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Capacity to consent to research in older adults with normal cognitive functioning, mild and major neurocognitive disorder: an Italian study

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Abstract

Background: A specific evaluation of the capacity to consent to research in older adults with cognitive decline is often not included routinely in research practice. However, there is a need to evaluate this competence adopting brief standardized instruments to guarantee their ethical rights. The present study evaluated in older adults with normal cognitive functioning, and major and mild neurocognitive disorders whether the Mini-Mental State Examination (MMSE) and a brief battery of neuropsychological tests are sensitive and specific to discriminate subjects able to provide consent to research.

Methods: 54 participants with Major Neurocognitive Disorder (MajorNCD), 22 with Mild Neurocognitive Disorder (MildNCD), and 37 Normal Cognitive Functioning individuals (NCF). The capacity to provide consent was assessed using the MacArthur Competence Assessment Tool for Clinical Research. Cognitive functioning was assessed using the MMSE, Verbal Fluency Tests, Trail Making Test (TMT-A), Immediate and Delayed Recall Test.

Results: In the MildNCD and NCF groups, the aggregate score of neuropsychological tests showed high sensitivity and specificity in classifying subjects able to provide consent to research. In the MajorNCD group, MMSE, Recall test, and TMT-A performed better than the aggregate score in classifying subjects as able of consenting to the hypothetical research.

Conclusion: The choice of the best tool to assess the ability to provide consent to research may depend on the degree of cognitive impairment. MMSE is a good tool for subjects with MajorNCD. A more comprehensive battery of neuropsychological tests would represent a better tool in NCF and MildNCD individuals.

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1. Introduction

Decisional capacity to provide consent to research is the ability of individuals to understand and process the necessary information to make an informed decision regarding their participation in a research study (Appelbaum & Grisso, 2001; Biros, 2018). Expressing valid consent is a complex decision-making process that implies that individuals can understand the nature of the study, reason about the risks/benefits of their participation, evaluate how their involvement may directly impact on themselves, and express the final choice (Appelbaum & Grisso, 2001; Moyeet al., 2013).

There is growing international attention to evaluating this competency in older adults with some degree of cognitive decline (de Medeiros et al., 2022; Isella et al., 2008; Gaubert & Chainay, 2021) to identify inclusive research practices that provide opportunities for them to be involved in research protocols adequately (Ries et al., 2020; Sacco et al., 2021). Indeed, although older adults with Mild Cognitive Impairment (MCI) and with mild to moderate Alzheimer disease (AD) are impaired in consent abilities of reasoning and understanding of disclosed material of a research protocol (e.g., Karlawish et al., 2002; Kim et al., 2001), in some studies these subjects showed a good performance on the consent ability to express a choice (Buckles et al., 2003; Karlawish et al., 2002; Jefferson et al., 2008; Moye et al., 2004; Warner et al., 2008; for a review see Parmigiani et al., 2021). This finding is important because individuals with cognitive impairments may choose to participate in a research protocol without adequately understanding their decisions' risks or potential benefits. Knowing whether participants with dementia or MCI fully understand the research's objective and are capable of providing informed consent is also essential for their families as well as for ethics committees (de Medeiros et al., 2022; Ho et al., 2021; Sacco et al., 2021).

The most widespread tool used to assess capacity to consent to research is the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR; Appelbaum & Grisso,

2001). It is considered the best instrument for assessing this ability (for review, see Dunn et al., 2006). The MacCAT-CR is a semi-structured interview, which takes into consideration the skills considered relevant in defining the subjects' decision-making capacity concerning research participation (Grisso & Appelbaum, 1997): ability to understand the most relevant information of the nature of the research (i.e., understanding dimension); ability to assess the current situation and its possible consequences (i.e., appreciation dimension); ability to manage information in a rational way (i.e. reasoning dimension); ability to communicate one's choice (i.e., expressing a choice dimension). On the one hand, previous studies found that AD subjects with very mild to moderate dementia performed worse than healthy controls in understanding, appreciation, and reasoning dimensions (e.g., Karlawish et al., 2002; Kim et al., 2001). On the other hand, studies comparing subjects with MCI and healthy controls found group differences only in understanding and reasoning dimensions (Jefferson et al., 2008). The Understanding dimension was found to be the best in discriminating subjects able and not able to provide informed consent (Jefferson et al., 2008; Palmer et al., 2017; Karlawish et al., 2008).

Although the MacCAT-CR is considered a gold standard instrument to measure the capacity to consent to research (Harmell et al., 2013; Sturman, 2005), it is not used routinely in research practice partly because it is not recognized from most countries' jurisdictions as a test tool (Porteri & Petrini, 2015; Southerland et al., 2022; West et al., 2017) and because of its complexity and length. Hence, to overcome these problems, many studies used the Mini-Mental State Examination (MMSE; Folstein et al.,1975), a brief test for assessing global cognitive functioning, to determine cognitive impairment severity in decisional capacity (Kim & Caine, 2022; Karlawish et al., 2002). Studies that tested whether the MMSE is a predictor of the ability to express a valid consent to research (Gregory et al., 2007; Karlawish et al., 2002; Kim & Caine, 2002; Whelan et al., 2009) suggested that it is a useful but not appropriate instrument for measuring a complex ability such as the context-dependent ability to understand, reasoning, and appreciate disclosed material about a research protocol in individuals with neurocognitive disorders (Dunn et al., 2006; Kim & Caine, 2002; Raymont et al., 2002).

Furthermore, other authors advocated using neuropsychological tests to assess subjects with doubtful decision-making skills in providing informed consent (e.g., Gurrera et al., 2006; Galeotti et al., 2012; Marson et al., 1997; Moberg & Kniele, 2006; Sacco et al., 2021). Particularly, verbal recall (both immediate and delayed recall) and simple executive functions on word fluency (phonemic and semantic) and visuomotor tracking (i.e., Trail Making Test – Part A) were found to be critical abilities in the evaluation of the capacity to consent to treatment in mild AD subjects (Marson et al., 1997). Other studies showed that the ability to understand consent information was related to declined memory of information disclosed in the consent

form (Guerrera et al., 2006; Marson et al., 1997; Marson et al., 1995; Moelter et al., 2016). In contrast, the consent ability of appreciation and reasoning was associated with executive functions, mental conceptualization, and sequencing of information (Guerera et al., 2006, Jefferson et al., 2008; Marson et al., 1996; Marson et al., 1995). However, many authors have criticized the idea that having an adequate consent capacity is linked to performance in neuropsychological tests (Glass, 1997) since the presence of a diagnosis of cognitive impairment does not imply an impairment of this ability (Harmell et al., 2013).

Given the need to assess decision-making ability to provide a valid consent to research in older adults with major and mild neurocognitive disorders adopting brief standardized instruments in different research fields (Ries et al., 2020; Sacco et al., 2021; Southerland et al., 2022), the present study aimed to evaluate whether the MMSE and a brief battery of neuropsychological tests assessing memory and executive functions on word fluency and visuomotor tracking are sensitive and specific to discriminate subjects able to understand and provide consent to research. To address this aim, we used the dimension of the Understanding scale of the MacCAT-CR (Appelbaum & Grisso, 2001) as a gold standard for assessing research-related decision-making capacity (Dunn et al., 2006; Harmell et al., 2013; Sturman, 2005). We decided to use this dimension for its brevity of administration and because it is considered the best dimension in discriminating subjects' ability to provide informed consent (Jefferson et al., 2008; Palmer et al., 2017; Karlawish et al. 2008). We recruited both healthy and cognitively impaired older adults, distinguishing the latter in subjects with a diagnosis of Mild Neurocognitive Disorder (MildNCD) and subjects with Major Neurocognitive Disorder (MajorNCD) according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013; see more details in the Method).

We expected to find the global functioning index (i.e., MMSE) a modest or not adequate discriminator of the MacCAT-CR decisional capacity (Kim & Cane, 2002; Whelean et al., 2009) compared to a more comprehensive assessment, including memory and simple executive functioning tests (Guerrera et al., 2006; Marson et al., 1997; Moelter et al., 2016).

2. Materials and Methods

2.1 Participants

A total of 113 participants (M_{age}= 75.59; DS = 8.20; age range: 61-93) were enrolled in this prospective, cross-sectional study. Inclusion criteria were age ≥ 60 years, individuals with MMSE > 10, and knowledge of the Italian language. Participants included 54 individuals with Major Neurocognitive Disorder (MajorNCD group), 22 individuals diagnosed with Mild

Neurocognitive Disorder (MildNCD group), and 37 Normal Cognitive Functioning individuals (NCF group). Participants in MajorNCD and MildNCD groups were recruited from the Neurological Institute IRCCS Mondino Foundation, while the normal cognitive functioning group was recruited from the general population.

Major and Mild Neurocognitive Disorder diagnoses were classified according to criteria of the DSM- 5 (American Psychiatric Association, 2013). The diagnosis was reached through a multidisciplinary screening that included physical, neurological and neuroradiological examination, neuropsychological testing, and assessment of daily living activities. MajorNCD diagnosis was based on a subjective and objective substantial impairment in one or more cognitive domains sufficient to interfere with independence in every day. MildNCD diagnosis was based on preservation of functional ability in daily life, subjective report of cognitive impairment, and objective cognitive impairment. The normal cognitive functioning group was free of any reported functional difficulties or subjective and objective cognitive impairment. See Table 1 for sample characteristics. This study was completed in accordance with the Helsinki Declaration and approved by the Pavia Ethical Committee (reference number: P-20190043453). Informed consent was obtained from all subjects involved in the study.

Table 1. Demographic Characteristics and Performance on Neuropsychological Tests and Decisional Capacity in Normal Cognitive Functioning (NCF), Mild Neurocognitive Disorder (MildNCD), and Major Neurocognitive Disorder (MajorNCD) Groups

	NCF (n=37)	**MildNCD (n=22)**	**MajorNCD (n=54)**	**F (2,113)**	**p-value**	**η_p^2**
Demographic characteristics						
Age	68.68 ± 6.57[a]	79.82 ± 6.96[b]	78.61 ± 6.59[b]	29.97	<.001	0.35
Years of education	10.43 ± 4.09[a]	7.32 ± 4.49[b]	6.80 ± 3.70[b]	9.61	<.001	0.15
Female, n (%)[§]	21 (57%)[a]	14 (63%)[a]	30 (54%)[a]	0.43 (2)	.806	0.06^
Neuropsychological test (Range)						
MMSE (0-30)	27.89 ± 1.73[a]	25.11 ± 1.46[b]	21.43 ± 2.76[c]	92.11	<.001	0.63
Babcock Story Recall test – total score (0-16)	12.25 ± 2.95[a]	6.79 ± 4.74[b]	4.53 ± 4.02[b]	44.29	<.001	0.45
Babcock Story Recall test – immediate recall (0-8)	5.70 ± 1.87[a]	3.35 ± 2.45[b]	2.53 ± 2.08[b]	27.27	<.001	0.33
Babcock Story Recall test – delayed recall (0-8)	7.09 ± 1.43[a]	4.28 ± 2.51[b]	2.78 ± 2.35[c]	45.09	<.001	0.45
TMT-A	0.04 ± 0.02[a]	0.02 ± 0.01[b]	0.01 ± 0.01[b]	28.13	<.001	0.34
Phonemic fluency test	31.70 ± 8.93[a]	23.73 ± 8.29[b]	20.35 ± 8.73[b]	18.79	<.001	0.25
Semantic fluency test	42.81 ± 7.43[a]	30.91 ± 9.28[b]	26.70 ± 7.96[b]	44.55	<.001	0.45
Aggregate score (0-4)	3.24 ± 0.66[a]	1.69 ± 0.94[b]	1.09 ± 0.76[c]	84.95	<.001	0.61
MacCAT-CR (Range)						
Understanding (0-26)	21.68 ± 4.80[a]	14.45 ± 5.75[a]	9.80 ± 5.94[b]	21.75	<.001	0.29

Note: F and p-values reported refer to one-way ANOVA; Means having the same alphabetical superscript are not significantly different [§]Chi-square test value is reported; ^Phi correlation coefficient as a measure of effect size.

MMSE = Mini Mental State Examination; TMT-A = Trail Making Test part A; MacCAT-CR = MacArthur Competence Assessment Tool for Clinical Research. Aggregate score is an aggregate index of equivalent Babcock Story recall test scores – total score, TMT-A, Phonemic and Semantic fluency tests.

2.2 Measures

2.2.1 Neuropsychological evaluation

The *Mini-Mental State Examination* (MMSE; Folstein et al., 1975) is a screening test widely used to assess global cognitive functioning. It comprises a series of items to measure temporal and spatial orientation, immediate and delayed memory, language, attention, and visual construction. All correct items are summed to obtain a total score ranging from 0 to 30.

The *Babcock Story Recall Test* (Spinnler & Tognoni, 1987) is a verbal memory test used to assess both immediate and delayed recall of verbal information. The examiner reads the story and then asks the subject for immediate recall. Following a 20-minute interval, the examiner asks the subject for delayed recall. Scores for immediate (range 0-8) and delayed (range 0-8) recall are summed to obtain a total recall score (range 0-16). The average intercorrelation between immediate and delayed recall was r = .79.

The *Trail making Test part A* (TMT A; Giovagnoli et al., 1996) consists of connecting, as quickly as possible, a series of numbers (1–25) randomly distributed on a sheet of paper. The total score is the total completion time of the test in seconds. We applied a transformation so that higher scores reflected better performance (i.e., the transformed score reflected 1/x, where x represents the score obtained by the subject in the task). In studies using multiple sessions, Cronbach's alpha is typically in the range of .70–.90 (Giovagnoli et al., 1996).

The *Verbal fluency test* (Novelli et al., 1968) consists of two subtests: phonemic fluency and semantic fluency. In the *phonemic fluency task*, participants are asked to generate as many words as possible beginning with the letter "F", "A", and "S", allowing 60 s for each letter. In the *semantic fluency task*, participants are asked to generate as many words as possible falling in the categories "Fruits", "Animals", and "Cars". Proper names, places, and words with the same suffix do not receive credit. The score in each subtest is the sum of the correct words generated for each letter (i.e., phonemic fluency task; Cronbach's alpha = .89) and each category (i.e., semantic fluency task; Cronbach's alpha = .87).

2.2.2 Decisional capacity evaluation

The *MacArthur Competence Assessment Tool for Clinical Research* (MacCAT-CR; Appelbaum & Grisso, 2001) is a 15–20-minute semi-structured interview widely used to assess whether a person has adequate capacity to provide informed consent to participate in research. The MacCAT-CR contains 21 questions assessing four dimensions of decisional capacity: Understanding (13 items) assesses the ability to comprehend disclosed information about the nature of the research project, its purpose, and procedure; Appreciation (3 items) evaluates the

ability to acknowledge the effect of research participation on own personal situation; Reasoning (4 items) assesses the ability to compare alternatives and to describe the consequences to everyday lives of participating or not to the research project; Expressing a Choice (1 item) assesses the ability to decide whether to participate or not in the research project. Accordingly, we created a hypothetical research project of a made-up medication for improving memory and the interview was adapted following the content of the research project. The research protocol consisted of a randomized, double-blind placebo-controlled study lasting two months that involved blood draw once a week and in alternate days interviews on subjects' wellbeing. Participants were told that the drug and project research study was hypothetical, and they were asked to imagine that they were invited to enroll in the study. Examiners read aloud each of the four sections of the MacCAT-CR. After each section, the examiner posed the question "Can you tell me your understanding of what I just said?". If the subject did not state the key topics, the examiner asked specific questions, such as "What is the aim of the described research project?". Interviews were recorded on a sheet of paper. Each answer could be scored as 0 reflecting no comprehension, 1 partial comprehension, and 2 indicating full comprehension of relevant information. Capacities to provide informed consent are expressed as the sum of each dimension' s score so that higher scores indicate an increased ability to consent to participate in research. The MacCATCR administration and scoring followed the standard method of Appelbaum & Grisso (2001). For the specific aim of the present study, we focused on the Understanding dimension (range 0-26), which is considered to be the best dimension in discriminating subjects able and not able to provide informed consent (Jefferson et al., 2008; Palmer et al., 2017; Karlawish et al. 2008).

2.3 Procedure

Participants provided written informed consent before beginning the neuropsychological assessment and MacCAT-CR interview. They were tested individually during a single session that generally lasted 1 hour. The order of the test administration was the same for all subjects: participants completed neuropsychological testing (MMSE, Babcock Story Recall Test, TMT-A, Phonemic Fluency, and Semantic Fluency) and MacCAT-CR interview. We administered the whole MacCAT-CR interview, but, as reported above, we focused analyses only on the Understanding dimension.

2.4 Statistical Analysis

The raw scores of all neuropsychological tests were adjusted for age and education (adjusted scores). The adjusted scores were classified into five categories (equivalent score; ES): 0 = declined performance that falls in the lower tail of the distribution below the 5th percentile;

1 = borderline performance, including the scores that are placed between the 5th percentile and the 20th percentile; 2 and 3 = intermediate scores comprising the performance placed between the central value of the distribution and the pathology threshold, that is between the 20th and 50th percentile; 4 = normal performance including scores higher than the median value of the distribution, that is beyond the 50th percentile. We created an aggregate score of neuropsychological tests by calculating a mean of equivalent scores (with the exclusion of MMSE) by summing each equivalent score and then dividing it for the total number of cognitive tests administered, according to the formula: $[(ES_{\text{Babcock story recall test}}+ES_{\text{TMT-A}}+ES_{\text{Phonemic fluency}}+ES_{\text{semantic fluency}})/4]$.

Preliminary one-way ANOVAs were conducted to test between-group differences (NCF vs. MildNCD vs. MajorNCD) for demographic characteristics (age and years of education), all single and aggregate scores of neuropsychological measures, and the Understanding dimension of the MacCAT-CR. The Chi-square test was used to evaluate the gender equivalence across groups. Tukey post-hoc test with a .05 level of significance was used to compare the three groups. Finally, to test the accuracy of MMSE and neuropsychological tests in classifying individuals who cannot provide informed consent through the Understanding dimension of the MacCAT-CR, we performed Receiver Operating Characteristic (ROC) curve analyses. Impairment score in the Understanding dimension of the MacCAT-CR was defined as performance ≤ 2 standard deviations below the NCFs' mean performance (see Results for details).

3. Results

3.1 Sample characteristics

Table 1 summarizes the sample characteristics and reported statistic values. There were group differences in terms of age and years of education, where both MildNCD and MajorNCD groups were significantly older (MildNCD vs NCF: $p < .001$, CI 95% [6.89,15.40]; MajorNCD vs NCF: $p = .001$, CI 95% [6.56,13.31]) and less educated (MildNCD vs NCF: $p = .013$, CI 95% [-5.67, -0.56]; MajorNCD vs NCF: $p < .001$, CI 95% [-5.66, -1.61]) compared the NCF group. There were no between-group differences in terms of gender, $\chi^2(2) = 0.43$, $p = .806$.

3.2 Preliminary analyses on neuropsychological tests and decisional capacity comparison between NCF, MildNCD, and MajorNCD groups

Table 1 reported means and standard deviations of neuropsychological tests and statistic values. The NCF group performed significantly better than the MildNCD and MajorNCD groups on the MMSE (NCF vs MildNCD: $p < .001$, CI 95% [1.33,4.22]; NCF vs. CI: $p = .001$, CI 95%

[5.31,7.60]). As well as the MildNCD group outperformed the MajorNCD group on the MMSE (p < .001, CI 95% [2.33,5.03]). The same group differences were observed for most other neuropsychological measures included in the study where NCF group performed significantly better than the MildNCD and MajorNCD groups on the total score of the Babcock Story Recall test – total score (NCF vs MildNCD: p < .001, CI 95% [2.99,7.93]; NCF vs. MajorNCD: p = .001, CI 95% [5.76,9.68]), Babcock Story Recall test - immediate recall (NCF vs MildNCD: p < .001, CI 95% [1.10,3.78]; NCF vs. MajorNCD: p = .001, CI 95% [2.20,4.33]), TMT-A (NCF vs MildNCD: p < .001, CI 95% [0.01,0.03]; NCF vs. MajorNCD: p < .001, CI 95% [0.02,0.03]), phonemic fluency test, (NCF vs MildNCD: p = .003, CI 95% [2.40,13.55]; NCF vs. MajorNCD: p < .001, CI 95% [6.93,15.77]), and semantic fluency test, (NCF vs MildNCD: p < .001, CI 95% [6.74,17.06]; NCF vs. MajorNCD: p < .001, CI 95% [12.02,20.20]). There were no group differences between MildNCD and MajorNCD in all neuropsychological tests (ps > .104), with the exclusion of the Babcock Story Recall test - delayed recall (p = 0.17, CI 95% [0.22,2.79]), where MildNCD group outperformed MajorNCD group. Finally, for the aggregate score of neuropsychological tests, the NCF group performed significantly better than the MildNCD and MajorNCD groups (NCF vs MildNCD: p < .001, CI 95% [1.04,2.05]; NCF vs. MajorNCD: p < .001, CI 95% [1.75,2.54]), and the MildNCD group outperformed the MajorNCD group (p = .009, CI 95% [0.12,1.07]).

Given that NCF participants were younger and more educated than MildNCD and MajorNCD groups, age and years of education were used as covariates in the one-way ANOVA to test between-group differences in the Understanding dimension of the MacCAT-CR. Results revealed significant between-group differences (p < .001), showing NCF group had better scores than MajorNCD groups (p < .001, CI 95% [4.14,9.76]), and MildNCD outperformed MajorNCD group (p < .001, CI 95% [1.96,7.45]). There were no differences between NCF and MildNCD groups (p = 0.331, CI 95% [-1.15,5.64]).

MacCAT-CR does not give a cut-off to categorize subjects able or not able to provide informed consent to participation in research. Hence, following methodological criteria used in previous studies (e.g., Moro et al., 2020), impairment score in MacCAT-CR was defined as performance ≤ 2 standard deviations below the NCFs' mean performance. Hence, we calculated and categorized subjects as able or not able to consent to the research project using a cut-off of ≤19.68 for the Understanding dimension. Accordingly, in the NCF group, 9 subjects were categorized as impaired and 28 as capable. In the MildNCD group, 18 subjects were categorized as impaired and 4 as capable. In the MajorNCD group, 52 subjects were categorized as impaired and 2 as capable.

3.3 ROC Analysis

To test the specificity and sensitivity of the neuropsychological instruments to correctly reallocate subjects of each group (NCF, MildNCD, and MajorNCD) to be able or not able to provide informed consent, we performed a ROC curve analysis to compare the Areas Under the Curve (AUC) of MMSE, single scores and aggregate score of neuropsychological tests. An AUC greater than 0.70 is considered a good model. In the ROC analyses, we used the understanding dimension as the state variable to discriminate able from not able subjects.

In the NCF group (see Figure 1A), the Babcock Story Recall test – immediate (AUC = .748; Sensitivity = 0.923; Specificity = 0.500; Criterion = 0.423; Cut-off = 3.60), delayed recall (AUC = .748; Sensitivity = 0.808; Specificity = 0.700; Criterion = 0.508; Cut-off = 7.10), and the aggregate score of neuropsychological tests (AUC = .740; Sensitivity = 0.885; Specificity = 0.500; Criterion = 0.385; Cut-off = 3.00) showed significant AUCs (*p*s ≤ .014) in the classification between able and not able subjects to provide a consent to participate in the research project. No significant differences between the Babcock Story Recall test - immediate recall and delayed recall ($\tilde{\chi}$ = 0.00, *p* = 1.00) or aggregate index ($\tilde{\chi}$ = 0.55, *p* = .956) and between Babcock Story Recall test - delayed recall and aggregate index ($\tilde{\chi}$ = 0.05, *p* = .956). The other tests were not significant (AUC ≤ .685; ps ≥ .070). All AUCs and p-values are reported in Table 2.

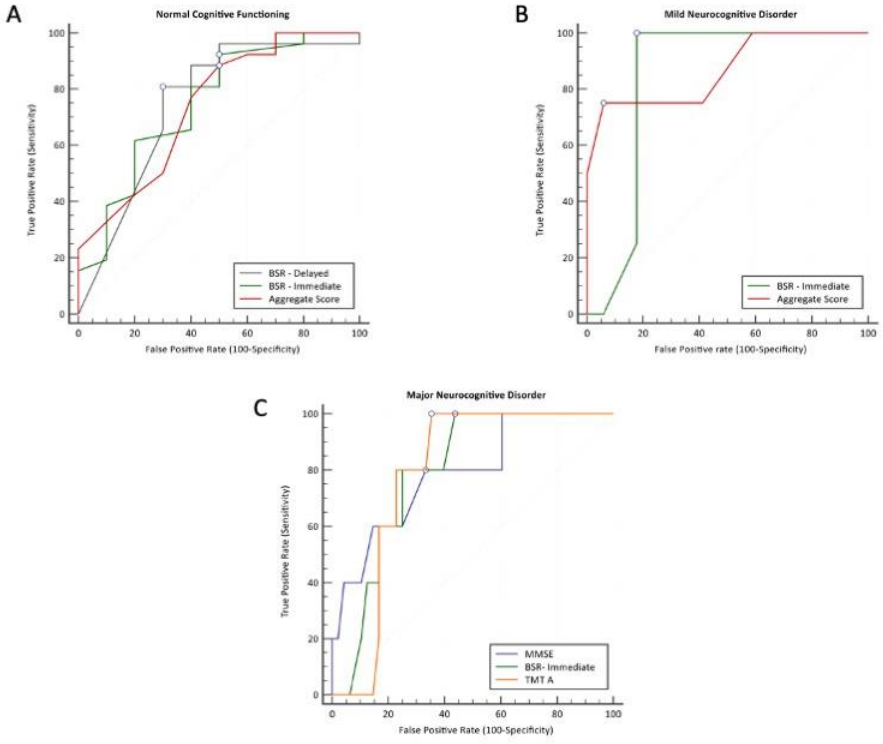

Figure 1. ROCs Curves for Normal Cognitive Functioning Group (panel A), Mild Neurocognitive Disorder (panel B), and Major Neurocognitive Disorder (panel C).

Table 2. AUC and p-values the ROC Curves Using MacCAT-CR Understanding Dimension as State Variable as a Function of Groups

		AUC	***p-value***
NCF	MMSE	0.579	0.449
	Babcock Story Recall- immediate	0.748	0.012
	Babcock Story Recall- delayed	0.748	0.012
	TMT-A	0.592	0.412
	Phonemic fluency	0.523	0.851
	Semantic fluency	0.685	0.070
	Aggregate score	0.740	0.014
MildNCD	MMSE	0.426	0.739
	Babcock Story Recall- immediate	0.838	<0.001
	Babcock Story Recall- delayed	0.669	0.251
	TMT-A	0.691	0.343
	Phonemic fluency	0.743	0.273
	Semantic fluency	0.713	0.126
	Aggregate score	0.868	0.004
MajorNCD	MMSE	0.790	0.012
	Babcock Story Recall- immediate	0.794	<0.001
	Babcock Story Recall- delayed	0.648	0.355
	TMT-A	0.788	<0.001
	Phonemic fluency	0.523	0.896
	Semantic fluency	0.313	0.078
	Aggregate score	0.665	0.263

Note: MMSE = Mini Mental State Examination; TMT-A = Trail Making Test part A

In the MildNCD group (see Figure 1B), the Babcock Story Recall test - immediate recall (AUC = .838; Sensitivity = 1.00; Specificity = 0.824; Criterion = 0.823; Cut-off = 4.50) and the aggregate score of neuropsychological tests (AUC = .868; Sensitivity = 0.750; Specificity = 0.941; Criterion = 0.069; Cut-off = 2.75) showed significant AUCs (*ps* ≤ .004) in the classification between able and not able subjects. No significant differences between the Babcock Story Recall test - immediate recall and the aggregate index (χ = 0.190, *p* = .849). All other tests were not significant (AUC ≤ .743; *ps* ≥ .126). All AUCs and p-values are reported in Table 2.

Finally, in the MajorNCD group (see Figure 1C), MMSE (AUC = .790; Sensitivity = 0.800; Specificity = 0.667; Criterion = 0.457; Cut-off = 23), Babcock Story Recall test - immediate recall (AUC = .794; Sensitivity = 1.00; Specificity = 0.562; Criterion = 0.562; Cut-off = 2.50), and the TMT-A (AUC = .788; Sensitivity = 1.00; Specificity = 0.646; Criterion = 0.646; Cut-off = 0.01) showed significant AUCs (ps ≤ .012) in the classification between able and not able subjects. No significant differences between the MMSE and Babcock Story Recall test - immediate recall (χ = 0.030, *p* = .976) or TMT-A (χ = 0.016, *p* = .987) and between Babcock

Story Recall test – immediate recall and TMT-A (z = 0.063, p = .949). All other tests were not significant (AUC ≤ .665; ps ≥ .078). All AUCs and p-values are reported in Table 2.

4. Discussion

Individuals with dementia or with some degree of cognitive impairment may express a choice to participate in a research protocol without adequately understanding the risks and potential benefits concerning their participation (Allegri et al., 2021; Kim et al., 2001; Moye et al., 2004, Jefferson et al., 2008). Hence, it is crucial assessing the capacity to consent to research in this population with brief standardized instruments useful for clinicians and researchers to guarantee their ethical rights (Cacchione, 2011; de Medeiros et al., 2022; Frisone, 2021; Southerland et al., 2022). For these reasons, this study aimed at examining whether the MMSE and a short battery of neuropsychological tests assessing memory and executive functioning on word fluency and visuomotor tracking have the same specificity and sensitivity to categorize subjects able of consenting to research with respect to the Understanding dimension of MacCAT-CR.

In line with previous studies, we found that the MajorNCD group performed significantly worse than MildNCD and normal cognitive functioning groups in the Understanding dimension of MacCAT-CR (Karlawish et al., 2002; Kim et al., 2001; Parmigiani et al., 2021). No significant differences emerged between normal cognitive functioning and MildNCD groups, showing that the presence of a diagnosis of cognitive impairment does not necessarily imply an impairment to understand disclosed material about a research protocol. To note, even if the normal cognitive functioning group was younger and more educated compared to the other two groups, when we controlled for age and for education level in the Understanding dimension of MacCAT-CR, no influence was found.

Looking at the categorization of subjects capable and not capable of providing informed consent, we found that, although normal cognitive functioning subjects were generally able of consent, 15% were judged not able of understanding the informed consent for the research protocol. This proportion is comparatively smaller than the proportion of MildNCD and MajorNCD groups (81% and 96%, respectively) judged to not understand informed consent. However, this result highlights the importance of assessing the capacity to consent in older adults with neurocognitive disorders and in normal cognitive functioning subjects to ensure that participants understand the research protocol and that the informed consent process is truly informed.

Crucially, the ROC analysis results (see Figure 1) showed a different pattern of results depending on the degree of cognitive impairment. Both MMSE, immediate verbal recall task, and TMT-A showed good parameters to classify subjects with MajorNCD as able of understanding and consenting to the clinical research presented. Our results suggest that scores that minimize the error of mistakenly judging a subject able of consent are for MMSE a score less than 23, for immediate verbal recall a score less than 2.50, and for TMT-A a score less than 0.01. In the MildNCD group, both immediate verbal recall (cut-off 4.50) and an aggregate score of neuropsychological tests (cut-off 2.75) reported high sensitivity and specificity to categorize subjects as able or not able. Similarly, also in the normal cognitive functioning group, both immediate (cut-off 3.60) and delayed (cut-off 7.10) verbal recall and the aggregate score (cut-off 3.00) showed good predictivity to classify subjects as capable. The high sensitivity and specificity of the verbal recall test to categorize subjects as able or not able in both three groups showed that this ability is closely related to the capacity to comprehend disclosed material about a research protocol, with the relative risks and benefits, and to understand consequences of participation (Guerrera et al., 2006; Moelter et al., 2016). Encoding and retaining key facts about a consent form and incorporating them into their response during the MacCAT-CR interview appear to be crucial to understand a consent form in pathological and normal aging (Moberg & Kniele, 2006). This result suggests that the assessment of immediate and delayed recall can provide valuable information in clinical and research evaluation of competency to consent.

Overall, our results showed that brief neuropsychological tests assessing memory and executive functions on word fluency and visuomotor tracking would represent a good neuropsychological battery for discriminate the decisional capacity to provide consent to research in normal cognitive functioning older adults or with a diagnosis of MildNCD, but not in individuals diagnosed with MajorNCD. Indeed, for these subjects, the adoption of single neuropsychological tests, such as the immediate and delayed recall test, the TMT-A, and the MMSE with a cut-off of 23 appear to be more sensitive and specific instruments to discriminate between able or not able subjects compared to the aggregate index of neuropsychological tests. The adoption of MMSE in subjects with MajorNCD seems to be in line with previous studies exploring the relationship between MMSE score and consent capacity in subjects with dementia (Gregory et al., 2007; Karlawish et al., 2002; Kim & Caine, 2002; Whelan et al., 2009). Kim and Caine (2002), for example, claim that MMSE, within a certain range of scores (21-25), is a modest discriminator of decisional capacity and show that the cut-off should be contextualized based on the risk-benefit ratio: for a nontherapeutic, greater-than-minimal-risk study, a cut-off of 26 might be used. Other studies identify different cut-offs: a cut-off score of 18 in subjects

with AD (Gregory et al., 2007); a cut-off of 13/14 in subjects over 60 years old living in a nursing home with cognitive decline. In an Italian context, the study of Galeotti and colleagues (2012) suggested a two steps procedure for assessing of the subjects 'competence to consent. As a first step, they suggested using the MMSE. If the score was ≥ 20, subjects were further evaluated in a second step with four neuropsychological tests. They were considered able to provide informed consent only if they obtained a score higher than the established cut-offs in all four tests. However, consistent with our hypothesis and with previous studies (Kim & Caine, 2002; Whelan et al., 2009), our results showed that for normal cognitive functioning and MildNCD subjects, the MMSE does not represent an appropriate instrument for measuring a complex ability such as the context-dependent ability to understand the content of a research protocol.

It is important to highlight that measuring consent to research competence with these instruments does not substitute for research-related decision-making assessment (Lai & Karlawish, 2007; Moberg & Kniele, 2006). The sensitivity cutoffs may be useful for researchers and clinicians to minimize the error of categorizing a not able subject as competent. It is also important to consider that the specific cut-off scores found in this study may be useful to categorize subjects able to provide consent to research only in research with similar risks and potential benefits and comparable study design complexity.

Several limitations need to be acknowledged. First, the sample size of our study was relatively small. Second, our hypothetical research protocol applies only to simple and minimal-risk study information and cannot be generalized to studies that involve more complicated and high-risk clinical research. Moreover, we used the Understanding dimension of the MacCAT-CR as a gold standard to measure decisional capacity, and we did not compare this tool with other measures assessing the same ability (e.g., University of California Brief Assessment of Capacity to Consent – UBACC; Jeste et al., 2007; for a review of other decision-making tools see Ho et al., 2021) or with expert-judgment validation of capacity thresholds (e.g., Karlawish et al., 2008). Indeed the MacCAT-CR has substantial limitations, such as its relative complexity, the need for specific training, the lack of a threshold or predetermined cut-off that would directly discriminate patients able to decide from those who are not, the lack of empirical documentation of the psychometric equivalence of tailored versions, and the duration of the test of ~20 minutes, which could also be a barrier in the process of patient enrollment in clinical trials (Coppola & Mento, 2013; Dunn et al., 2006; Gilbert et al., 2017). We expect that our study raises awareness among clinicians, researchers, and ethical boards to pay more attention to the procedures for patient inclusion in study protocols and highlights the need for accurate and efficient capacity

evaluation not only in this vulnerable group of patients (de Madeiros et a., 2022; Ries et al., 2020) but also in older adults with normal cognitive functioning (Bellardita et al., 2019). The findings of this study should also be interpreted with a view of promoting ethical rights, autonomy, and dignity as a vital component for quality of life in older people towards complex situations such as the decision to consent to a research protocol or medical treatments (Caruso et al., 2014; Passmore, 2013; Pesonen et al., 2011; Zambianchi, 2020)

In conclusion, our results show that the choice of the best tool in discriminating subjects able to understand disclosed material to consent to research may depend on the degree of cognitive impairment: MMSE is a good tool for subjects with MajorNCD, while a short battery of neuropsychological tests assessing verbal recall and simple executive functions would represent a good tool in subjects with no cognitive impairment or with a diagnosis of MildNCD. Nonetheless, consistent with previous studies (Kim & Caine, 2002; Whelan et al., 2009), the MMSE score alone has a modest discriminating power of consent ability, and it may reflect the instrument's relative insensitivity in detective executive disfunction. Moreover, our study shows that cognitive impairment is a risk factor for impaired capacity to consent to research, but it is inappropriate to discriminate ground solely on a diagnosis (Haremll et al., 2013). With the increasingly aging population at risk of having a cognitive impairment and impaired decisional capacity, there is an undeniable need for a pragmatic approach to evaluating consent capacity (Hamilton et al., 2020). Researchers and clinicians should carefully find a proper balance between respecting the right of not able patients to be protected and the right of able patients to be protected by a violation of their autonomy rights.

Ethical approval: The study was approved by the Pavia Ethical Committee (reference number: P-20190043453).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding authors.

Conflict of interest statement: The authors report no conflicts of interest.

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