645 should suggest a clinically relevant decrease in the score).

Discussion

The early detection of cognitive decline is crucial for preventing cognitive deterioration and for aiding in therapeutic intervention. Moreover it can help people with dementia to have access to important resources and support, talk to family and friends, and to appropriately deal with legal, financial and care decisions.

The assessment of subtle cognitive changes is a cheaper and less invasive way to detect early signs of preclinical AD (Tarnanas et al., 2014) compared with the analysis of AD biomarkers.

Most existing psychometric tests focus on the detection of early dementia or MCI, and most of them need an expert examiner to actively submit the tasks, spending a lot of time and financial resources, and possibly excluding or delaying the evaluation of those with slight cognitive decline or even in a silent phase. COGITAB was conceived for an accessible and brief evaluation of those cognitive domains found to be compromised early in MCI, and especially in preclinical AD. This new web application was designed to be almost self-administered via tablet in a GP office. In the present study we preliminarily presented the tool features and its normative data in a sample of cognitively healthy subjects. An ongoing validation study that includes patients with subjective and objective cognitive diseases is necessary to determine diagnostic accuracy.

Because it is known that a family history of AD and certain acquired risk factors may predispose an individual to a cognitive decline, we also investigated the impact of these conditions on COGITAB performances. Each participant was classified based on the presence

of family history of dementia and specific acquired risk factors. Statistical analysis showed that the COGITAB TS was normally distributed, without ceiling and floor effects. Younger and well-educated participants performed significantly better than older and/or less educated subjects. Correction grids with age/education adjustments and ESs for the TS were provided, thus allowing us to judge future performances as pathological, normal or excellent. For example, the adjusted score of an individual aged 50 years old, with 16 years of education, who achieves a raw score of 80, is 73.86 which corresponds to an ES=3.

The TS was not significantly influenced by either the family history of dementia or the acquired risk factors. The only discriminating factor among the four cohorts was the TET. Participants with higher risk factors (mainly dyslipidemia/hypertension under pharmacological treatment and/or subclinical anxiety/depression and/or smoking habit) were significantly slower (more than one minute) than those belonging to the low risk groups, regardless of the presence of a family history of AD. This finding suggests that recording the execution speed can possibly contribute to the assessment of cognition. Future studies should determine whether it is also essential for the detection of cognitive changes. Because most of the cognitive screening tools commonly used by GPs, geriatricians and general neurologists do not consider the execution time, this is an important observation.

Compared with the traditional paper-and-pencil tests, this new technological approach has some advantages. First of all, computerized tests allow us to control the stimulus presentation time and accurately collect promising data (e.g., reaction times, TET) in a more cost-effective and more accessible way. As the use of technological devices, such as smartphones and tablets, continues to spread worldwide, familiarity with these devices is growing, and they are almost replacing the use of paper and pencils in many tasks. Nowadays computerized tests can be considered as reliable as paper-and-pencil tests. Even individuals with lower technological familiarity can comfortably use a touchscreen device (Holzinger et al., 2002; Canini et al.,

2014). The COGITAB procedure was well tolerated by the subjects who described an overall positive experience and low frustration levels only related to possible technical problems.

Moreover no extensive specific training is needed to administer the test. However, to minimize potential risks (e.g. misinterpretation of the results, inappropriate setting or recommendation, useless or expensive clinical prescriptions, etc.), the examiner (GP and other specialists) needs to be exhaustively instructed about how to prepare the setting, how to introduce the tool, how to address possible questions and doubts, how to communicate the results and when/how to possibly address the individual to a specialist diagnostic path. For easier clinical use, which will be available only after a proper validation study, we are developing an immediate and intuitive outcome report. Based on the ES obtained by the patient, a message will be automatically provided on the screen of the tablet. In the case of ES=3/4, a green light will appear, suggesting a normal performance compared with the normative sample; in the case of ES=1/2, an orange light will appear, suggesting a GP prescription for possible further neuropsychological assessment or a retest after about 16 months; in the case of ES=0, a red light will appear, suggesting the need for a detailed neuropsychological/neurological evaluation. Specific instruction will highlight the nondiagnostic power of the outcome.

The present study has some limitations.

As we specified, this is a preliminary study aimed at the investigation of the normative data in a sample of cognitively healthy subjects. Only after a proper validation study, which is ongoing and include clinical cohorts composed of individuals affected by MCI and SCD, it will be possible to extensively discuss the results. The construct validity of every single sub-test will be also explored.

Moreover, SCD patients and subjects with lower ESs (ES=0, 1 or 2) should be longitudinally monitored to determine possible development of MCI or dementia.

Although COGITAB was conceived as being completely self-administered, the participants needed a support for solving technical problems to ensure an optimal saving of the data. The presence of the examiner ensured immediate feedback in the case of possible doubts or difficulties, thus protecting the performance reliability of the tool.

It is worth noting that the population with only primary schools was rather limited. Clinicians should be careful about the generalization of findings to individuals with lower levels of education.

Another limitation of the current study was the absence of an extensive neuropsychological, neuroradiologic and biomarker analysis to exclude slight cognitive impairment or brain alterations in the control subjects. However, all the participants obtained excellent performances at the traditional cognitive screening, resulting negative for cognitive deficits, with previous significant neurological problems being denied. A first longitudinal follow-up (16 months later) shows cognitive stability in all the tests (MMSE, MoCA and COGITAB). Furthermore, the positive correlation between self-evaluations and higher total scores suggested good meta-cognitive skills.

The test retest COGITAB low consistency (nonsignificant slight enhancement of 3.5 points) can possibly be related to an insufficient representativeness of the small sample size. However either practice effects or other factors cannot be excluded. Further analyses about the test-retest reliability are needed. Further follow-ups will be essential to confirm the absence of an underlying neurodegenerative process. Ongoing statistical analysis will examine the distribution of COGITAB subtest scores to provide specific cutoffs. The predictive value of performance in every single task will be discussed in future reports.

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Normative data for COGITAB: an Italian tablet-based test battery conceived for the preclinical phase of Alzheimer's disease

Authors

Daniela Beltrami[a], Caterina Barletta-Rodolfi[a*], Flavio Bertini[b], Luca Braglia[d], Laura Calzà[g,h], Massimo Corbo, Federico Gasparini[a], Alessandro Marti[a], Danilo Montesi[c], Marta Pisano[a], Maria Luisa Rusconi[e], Matteo Sozzi[f], Cecilia Tonon[a], Enrico Ghidoni[a]

[a] Clinical Neuropsychology, Cognitive Disorders and Dyslexia Unit, Neurology, Department of Neuro-Motor Diseases, AUSL IRCCS, Reggio Emilia, Italy

[b] Department of Mathematical, Physical and Computer Sciences, University of Parma, Parma, Italy

[c] SmartData Research Group, Department of Computer Science and Engineering, University of Bologna, Bologna, Italy

[d] Research and Statistics Infrastructure, AUSL - IRCCS di Reggio Emilia, Reggio Emilia, Italy

[e] Department of Human and Social Sciences, University of Bergamo, Bergamo, Italy

[f] Department of Neuroscience, Neurology. ASST "A. Manzoni", Lecco, Italy

[g] Interdepartmental Centre for Industrial Research in Health Sciences and Technologies, University of Bologna, Bologna, Italy

[h] Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy

[i] Casa Cura Igea (CCI), Department of Neurorehabilitation Sciences, Milano, Italy

Corresponding author: Daniela Beltrami (daniela.beltrami@ausl.re.it)

†Deceased. The author died prior to the submission of the manuscript

Abstract

The number of people with dementia is increasing worldwide. Two main approaches have been adopted to identify subjects with Alzheimer's disease (AD): the neuropsychological evaluation and the identification of biomarkers of AD. The first method is less invasive and easier to perform. This study assesses the psychometric properties of COGITAB, a novel web application designed to be sensitive to the subtle cognitive changes distinctive of the early Mild Cognitive Impairment (MCI) and the preclinical phase of AD. We enrolled 518 healthy controls, classified according to several risk factors and the presence of a family history of dementia. The participants were given COGITAB after a neuropsychological screening. The COGITAB Total Score (TS) was significantly affected by age and years of education. Acquired risk factors and family history of dementia significantly impacted only the COGITAB total execution time (TET), not the TS. This study provides normative data for a newly developed web application. Control subjects with acquired risk factors performed slower, giving an important role to the TET recording. Further studies should examine the ability of this new technology to discriminate between healthy subjects and subjects with initial cognitive decline, even when not detected by standard neuropsychological assessments.

Keywords: Digital cognitive assessment tool; Alzheimer's disease; Preclinical AD; cognitive screening

Introduction

As a result of the aging of the population, dementia is emerging as a major health problem. It is estimated that more than 44 million people worldwide are affected by Alzheimer's disease (AD) or a related form of dementia, and it is believed that this number will reach approximately 150 million in 2050, as reported by the U.S. National Institute of Aging. The costs for dementia are also significant, at approximately US$1 trillion per year, rising to 2 trillion over the next 10 years (Patterson, 2018).

The development of disease-modifying drugs represents a promising chance for individuals suffering of AD, especially at the preclinical or prodromal stages of AD (Mild Cognitive Impairment, MCI, due to AD). An early diagnosis is also important for nonpharmacological interventions, to globally improve physical and cognitive functions, ADL skills, and behavioral and psychological symptoms (Lowrani et al., 2020). In fact, although much of the risk of developing AD can be attributed to genetics, some acquired factors may predispose an individual to a cognitive decline: vascular diseases (Mayeux & Stern, 2012; Imtiaz et al., 2014), excessive alcohol consumption (Kim et al., 2012; Piazza-Gardner et al., 2013; Panza et al., 2013), depression (Byers & Yaffe, 2011; Vilalta-Franch et al., 2013; Zverova et al., 2013; Wu et al., 2018) and insomnia (Shi et al., 2018); smoking cessation is highly recommended to reduce the incidence of dementia (Durazzo et al., 2014).

Therefore, an early diagnosis could be the best way to promptly access medical and support services, increasing the chances of early interventions to maintain a good quality of life for as long as possible, thus reducing the cost of care, and permitting more time to deal with legal, financial and care decisions (Bondi et al., 2008; Rentz et al., 2013; Sperling et al., 2014).

It is known that neuropathological process of AD may begin many years before the onset of clinical symptoms (Dubois et al. 2014) and that the preclinical or prodromal phase is

characterized by the alteration of AD biomarkers, including amyloid **β** 42 (A**β**42) and tau in the cerebrospinal fluid (CSF), amyloid deposition, magnetic resonance imaging alterations, fluoro-2-deoxyglucose (FDG)-PET abnormalities and cognitive changes (Han et al., 2017; Schindler et al., 2017; Alzheimer's Association, 2020).

Despite the importance of biomarkers for the diagnosis of AD, neuropsychological evaluation plays a significant role in early diagnosis offering advantages to the high costs and invasiveness of organic biomarker analysis (Tarnanas et al., 2014).

A recent review about cognitive changes in preclinical AD (Mortamais et al., 2017) shows that the earliest variations involve episodic and semantic memory, as well as executive functions. A decline in episodic memory is typically the earliest and most robust symptom of MCI and dementia, and it can arise 6-10 years before the onset of the symptomatic phase (Bäckman et al., 2001; Bondi et al., 2008; Sperling et al., 2011; Mortamais et al., 2017;). Because it is not clear whether immediate or delayed measures are the most sensitive for early dementia, the analysis of both is recommended. Associative memory is especially sensitive to early AD (Parra et al., 2010, Della Sala et al., 2012) and older adults with deficits in this cognitive area are at increased risk for dementia (Buschke et al., 2017; Mowrey et al., 2018); moreover, there is evidence of deficits in short-term associative memory in older adults with AD, familial AD and asymptomatic carriers of the E280A single presenilin-1 mutation (Parra, Abrahams, Fabi et al., 2009; Parra, Abrahams, Logie et al., 2010). The assessment of executive functioning is often missed in short cognitive screening, especially regarding the so-called “hot” components (Allain et al., 2013), which involve “emotional”, “belief” or “desires”, such as experiences of reward and punishment, regulation of social behavior and decision making. “Cold” components, such as the coordination mechanism of the central executive, inhibition and shifting, can be affected many years before the clinical phase and the decline seems to accelerate two or three years before (Grober et al., 2008; Allain et al., 2013).

Meta-analysis (Wild et al., 2008; Ismail et al., 2010; Zygouris et al., 2014; Tsoi et al., 2015) indicated cognitive screening as an excellent tool in terms of accuracy, availability and cost, to discriminate between cognitively healthy participants and people affected by MCI or dementia. In the past few years, research focused on automated tests, which can be administered via a tablet/smartphone or computer (for a review, see Thabtah et al., 2020), and differed for various properties from the traditional paper and pencil screening.

Most of the existing tests focus on discrimination among subjects with MCI or dementia and cognitively healthy subjects (Wild et al., 2008; Ismail et al., 2010; Tsoi et al., 2015; Zygouris et al., 2014; Mortamais et al., 2017;). Despite being very accurate in detecting early or mild cognitive decline, these tests do not seem to register the slight changes that are distinctive of a preclinical phase (Mortamais et al., 2017). This is why a more cognitively demanding and sensitive tool is needed.

We have developed a new web application named COGITAB which is conceived to be almost self-administered via a tablet in a general practitioner's (GP) office in approximately 30 minutes. Primary care is an ideal place to early identify people with cognitive concerns, but also to manage the risk of developing dementia after the patient is screened. COGITAB was designed to be quick to administer and easy to score. It is run, scored, and processed by software and it will provide an immediate non-numerical outcome of a subject's performance compared with the normative sample.

In the present study (phase one), we preliminarily analyzed the Italian normative data of this new cognitive battery, and we examined its user-friendliness and feasibility, underlying possible weaknesses or problems. These aspects are indispensable for future validation and dissemination phases. Moreover, we explored the possible differences related to the presence of a family history of dementia (genetic factors) and of some acquired risk factors for AD

development (e.g. vascular diseases, smoking, depression, anxiety, etc.) that can negatively impact cognitive efficiency.

The aim of a second ongoing study (phase two) was to investigate the validity of COGITAB for cognitive screening of subjects with objective and subjective cognitive impairment. For the first group we recruited patients diagnosed with early dementia and Mild Cognitive Disorder (MCI). The second sample was composed of patients diagnosed with Subjective Cognitive Disorder (SCD), claiming a persistent decline in cognitive capacities despite a normal performance on standard neuropsychological tests. In the case of a positive outcome in terms of diagnostic accuracy, a third "dissemination" step (phase three) will take place. GPs and other specialists will be exhaustively instructed about how to correctly manage the tool (for further details, see COGITAB Battery and Discussion).

Materials and Methods

Participants

We enrolled 537 participants aged between 45 and 75 years, with varied levels of education (5-18 years) from two regions of northern Italy (Emilia Romagna, Lombardia). The inclusion criteria were having Italian as one's native language, absence of current or previous disabling neurological pathologies, blindness, deafness or other serious sensory impairment, intellectual or cognitive disability, and serious psychiatric diseases.

Nineteen participants were discarded because of the incompleteness of the anamnestic interview or COGITAB procedure because of technical issues (e.g. inadequate internet connection).

The final sample was composed of 518 subjects (231 males; 287 females) aged between 45 and 75 years (mean=59.26; SD=8.22) with varied years of education (range: 5-18; mean=12.63; SD=3.88). A description of age and years of education can be found in Table 1.

Each participant was classified according to two categories: acquired risk factors (high vs. low) and family history of dementia (yes vs. no). High risk was determined if at least two of the following conditions were detected: health risk factors (at least two between hypertension, diabetes, minor cardiovascular disease, thyroid dysfunction, dyslipidemia and other internal pathologies), lifestyle risk factors (smoking, drinking or drug addiction) or psychological risk factors (subclinical anxiety or depression, and the feeling of a physiological memory decline without any previous request for clinical assessment). The most common recurring risk factors were dyslipidemia and hypertension (both in pharmacological treatment), subclinical anxiety/depression and smoking habit. None of the participants reported alcohol or drug addiction. A family history of the disease was based on the presence of first-third degree relatives with a neurodegenerative pathology. In fact, even in the absence of a first degree family history, a second or third-degree family history can be indicative of an elevated risk (Cannon-Albright et al., 2019). Participants were divided into four groups: 271 low risk without a family history, 71 high risk without a family history, 129 low risk with a family history and 47 high risk with a family history. The age distribution among the four cohorts is reported in Table 2.

Procedure

Each session lasted approximately 60 minutes. The procedure was approved by the local research ethics committees and fully explained to the subjects, informed written consent was obtained.

All participants were first requested to complete a clinical interview conducted by a neuropsychologist (anagraphic data and clinical information; occupation/retirement; family history of dementia; lifestyle habits, psychosocial and physiopathological factors). After the anamnestic phase, the participants were assessed using the Mini-mental State Examination

(MMSE) and Montreal Cognitive Assessment (MoCA), which are two 30-point screening tests widely used in clinical practice to detect cognitive decline.

After this cognitive screening, the examiner manually entered information regarding the subject code, the presence of subclinical anxiety/depression and family history of dementia, on a tablet which was then placed on the table about 15 cm in front of the subject. COGITAB was introduced as follows: "Now, you'll be asked to follow the instructions that will appear on the screen. The same instructions will be audible by tapping the speaker icon that you'll see on the screen". The first three requests (date, month and year of birth) allowed the subject to become familiar with the instrument, possibly receiving suggestions on the correct way to tap the screen (e.g., "wait a while before tapping again", "press the screen more slightly", etc.).

After this first phase, the examiner was exclusively available for technical support, such as internet connection issues. The examiner was previously instructed on how to use COGITAB and on how to answer to the subject's possible questions. The COGITAB evaluation lasted for about 30 minutes.

To assess possible variations in COGITAB performance over time, we scheduled a second complete evaluation after approximately 16 months (mean=16.20; SD=4.86). Unfortunately, because of the Covid-19 pandemic, only a small sample of 45 participants accepted the follow-up (Table 3).

COGITAB battery

COGITAB was designed as a web application that implemented a client server architectural pattern. A web application is a program that uses a browser and web technologies to perform tasks over the internet, while a client-server pattern allows us to partition workloads between two modules, the service requester (i.e., the client, a computer or a tablet) and the provider of a service (i.e., the server). In COGITAB, the client module includes the user interfaces and

logic of the tasks and runs in a web browser, while the server module provides the cognitive tests, safely stores the results and provides authorized users with a report of the outcomes for each subject. These design solutions provide the following advantages: COGITAB runs on multiple platforms (browsers and devices) regardless of the operating system and underlying hardware; all users access the same version, and updates can be performed easily just by updating the server; all the results are stored in a centralized server and are protected using high-level solutions. This makes it possible to conduct comparative analyses over time for the same patient and to pursue advanced epidemiological studies.

The two modules use state-of-the-art open-source web technologies; in particular, the client module was developed using the Angular JS framework and the following front-end technologies: HTML version 5, CSS version 3, and JavaScript version 5. The server module was developed using the framework Django the following back-end technologies: Python version 2.7 and PostgreSQL version 9. COGITAB can be administered through any browser using a tablet or computer; however, it was optimized for Google Chrome and Mozilla Firefox browsers running on a 10-inch tablet or greater.

COGITAB is composed of ten subtests (see Table 4 for a summary) conceived to assess those cognitive domains found to be compromised early in MCI and preclinical dementia. Temporal orientation, episodic and semantic memory, and visuo-constructive and visuo-spatial abilities are examined. Executive functions such as divided attention, shifting, verbal fluency, perceptual speed, and inhibition/switching are also analyzed. Moreover, the subjects were asked to self-evaluate their own performance, thus testing meta-cognitive skills, which have predictive value regarding their progression to dementia in MCI patients (Vogel, Stokholm et al., 2004; Vogel, Hasselbalch et al., 2005; Galeone et al., 2011; Wolfsgruber et al., 2014), even though levels of awareness are heterogeneous among them (Roberts et al., 2009). Instructions were made available as text and via audio. Most of the subtests were inspired by existing

cognitive tests, such as the Trail Making Test (Reitan, 1958), object recognition and lexical access tasks (Sartori & Job, 1988), the Stroop Test (Stroop, 1935), the Judgment of Line Orientation Test (Benton, 1978), the Multiple Features Target Cancellation Test or the Bell Test (Marra et al., 2013; Gauthier et al., 1989) and the Rivermead Behavioral Memory Test (Wilson et al, 1985). The exposure time was reduced and different cognitive functions were examined in parallel to create more cognitively demanding tasks. The most articulated, challenging and ecological task of COGITAB is the third one. The subject was requested to remember a character (face, name and surname), a shopping itinerary and all the purchased items, in terms of categories and quantities. The same questions were submitted right after the exposure and after 20 minutes. This task examined visual and verbal immediate and delayed memory, associative memory, recall and recognition processes, and implicit memory.

At the end of the test, data were automatically sent to a central server, and the examiner has access to an easy and immediate total score (TS), which was computed considering correct answers, errors and reaction times (Table 4, last column). The total execution time (TET), which reflects the overall activity duration, was also registered. The outcome datasheet was enriched with different quantitative (single scores, number of errors, latencies, reaction times, etc. for every single task) and qualitative details (type of errors, visual reproduction of the single tasks, etc.). After the tool validation, these details will be available to neuropsychologists, neurologists, and geriatricians in case of GP prescriptions for further diagnostic assessment. For a screening use (GP office), we designed an easier and more intuitive non-numerical outcome report that is still underway (see Discussion).

Statistical Analysis

The present study is descriptive in nature and aimed at describing the normative data of a sample of healthy subjects. The sample size was not determined according to a prespecified target/outcome. We analyzed data from 518 patients, a method that was judged to be both

adequate for the linear regression model used for equivalent score determination and feasible from a logistic/organizational standpoint.

The performed tests were considered to show statistically significant results if the *p*-values were < 0.05; confidence intervals of estimates were two tailed and calculated considering a 0.95 confidence level. Statistical analyses were performed using R version 4.0.4.

The primary aim was to describe the distribution of TSs. We estimated the mean and confidence interval, median and (bootstrap) confidence interval, distribution quantiles, asymmetry index, kurtosis index and Shapiro–Wilk test *p* value to assess the normality of the sample.

Furthermore, we computed the equivalent scores (ESs) following the Capitani and Laiacona procedure (2017). The analysis entailed outer and inner tolerance limit calculations, regression equation estimation and correction factor determination, and equivalent score table derivation. The analysis consisted of estimating the relationship between the score (dependent variable) and sex, age and education (independent variables) by a linear regression model; this model is then used to estimate correction factors applied to the raw score obtained by an individual to produce an adjusted score (corrected given age and education) comparable with those produced by other individuals. Finally, the adjusted scores can be classified into different levels or equivalent scores, given the table of the equivalent scores, where the ES is on the 0-4 scale. An ES score of 0 indicates an adjusted score under the outer tolerance limit (suggesting an abnormal situation), an ES of 4 is for the patient with an adjusted score above the median of adjusted scores, and ES scores of 1-3 suggest an increasing level of performance.

TS and TET were analyzed with ANOVA and ANCOVA-style linear regression models: the first used the presence of a family history, risk group and their interaction as main covariates; the latter adjusted estimates by sex, age, and years of education. We also measured the correlation between TSs and self-evaluations. MMSE and MoCA adjusted scores were also analyzed across the four cohorts by the Kruskal–Wallis test.

Finally we assessed the variation between test and retest scores. The retest assessment was conducted approximately 16 months later (Bartels et al., 2010).

Results

All the subjects performed normally at the traditional cognitive screening tests (MMSE adjusted score mean=29, SD=1.24; MoCA adjusted score mean=25.23, SD=2.46) according to the respective standardization studies (Measso et al., 1993 and Conti et al., 2014). MMSE and MoCA performances were positively correlated (rho 0.29, [0.21, 0.37], p<0.001). Table 5 shows mean and confidence interval, median and (bootstrap) confidence interval, asymmetry, kurtosis and p value from the Shapiro–Wilk test for each cohort, all corroborating the approximately normal shape of the distribution.

A linear regression model was used to assess the influences of age, education and sex on the TS ($F(3.514)=44.134$, $p<0.0001$). Because only age and education (respectively $t(514)=-10.03$, $p<0.0001$; $t(514)=4.50$, $p<0.0001$) were significantly associated with the TS, the final estimated model was $y=80.13–0.64(age–59.26)–0.02(age–59.26)^2+0.60(education-12.63)$, where 59.26 was the average age of the normative sample and 12.63 was the average years of education. We derived the correction grid accordingly with raw score adjustments (for some education/age values; see Table 6 and the appendix for full reference of adjustments). The adjustment had to be added to the raw score to obtain the adjusted score (adjusted score = raw score + y).

The adjusted scores of the normative samples were used to develop rules to classify adjusted scores into five ES by using the outer tolerance limit (59, the 18the ordered adjusted score of the normative sample), adjusted scores median (79.9) and z values of the normal distribution. The criteria used to categorize individuals' adjusted scores can be found in Table 7. The scores of group 0 were lower than the outer tolerance limits; scores of group 4 were higher than the

median value of the sample; those of groups 1, 2, and 3 were intermediate between the central value and the pathology threshold on a quasi-interval scale.

To explore possible differences related to the family history of dementia and acquired risk factors, the COGITAB TS was compared between the four cohorts (Table 8). Only the high-risk group was associated with a diminished mean score (-6.2 points, CI: -9.656 to -2.791, $p<0.001$). However, once controlled for sex, age and education, the high-risk group effect was no longer significant ($p=0.128$). Therefore, neither the family history nor the risk factors showed a significant impact on TS.

The TSs positively correlated with self-observations ($p<0.001$). The subjective perception of a good cognitive performance was actually related to a higher TS, suggestive of good meta-cognitive skills (Table 9).

We analyzed the TET similarly to the TS. The high-risk group was slower than the lower-risk group (approximately +2.1 minutes; CI: 1.17 to 3.01, $p <0.001$); when controlling for sex, age and education the difference was 1.3 minutes (CI 0.4 to 2.2); the family history group showed no association at all (p value = 0.514) (Table 10).

As previously described, a small sample of 45 participants underwent COGITAB a second time after about 16 months to analyze the practice effect and test-retest correlation. We observed a nonsignificant slight enhancement in the retest (+3.5 points, CI=-0.23 to 8.30, $p=0.065$; $r=0.25$, CI -0.05 to 0.51, $p=0.098$, Table 11).

Finally, despite being somewhat limited by the small sample of test/retest observation, we estimated the linear model useful for Reliable Change Index estimation, using the retest score as explained variable, baseline score and age as covariate, following Duff (2012). The estimated model was retest = $121.733 + 0.124 \cdot \text{score} - 0.816 \cdot \text{age}$, with reasonably normally distributed residuals (Shapiro Wilks test $p=0.147$) and a standard error of 9.16. In this

framework a physician interested in judging a change to be clinically significant could apply the equation (retest − (121.733 + 0.124 · score − 0.816 · age))/9.16 and compare this score with the standard normal distribution cutoffs (e. g. accepting a 5% false positive rate, a value below -1.645 should suggest a clinically relevant decrease in the score).

Discussion

The early detection of cognitive decline is crucial for preventing cognitive deterioration and for aiding in therapeutic intervention. Moreover it can help people with dementia to have access to important resources and support, talk to family and friends, and to appropriately deal with legal, financial and care decisions.

The assessment of subtle cognitive changes is a cheaper and less invasive way to detect early signs of preclinical AD (Tarnanas et al., 2014) compared with the analysis of AD biomarkers.

Most existing psychometric tests focus on the detection of early dementia or MCI, and most of them need an expert examiner to actively submit the tasks, spending a lot of time and financial resources, and possibly excluding or delaying the evaluation of those with slight cognitive decline or even in a silent phase. COGITAB was conceived for an accessible and brief evaluation of those cognitive domains found to be compromised early in MCI, and especially in preclinical AD. This new web application was designed to be almost self-administered via tablet in a GP office. In the present study we preliminarily presented the tool features and its normative data in a sample of cognitively healthy subjects. An ongoing validation study that includes patients with subjective and objective cognitive diseases is necessary to determine diagnostic accuracy.

Because it is known that a family history of AD and certain acquired risk factors may predispose an individual to a cognitive decline, we also investigated the impact of these conditions on COGITAB performances. Each participant was classified based on the presence

of family history of dementia and specific acquired risk factors. Statistical analysis showed that the COGITAB TS was normally distributed, without ceiling and floor effects. Younger and well-educated participants performed significantly better than older and/or less educated subjects. Correction grids with age/education adjustments and ESs for the TS were provided, thus allowing us to judge future performances as pathological, normal or excellent. For example, the adjusted score of an individual aged 50 years old, with 16 years of education, who achieves a raw score of 80, is 73.86 which corresponds to an ES=3.

The TS was not significantly influenced by either the family history of dementia or the acquired risk factors. The only discriminating factor among the four cohorts was the TET. Participants with higher risk factors (mainly dyslipidemia/hypertension under pharmacological treatment and/or subclinical anxiety/depression and/or smoking habit) were significantly slower (more than one minute) than those belonging to the low risk groups, regardless of the presence of a family history of AD. This finding suggests that recording the execution speed can possibly contribute to the assessment of cognition. Future studies should determine whether it is also essential for the detection of cognitive changes. Because most of the cognitive screening tools commonly used by GPs, geriatricians and general neurologists do not consider the execution time, this is an important observation.

Compared with the traditional paper-and-pencil tests, this new technological approach has some advantages. First of all, computerized tests allow us to control the stimulus presentation time and accurately collect promising data (e.g., reaction times, TET) in a more cost-effective and more accessible way. As the use of technological devices, such as smartphones and tablets, continues to spread worldwide, familiarity with these devices is growing, and they are almost replacing the use of paper and pencils in many tasks. Nowadays computerized tests can be considered as reliable as paper-and-pencil tests. Even individuals with lower technological familiarity can comfortably use a touchscreen device (Holzinger et al., 2002; Canini et al.,

2014). The COGITAB procedure was well tolerated by the subjects who described an overall positive experience and low frustration levels only related to possible technical problems.

Moreover no extensive specific training is needed to administer the test. However, to minimize potential risks (e.g. misinterpretation of the results, inappropriate setting or recommendation, useless or expensive clinical prescriptions, etc.), the examiner (GP and other specialists) needs to be exhaustively instructed about how to prepare the setting, how to introduce the tool, how to address possible questions and doubts, how to communicate the results and when/how to possibly address the individual to a specialist diagnostic path. For easier clinical use, which will be available only after a proper validation study, we are developing an immediate and intuitive outcome report. Based on the ES obtained by the patient, a message will be automatically provided on the screen of the tablet. In the case of ES=3/4, a green light will appear, suggesting a normal performance compared with the normative sample; in the case of ES=1/2, an orange light will appear, suggesting a GP prescription for possible further neuropsychological assessment or a retest after about 16 months; in the case of ES=0, a red light will appear, suggesting the need for a detailed neuropsychological/neurological evaluation. Specific instruction will highlight the nondiagnostic power of the outcome.

The present study has some limitations.

As we specified, this is a preliminary study aimed at the investigation of the normative data in a sample of cognitively healthy subjects. Only after a proper validation study, which is ongoing and include clinical cohorts composed of individuals affected by MCI and SCD, it will be possible to extensively discuss the results. The construct validity of every single sub-test will be also explored.

Moreover, SCD patients and subjects with lower ESs (ES=0, 1 or 2) should be longitudinally monitored to determine possible development of MCI or dementia.

Although COGITAB was conceived as being completely self-administered, the participants needed a support for solving technical problems to ensure an optimal saving of the data. The presence of the examiner ensured immediate feedback in the case of possible doubts or difficulties, thus protecting the performance reliability of the tool.

It is worth noting that the population with only primary schools was rather limited. Clinicians should be careful about the generalization of findings to individuals with lower levels of education.

Another limitation of the current study was the absence of an extensive neuropsychological, neuroradiologic and biomarker analysis to exclude slight cognitive impairment or brain alterations in the control subjects. However, all the participants obtained excellent performances at the traditional cognitive screening, resulting negative for cognitive deficits, with previous significant neurological problems being denied. A first longitudinal follow-up (16 months later) shows cognitive stability in all the tests (MMSE, MoCA and COGITAB). Furthermore, the positive correlation between self-evaluations and higher total scores suggested good meta-cognitive skills.

The test retest COGITAB low consistency (nonsignificant slight enhancement of 3.5 points) can possibly be related to an insufficient representativeness of the small sample size. However either practice effects or other factors cannot be excluded. Further analyses about the test-retest reliability are needed. Further follow-ups will be essential to confirm the absence of an underlying neurodegenerative process. Ongoing statistical analysis will examine the distribution of COGITAB subtest scores to provide specific cutoffs. The predictive value of performance in every single task will be discussed in future reports.

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Sex	N	Age (years) Mean (SD)	Education (years) Mean (SD)
Males	231	59.0 (±8.2)	12.5 (±3.9)
Females	287	59.4 (±8.2)	12.8 (±3.8)
Overall	518	59.2 (±8.2)	12.6 (±3.9)

Table 1. Demographic data of the study population

	N	Mean (SD)
Low risk without a family history	271	57.6 (±8.4)
High risk without a family history	71	63.3 (±7.3)
Low risk with a family history	129	58.9 (±7.6)
High risk with a family history	47	63.7 (±6.6)
All	518	59.3 (±8.2)

Table 2. Age distribution among the four cohorts (Kruskal–Wallis test p <0.001)

Sex	N	Age (years) Mean (SD)	Education (years) Mean (SD)
Males	16	66.4 (±4.2)	13.0 (±4.6)
Females	29	64.0 (±6.2)	14.8 (±5.5)
Overall	45	64.9 (±5.8)	14.4 (±5.2)

Table 3. Demographic data of retest population

N.	*Task*	*Description*	*Cognitive function assessed*	*Scoring (range)*
1	Personal information	The subject is asked to enter some basic information, such as birth date, sex and the number of years of school attended	Personal orientation	Qualitative
2	Temporal orientation	Participants should type the date (day of the week, month and year)	Temporal orientation	Accuracy (0-4)
3	The shopping day	This is the most articulated and ecological task. A character placed in the middle of the screen introduces himself with a face, name and surname (e.g., "Good morning! My name is Albert Jones. Please remember my name!"); the participant is asked to pay attention to the grocery list (categories and quantities of the purchased items) and to the itinerary ("Now I'll show you my route on the map. Pay attention because later I'm going to ask you about it"). He is then required to retrace the route he was shown earlier on the screen and to answer a few questions about the purchases (e.g., "What did I buy from the cake shop?"; "How many slices of cake did I buy?"). The same questions are asked again after the completion of Parts 4 to 8, later illustrated and which take approximately 20 minutes to complete. The participant is moreover required to recognize the face of the character among 7 other faces and to recall his name and surname. This test was inspired by the RBMT.	Visual/verbal immediate/delayed implicit and explicit memory (recall and recognition), associative memory	Accuracy Immediate recall (0-40) Delay recall (0-53)
4	Numbers and letters	Participants should connect varied categories of items that are displayed on the screen: numbers from the smallest to the largest (e.g., 1-2-3), letters in alphabetical order (e.g., A-B-C), and alternating numbers and letters (e.g., 1-A-2-B). This is a shorter version of the TMT.	Executive functioning, visual search speed, shift, speed of processing, mental flexibility	Accuracy Speed (0-7)
5	Completion of a geometric shape	The subject is instructed to carefully watch a cube (which appears on the screen for a few seconds) and then to complete the missing parts of the same shape. This subtest is a more difficult version of other copy of complex figure tests since the geometric model disappears after a few seconds.	Visual-spatial memory, iconic reproduction, visuo-constructive praxis abilities	Accuracy (0-3)
6	Picture selection	Inspired by the MFTC and the Bell Test, the request of this task is to select as quickly as possible all the items identical to one or two of the models previously shown (a dog in the first trial; a cat and a man in the second trial).	Visual-spatial exploration, selective and divided attention, psychomotor speed, inhibition abilities	Accuracy Speed (0-10)
7	Visual fluency	Several sketches appear on the screen one at a time. The participant is asked to select the drawing only when the first letter of its name corresponds to a specific target (letter C for the first trial, e.g., "CAT"; letters A and F for the second trial, e.g., "AIRPLANE" or "FLOWER"). Object recognition and lexical access tasks influenced this test.	Selective and divided attention, visual recognition, executive functioning, verbal fluency	Accuracy Speed (0-10)
8	Correct answer inhibition	The request is to select as quickly and as accurately as possible the wrong answer (e.g., "What is Everest? A mountain; a lake". "A lake" is correct). This subtest was inspired by the Stroop test, which is a well-established test of response inhibition.	Semantic memory, inhibition, control interference abilities	Accuracy Speed (0-13)
9	Line orientation	This subtest was inspired by the Judgment of Line Orientation Test. In contrast to the Benton version, however, the subject should carefully watch a couple of lines for a few seconds and then, once they disappear, to match those lines to a set of lines arranged in a semicircle.	Visual-spatial abilities, iconic memory	Accuracy (0-10)
10	Self-assessment	"That's the end of the test! How do you think it went?" (Very bad/Bad/Don't know/Good/Very good).	Meta-cognitive ability	Qualitative
			Total Score (TS)	0-150

Table 4. COGITAB tasks descriptions

	N	Min	Max	MEAN	Lower.CI	Upper.CI	MEDIAN	Lower.CI.1	Upper.CI.1	SD	Asim	Curt	Shapiro_*p*
Low risk without a family history	271	38	127	80.46	78.77	82.15	80.00	78.00	81.00	14.12	0.04	3.55	0.25
High risk without a family history	71	48	96	74.24	71.51	76.97	74.50	71.00	78.00	11.52	-0.20	2.51	0.49
Low risk with a family history	129	44	108	79.17	77.24	81.11	80.00	75.00	80.00	11.13	-0.29	3.32	0.28
High risk with a family history	47	36	102	74.23	70.05	78.42	74.00	68.00	77.00	14.26	-0.36	3.15	0.61
All	518	36	127	78.72	77.58	79.87	79.00	77.00	80.00	13.30	-0.04	3.59	0.10

Table 5. Description of the distribution of the TS. Mean, median and confidence interval; SD=standard deviation. Asim=skewness (0=symmetrical distribution; >0=positive skew; <0=negative skew); Curt=Kurtosis index (3=normal distribution; <3=platykurtic distribution; >3=leptokurtic distribution); Shapiro_p=$p<0.05$ indicates a nonnormal distribution of TS.

Education (years)	Age (years)						
	45	50	55	60	65	70	75
5	-0.2	0.5	2.3	5.1	8.9	13.8	19.8
8	-2.1	-1.3	0.5	3.3	7.1	12.0	18.0
13	-5.1	-4.3	-2.6	0.3	4.1	9.0	15.0
16	-6.9	-6.1	-4.4	-1.5	2.3	7.2	13.2
18	-8.1	-7.3	-5.6	-2.8	1.1	6.0	11.9

Table 6. Correction grid with age and education adjustments for individual scores. Adjusted score=raw score+adjustment. Adjustment=$0.64(\text{age}-59.26)+0.02(\text{age}-59.26)^2-0.60$ (education–12.63).

	Min	Max	Frequency	Criteria
ES 0	37.0	59.0	18	<= 59.0
ES 1	59.1	67.2	41	(59.0-67.2)
ES 2	67.4	73.8	82	(67.2-73.8)
ES 3	73.8	79.9	118	(73.8-79.9)
ES 4	79.9	129.8	259	> 79.9

Table 7. Equivalent scores for the total score. ES=0 corresponds to an adjusted score under the outer tolerance limit (suggesting an abnormal situation); ES=4 is above the median of the adjusted score; ES=1, 2, 3 suggests increasing levels of ability. The upper limit of the interval score for criteria is included in the interval itself.

	Anova			Ancova		
	Est	95% CI	*p* value	Est	95% CI	*p* value
(Intercept)	80.5	(78.9 to 82)	<0.001	84.1	(77.2 to 91.1)	<0.001
High-risk group	-6.2	(-9.7 to -2.8)	<0.001	-2.5	(-5.8 to 0.7)	0.128
Family history group	-1.3	(-4 to 1.5)	0.358	-1.2	(-3.8 to 1.4)	0.352
High-risk group x Family history group	1.3	(-4.3 to 6.9)	0.651	0.9	(-4.2 to 6)	0.736
Female				-1.1	(-3.2 to 1.1)	0.336
age 56-65				-2.7	(-5.2 to -0.3)	0.029
age 66-75				-12.3	(-15.1 to -9.5)	<0.001
educ 6-8				-3.8	(-10.9 to 3.2)	0.289
educ 9-13				0.9	(-6 to 7.7)	0.804
educ >13				2.7	(-4.2 to 9.7)	0.442

Table 8. Anova and Ancova linear models on COGITAB score

	N	Spearman Rho	*p*
Low risk without a family history	271	0.24	<0.001
High risk without a family history	71	0.02	0.861
Low risk with a family history	129	0.02	0.815
High risk with a family history	47	0.27	0.066
All	518	0.19	<0.001

Table 9 Correlation between TS and self-observations; $p<0.05$ indicates a correlation different from 0.

	Anova			Ancova		
	Est	95% CI	*p* value	Est	95% CI	*p* value
(Intercept)	13.5	(13.1 to 14)	<0.001	12.7	(10.7 to 14.6)	<0.001
High-risk group	2.1	(1.2 to 3)	<0.001	1.3	(0.4 to 2.2)	0.005
Family history group	0.3	(-0.4 to 1.1)	0.383	0.2	(-0.5 to 0.9)	0.514
High-risk group x Family history group	0.0	(-1.5 to 1.4)	0.950	0.0	(-1.5 to 1.4)	0.953
Female				0.5	(-0.1 to 1.1)	0.078
age 56-65				1.3	(0.6 to 2)	<0.001
age 66-75				2.6	(1.9 to 3.4)	<0.001
educ 6-8				0.8	(-1.2 to 2.7)	0.427
educ 9-13				-0.9	(-2.8 to 1)	0.331
educ >13				-0.5	(-2.4 to 1.4)	0.618

Table 10. Anova and Ancova linear models of COGITAB execution time (minutes)

	N	Mean_diff	lower	upper	p_value	Spearman Rho	Lower.CI	Upper.CI	*p*
Low risk without a family history	14	6.3	0.2	12.4	0.043	0.32	-0.25	0.73	0.259
High risk without a family history	10	-2.1	-15.0	10.7	0.714	0.20	-0.62	0.64	0.956
Low risk with a family history	16	6.9	2.0	11.7	0.009	0.40	-0.12	0.75	0.128
High risk with a family history	5	-3.6	-17.0	9.8	0.497	0.29	-0.80	0.93	0.633
All	45	3.5	-0.2	7.3	0.065	0.25	-0.05	0.51	0.098

Table 11 Practice effect and correlation between test and retest measures. Spearman's rho (r_s)=r_s between .20 and .39 indicates a weak correlation, r_s between .40 and .59 indicates a moderate correlation; Lower. CI and Upper. CI = lower and upper confidence intervals of Spearman's rho; $p<0.05$ indicates a correlation different from 0.

Appendix A. Correction grid with age and education adjustments for individual scores

Education (years)	Age (years)														
	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59
5	-0,25	-0.18	-0.08	0.07	0.26	0.49	0.76	1.07	1.43	1.82	2.26	2.74	3.27	3.83	4.43
6	-0.85	-0.79	-0.68	-0.53	-0.35	-0.12	0.16	0.47	0.83	1.22	1.66	2.14	2.66	3.23	3.83
7	-1.45	-1.39	-1.28	-1.14	-0.95	-0.72	-0.45	-0.13	0.22	0.62	1.06	1.54	2.06	2.62	3.23
8	-2.06	-1.99	-1.89	-1.74	-1.55	-1.32	-1.05	-0.74	-0.38	0.02	0.46	0.94	1.46	2.02	2.63
9	-2.66	-2.59	-2.49	-2.34	-2.15	-1.92	-1.65	-1.34	-0.98	-0.59	-0.15	0.33	0.85	1.42	2.02
10	-3.26	-3.20	-3.09	-2.95	-2.76	-2.53	-2.25	-1.94	-1.59	-1.19	-0.75	-0.27	0.25	0.82	1.42
11	-3.86	-3.80	-3.69	-3.55	-3.36	-3.13	-2.86	-2.54	-2.19	-1.79	-1.35	-0.87	-0.35	0.21	0.82
12	-4.47	-4.40	-4.30	-4.15	-3.96	-3.73	-3.46	-3.15	-2.79	-2.39	-1.96	-1.47	-0.95	-0.39	0.22
13	-5.07	-5.01	-4.90	-4.75	-4.56	-4.33	-4.06	-3.75	-3.39	-3.00	-2.56	-2.08	-1.56	-0.99	-0.39
14	-5.67	-5.61	-5.50	-5.36	-5.17	-4.94	-4.66	-4.35	-4.00	-3.60	-3.16	-2.68	-2.16	-1.59	-0.99
15	-6.27	-6.21	-6.11	-5.96	-5.77	-5.54	-5.27	-4.95	-4.60	-4.20	-3.76	-3.28	-2.76	-2.20	-1.59
16	-6.88	-6.81	-6.71	-6.56	-6.37	-6.14	-5.87	-5.56	-5.20	-4.80	-4.37	-3.89	-3.36	-2.80	-2.19
17	-7.48	-7.42	-7.31	-7.16	-6.97	-6.74	-6.47	-6.16	-5.80	-5.41	-4.97	-4.49	-3.97	-3.40	-2.80
18	-8.08	-8.02	-7.91	-7.77	-7.58	-7.35	-7.08	-6.76	-6.41	-6.01	-5.57	-5.09	-4.57	-4.01	-3.40

Education (years)	Age (years)															
	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75
5	5.08	5.77	6.50	7.27	8.09	8.94	9.84	10.78	11.76	12.78	13.84	14.95	16.09	17.28	18.51	19.78
6	4.48	5.17	5.90	6.67	7.48	8.34	9.23	10.17	11.15	12.18	13.24	14.34	15.49	16.68	17.91	19.18
7	3.88	4.56	5.29	6.07	6.88	7.74	8.63	9.57	10.55	11.57	12.64	13.74	14.89	16.08	17.31	18.58
8	3.27	3.96	4.69	5.46	6.28	7.13	8.03	8.97	9.95	10.97	12.03	13.14	14.29	15.47	16.70	17.98
9	2.67	3.36	4.09	4.86	5.67	6.53	7.43	8.37	9.35	10.37	11.43	12.54	13.68	14.87	16.10	17.37
10	2.07	2.76	3.49	4.26	5.07	5.93	6.82	7.76	8.74	9.76	10.83	11.93	13.08	14.27	15.50	16.77
11	1.47	2.15	2.88	3.66	4.47	5.32	6.22	7.16	8.14	9.16	10.23	11.33	12.48	13.67	14.90	16.17
12	0.86	1.55	2.28	3.05	3.87	4.72	5.62	6.56	7.54	8.56	9.62	10.73	11.87	13.06	14.29	15.57
13	0.26	0.95	1.68	2.45	3.26	4.12	5.02	5.95	6.94	7.96	9.02	10.13	11.27	12.46	13.69	14.96
14	-0.34	0.35	1.08	1.85	2.66	3.52	4.41	5.35	6.33	7.35	8.42	9.52	10.67	11.86	13.09	14.36
15	-0.95	-0.26	0.47	1.25	2.06	2.91	3.81	4.75	5.73	6.75	7.82	8.92	10.07	11.26	12.49	13.76
16	-1.55	-0.86	-0.13	0.64	1.46	2.31	3.21	4.15	5.13	6.15	7.21	8.32	9.46	10.65	11.88	13.15
17	-2.15	-1.46	-0.73	0.04	0.85	1.71	2.61	3.54	4.52	5.55	6.61	7.72	8.86	10.05	11.28	12.55
18	-2.75	-2.06	-1.33	-0.56	0.25	1.11	2.00	2.94	3.92	4.94	6.01	7.11	8.26	9.45	10.68	11.95