Evaluation of the National Institute of Neurological Disease and Stroke-Canadian Stroke Network (NINDS-CSN) 5-Minutes Protocol as a cognitive screening test to detect Parkinson’s disease dementia: a study of a Brazilian sample.

Dissertation presented to Federal University of São Paulo – Paulista School of Medicine to obtain the title of Master's Degree in Neurology and Neurosciences.

São Paulo
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Advisor:
Prof. Dr. Henrique Ballalai Ferraz.

Co-Advisor:
Prof. Dra. Vanderci Borges

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Head of the Departament:

Prof. Dr. Denis Bernardi Bichuetti

Coordinator of the Postgraduate Course:

Prof. Dr. Prof. Dr. Gilmar Fernandes do Prado
Evaluation of the National Institute of Neurological Disease and Stroke-Canadian Stroke Network (NINDS-CSN) – 5 Minute Protocol as a cognitive screening test to detect Parkinson’s disease dementia: a study of a Brazilian sample.

President of the Examination Board

Prof(a). Dr(a). Henrique Ballalai Ferraz

Examination Board:

Prof(a). Dr(a).: Paulo Henrique Ferreira Bertolucci

Prof(a). Dr(a).: Rodrigo Bazan

Prof(a). Dr(a).: Ivan Hideyo Okamoto

Approval date: 22/08/22
Dedication

“To my mother Iris and my fiancée Vanessa who are essential in my life, believing in me when I didn't even believe in myself anymore.

To my great masters, especially Doctor Henrique and Doctor Paulo for trusting me with their knowledge and supporting me to take higher flights.

And to all those who somehow helped me get here, there are many and would not fit on this page, but without you all this would never have been possible.”
Acknowledgments

In carrying out this dissertation, I had the direct or indirect support of multiple people and institutions to which I am deeply grateful. At the risk of unfairly not mentioning any of the contributions, I want to express my thanks:

To the advisor of this dissertation, Prof. Dr. Henrique Ballalai Ferraz, for the guidance provided, for his encouragement, availability and support that he has always shown. Here I express my gratitude to you.

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To all friends and colleagues who, directly or indirectly, contributed or helped in the preparation of this study, for the patience, attention and strength they provided in less easy times.
“This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) - Finance Code 001”.
“Little knowledge makes people feel with knowledge.

A Lot of knowledge, make them feel humble.

Just like the ears devoid of wheat lift their heads disdainfully to the sky,

while the fullfilled ones lower them to the earth, their mother.”

Leonardo da Vinci
Abstract:

Introduction: Many cognitive screening tests have been investigated for the diagnosis of Parkinson's Disease Dementia (PDD), due to its prevalence and its interference in the evolution of the disease, in the quality of life and in the treatment response of the patients with Parkinson’s Disease (PD). Therefore, more effective and faster cognitive screening tests are needed. Objective: To evaluate the usefulness of the NINDS-CSN 5 Minutes Protocol Assessment (NC5MPA) in PD patients as screening test for the detection of PDD, as well as to test if the association with the Cube Drawing Test (CDT) can increase the test accuracy. Methods: A total of 98 patients with PD were evaluated using the NC5MPA, combined with the CDT, Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). These patients were also evaluated for mild cognitive impairment (MCI) and dementia by the Clinical Dementia Rating Scale (CDR). Results: In a bivariate analysis of the 3 tests, there was a good correlation (with p value < 0.000) between the test scores and PDD, but the results of the 3 tests for MCI was > 0.05. The NC5MPA test has had sensitivity of 78.5%, specificity of 85.7%, accuracy of 82.6%, positive predictive value (PPV) of 80.4% and negative predictive value (NPV) of 84.2%, in addition to demonstrate an average performance time of 3.2 minutes (3.08 - 3.31). The association with the CDT has led to a little significant increase in sensitivity and has showed a decrease in specificity and accuracy, besides increase the test performance time. In assessing the interference of education level, the results were influenced by the small sample size of the 5 to 8 years of education group. Conclusion: The NC5MPA test has proven up to be a good screening test for PDD, being even faster and easier to perform, but more tests with larger
populations are necessary to assess the accuracy of this test for MCI and to assess if there is interference of education level in the test accuracy.

**Keywords:** Parkinson's disease; cognitive screening tests; NINDS-CSN 5-Minutes Protocol Assessment; Parkinson's disease cognitive disorders; Parkinson's disease dementia.
List of Graphs, Tables and Figures
List of Graphs, Tables and Figures

Figure 1 - Flowchart of the study sample

79 patients from UNIFESP

54 patients from UNESP

133 patients in the initial sample

35 of the patients were excluded because they had a BDS ≥ 28 (severe depression) or any of the other contraindications.

15 patients excluded from the initial UNIFESP sample.

20 patients excluded from the initial UNESP sample.

98 patients in the final sample.
Table 1 - Profile of selected patients with PD.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean (Minimum-Maximum)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (N)</td>
<td>69 (70.4%)</td>
<td></td>
</tr>
<tr>
<td>Age during the interview (in years)</td>
<td>65.4 (37-84)</td>
<td>66.0</td>
</tr>
<tr>
<td>Disease onset age (in years)</td>
<td>53.7 (18-78)</td>
<td>53.0</td>
</tr>
<tr>
<td>Disease Duration (in years)</td>
<td>11.6 (04-33)</td>
<td>10.0</td>
</tr>
<tr>
<td>Schooling level (in years)</td>
<td>07.2 (00-19)</td>
<td>05.0</td>
</tr>
<tr>
<td>Levodopa Daily Dose (LED - in mg/day)</td>
<td>892.8 (100-2000)</td>
<td>800.0</td>
</tr>
<tr>
<td>CDR score-Global Score (in points)</td>
<td>00.9 (00-03)</td>
<td>00.5</td>
</tr>
<tr>
<td>CDR - Sum of Boxes (in points)</td>
<td>04.4 (00-15)</td>
<td>03.5</td>
</tr>
<tr>
<td>Modified Hoehn-Yahr Scale (in points)</td>
<td>02.8 (01-05)</td>
<td>02.5</td>
</tr>
<tr>
<td>Schwab-England Scale (in percentage)</td>
<td>81.1 (10-90)</td>
<td>60.0</td>
</tr>
<tr>
<td>Beck Depression Scale (in points)</td>
<td>12.0 (00-28)</td>
<td>11.0</td>
</tr>
<tr>
<td>Mini Mental Status Examination (MMSE-in points)</td>
<td>23.3 (05-30)</td>
<td>24.0</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment (MOCA-in points)</td>
<td>18.8 (01-29)</td>
<td>20.0</td>
</tr>
<tr>
<td>NINDS-CSI 5 Minutes Protocol (in points)</td>
<td>07.8 (00-12)</td>
<td>08.0</td>
</tr>
<tr>
<td>UPDRS – part 3 (in points)</td>
<td>46.2 (11-97)</td>
<td>46.0</td>
</tr>
</tbody>
</table>
Table 2 – Epidemiological data comparison analysis between CDR scale groups separated in $\geq 1$ point and $< 1$ point.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean Score (Maximum - Minimum) - Median</th>
<th>CDR &lt; 1 (57.1%)</th>
<th>p-value</th>
<th>CDR &gt; 1 (42.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Mental State Examination (in points)</td>
<td>25.83 (30-19) m = 26 (p=0.00000)</td>
<td>19.15 (30-02) m = 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montreal Cognitive Assessment (in points)</td>
<td>22.33 (29-14) m = 23 (p=0.00000)</td>
<td>14.15 (25-01) m = 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NINDS-CSN 5 minutes protocol (in points)</td>
<td>09.41 (12-05) m = 10 (p=0.00000)</td>
<td>05.75 (12-00) m = 06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NINDS-CSN 5 minutes protocol +</td>
<td>09.59 (13-05) m = 10 (p=0.00000)</td>
<td>05.74 (12-00) m = 06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cube Drawing Test – qualitative (in points)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NINDS-CSN 5 minutes protocol +</td>
<td>11.15 (15-05) m = 12 (p=0.00000)</td>
<td>06.34 (12-00) m = 06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cube Drawing Test – quantitative (in points)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schooling (in years)</td>
<td>08.49 (19-02) m = 08 (p=0.00001)</td>
<td>04.91 (13-00) m = 04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at disease onset (in years)</td>
<td>51.15 (74-35) m = 51 (p=0.00066)</td>
<td>57.35 (78-18) m = 59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration (in years)</td>
<td>10.03 (18-04) m = 08 (p=0.00060)</td>
<td>13.64 (28-05) m = 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at interview (in years)</td>
<td>61.21 (74-37) m = 61 (p=0.00000)</td>
<td>71.24 (84-52) m = 71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwab&amp;England (in percentage)</td>
<td>70.83 (90-20) m = 75 (p=0.00000)</td>
<td>48.66 (90-10) m = 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoehn&amp;Yahr (in points)</td>
<td>02.61 (05-01) m = 2,5 (p=0.00002)</td>
<td>03.21 (05-02) m = 03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEDD (in mg/day)</td>
<td>882.66 (2000-200) m = 762.5 (p=0.12507)</td>
<td>947.64 (1800-100) m = 900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS - part 3 (in points)</td>
<td>41.55 (11-83) m = 41 (p=0.02222)</td>
<td>59.47 (18-97) m = 59.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDR - Sum of Boxes (in points)</td>
<td>02.01 (00-06) m = 02 (p=0.00000)</td>
<td>07.37 (01-15) m = 06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Graphic 1** - Analysis of the MMSE subtests in patients with PD.

![Bar chart for MMSE subtests](chart1)

**Graphic 2** - Analysis of MoCA subtests in patients with PD.

![Bar chart for MoCA subtests](chart2)
Table 3 - Bivariate Associations by Simple Poisson Regression for CDR

Prevalence ≥ 0.5.

<table>
<thead>
<tr>
<th>Variables</th>
<th>b</th>
<th>IC95%b</th>
<th>RP</th>
<th>IC95%RP</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient resident of Botucatu</td>
<td>0.00</td>
<td>-0.43</td>
<td>0.44</td>
<td>1.002</td>
<td>0.645</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.16</td>
<td>-0.32</td>
<td>0.63</td>
<td>1.170</td>
<td>0.726</td>
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<tr>
<td>Age at Interview</td>
<td>0.01</td>
<td>-0.02</td>
<td>0.03</td>
<td>1.007</td>
<td>0.385</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>0.00</td>
<td>-0.02</td>
<td>0.02</td>
<td>1.004</td>
<td>0.385</td>
</tr>
<tr>
<td>Disease Time since Onset</td>
<td>0.01</td>
<td>-0.03</td>
<td>0.04</td>
<td>1.005</td>
<td>0.979</td>
</tr>
<tr>
<td>Years of Schooling</td>
<td>-0.01</td>
<td>-0.05</td>
<td>0.04</td>
<td>0.995</td>
<td>0.948</td>
</tr>
<tr>
<td>Hoehn&amp;Yahr scale score</td>
<td>0.01</td>
<td>-0.23</td>
<td>0.26</td>
<td>1.014</td>
<td>0.791</td>
</tr>
<tr>
<td>Schwab&amp;England scale score</td>
<td>0.00</td>
<td>-0.01</td>
<td>0.01</td>
<td>0.988</td>
<td>0.985</td>
</tr>
<tr>
<td>Mean equivalent daily dose of levodopa (LEDD)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Symptoms starting on the left side of the body</td>
<td>-0.04</td>
<td>-0.48</td>
<td>0.38</td>
<td>0.962</td>
<td>0.631</td>
</tr>
<tr>
<td>Beck Depression Scale Score</td>
<td>0.00</td>
<td>-0.03</td>
<td>0.04</td>
<td>1.001</td>
<td>0.967</td>
</tr>
<tr>
<td>Mini Mental State Examination Scale Score</td>
<td>-0.01</td>
<td>-0.05</td>
<td>0.03</td>
<td>0.989</td>
<td>0.951</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment Scale Score</td>
<td>-0.01</td>
<td>-0.04</td>
<td>0.02</td>
<td>0.990</td>
<td>0.959</td>
</tr>
<tr>
<td>NINDS-CSN 5 minutes protocol Score</td>
<td>-0.03</td>
<td>-0.10</td>
<td>0.04</td>
<td>0.971</td>
<td>0.903</td>
</tr>
<tr>
<td>Cube drawing test scores (0/1)</td>
<td>-0.01</td>
<td>-0.50</td>
<td>0.47</td>
<td>0.988</td>
<td>0.609</td>
</tr>
<tr>
<td>Cube drawing test scores (0/3) - score 3</td>
<td>-0.12</td>
<td>-0.71</td>
<td>0.47</td>
<td>0.888</td>
<td>0.491</td>
</tr>
<tr>
<td>Cube drawing test scores (0/3) - score 2</td>
<td>-0.29</td>
<td>-0.95</td>
<td>0.37</td>
<td>0.748</td>
<td>0.387</td>
</tr>
<tr>
<td>Cube drawing test scores (0/3) - score 1</td>
<td>-0.03</td>
<td>-0.56</td>
<td>0.49</td>
<td>0.967</td>
<td>0.573</td>
</tr>
<tr>
<td>Cube drawing test scores (0/3) - score 0</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4 – Bivariate Associations by Simple Poisson Regression for CDR Prevalence > 1.0.

<table>
<thead>
<tr>
<th>Variables</th>
<th>b</th>
<th>LC95%b</th>
<th>RP</th>
<th>LC95%RP</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient resident of Botucatu</td>
<td>0.88</td>
<td>-0.56</td>
<td>0.68</td>
<td>1.06</td>
<td>1.93</td>
</tr>
<tr>
<td>Male gender</td>
<td>-0.58</td>
<td>-1.19</td>
<td>-0.03</td>
<td>0.55</td>
<td>0.30</td>
</tr>
<tr>
<td>Age at Interview</td>
<td>0.07</td>
<td>0.04</td>
<td>0.11</td>
<td>1.07</td>
<td>1.04</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>0.03</td>
<td>0.00</td>
<td>0.06</td>
<td>1.03</td>
<td>1.00</td>
</tr>
<tr>
<td>Disease Time since Onset</td>
<td>0.05</td>
<td>0.01</td>
<td>0.09</td>
<td>1.05</td>
<td>1.01</td>
</tr>
<tr>
<td>Years of Schooling</td>
<td>-0.15</td>
<td>-2.25</td>
<td>-0.66</td>
<td>0.68</td>
<td>0.76</td>
</tr>
<tr>
<td>Hoehn&amp;Yahr scale score</td>
<td>0.48</td>
<td>0.17</td>
<td>0.80</td>
<td>1.62</td>
<td>1.18</td>
</tr>
<tr>
<td>Schwab&amp;England scale score</td>
<td>-0.03</td>
<td>-0.4</td>
<td>-0.01</td>
<td>0.97</td>
<td>0.96</td>
</tr>
<tr>
<td>Mean equivalent daily dose of levodopa (LED)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Symptoms starting on the left side of the body</td>
<td>-0.06</td>
<td>-1.14</td>
<td>-0.55</td>
<td>0.95</td>
<td>0.52</td>
</tr>
<tr>
<td>Beck Depression Scale Score</td>
<td>0.04</td>
<td>0.00</td>
<td>0.09</td>
<td>1.05</td>
<td>1.00</td>
</tr>
<tr>
<td>Mini Mental State Examination Scale Score</td>
<td>-0.09</td>
<td>-1.4</td>
<td>-0.05</td>
<td>0.91</td>
<td>0.87</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment Scale Score</td>
<td>-0.10</td>
<td>-1.4</td>
<td>-0.06</td>
<td>0.91</td>
<td>0.87</td>
</tr>
<tr>
<td>NINDS-CSN 5 minutes protocol Score</td>
<td>-0.23</td>
<td>-3.3</td>
<td>-1.13</td>
<td>0.80</td>
<td>0.72</td>
</tr>
<tr>
<td>Cube drawing test scores (0/1)</td>
<td>-0.93</td>
<td>-1.86</td>
<td>0.00</td>
<td>0.39</td>
<td>0.16</td>
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<tr>
<td>Cube drawing test scores (0/3) - score 3</td>
<td>2.57</td>
<td>4.58</td>
<td>-5.55</td>
<td>0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>Cube drawing test scores (0/3) - score 2</td>
<td>-0.80</td>
<td>-1.79</td>
<td>-0.19</td>
<td>0.45</td>
<td>1.17</td>
</tr>
<tr>
<td>Cube drawing test scores (0/3) - score 1</td>
<td>-0.03</td>
<td>-0.69</td>
<td>0.62</td>
<td>0.97</td>
<td>0.50</td>
</tr>
<tr>
<td>Cube drawing test scores (0/3) - score 0</td>
<td>0.6</td>
<td>0.6</td>
<td>1.1</td>
<td>1.00</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Graph 3 – ROC curve of the screening tests analyzed.

Table 5 – Analysis of screening tests ROC curves compared in the best ROC scores.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Area (AUC); (IC95%)</th>
<th>p</th>
<th>Cutoff</th>
<th>(Sen,Spe)</th>
<th>ROC curve</th>
<th>Sen</th>
<th>Spe</th>
<th>Ac</th>
<th>VPP</th>
<th>VPN</th>
<th>Kappa (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS</td>
<td>0.86 (0.78 - 0.94); p &lt; 0.001</td>
<td>≤ 7.5</td>
<td>33/42 (78.5%)</td>
<td>50/56 (85.7%)</td>
<td>81/98 (82.6%)</td>
<td>33/41 (80.4%)</td>
<td>48/57 (84.2%)</td>
<td>0.64 (p &lt; 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOCA</td>
<td>0.85 (0.77 - 0.93); p &lt; 0.001</td>
<td>≤ 19.5</td>
<td>32/42 (76.1%)</td>
<td>43/56 (76.7%)</td>
<td>75/90 (76.5%)</td>
<td>32/45 (71.1%)</td>
<td>43/53 (81.1%)</td>
<td>0.52 (p &lt; 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEEM</td>
<td>0.81 (0.73 - 0.90); p &lt; 0.001</td>
<td>≤ 24.5</td>
<td>32/42 (76.1%)</td>
<td>38/56 (67.8%)</td>
<td>70/90 (71.4%)</td>
<td>32/59 (64.0%)</td>
<td>38/48 (73.1%)</td>
<td>0.43 (p &lt; 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Graph 4 – Comparison of performance times of the analyzed tests.
Table 6 - Sensitivity, Specificity and Accuracy of the NC5MPA test analyzed with and without association with the Cube Drawing Test.

<table>
<thead>
<tr>
<th>Tests</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC5MPA ≤ 9 - ROC curve cutoff</td>
<td>37/42 (88.1%)</td>
<td>30/56 (53.5%)</td>
<td>67/98 (68.3%)</td>
</tr>
<tr>
<td>NC5MPA ≤ 8 - Sample Median</td>
<td>35/42 (83.3%)</td>
<td>39/56 (69.6%)</td>
<td>74/98 (75.5%)</td>
</tr>
<tr>
<td>NC5MPA ≤ 7 - ROC curve cutoff</td>
<td>33/42 (78.7%)</td>
<td>48/56 (85.7%)</td>
<td>81/98 (82.6%)</td>
</tr>
<tr>
<td>CDT - qualitative (0 to 1)</td>
<td>37/42 (88.1%)</td>
<td>20/56 (35.7%)</td>
<td>57/98 (58.1%)</td>
</tr>
<tr>
<td>CDT - qualitative (0 to 3) binarized</td>
<td>36/42 (85.7%)</td>
<td>33/56 (58.9%)</td>
<td>69/98 (70.4%)</td>
</tr>
<tr>
<td>NC5MPA + CDT (0 to 1) binarized</td>
<td>37/42 (88.1%)</td>
<td>20/56 (35.7%)</td>
<td>57/98 (58.1%)</td>
</tr>
<tr>
<td>NC5MPA + CDT (0 to 3) binarized</td>
<td>36/42 (85.7%)</td>
<td>33/56 (58.9%)</td>
<td>69/98 (70.4%)</td>
</tr>
<tr>
<td>NC5MPA + CDT (0 to 1) - Sum of Scores</td>
<td>35/42 (83.3%)</td>
<td>41/56 (73.2%)</td>
<td>76/98 (77.5%)</td>
</tr>
<tr>
<td>NC5MPA + CDT (0 to 3) - Sum of Scores</td>
<td>35/42 (83.3%)</td>
<td>41/56 (73.2%)</td>
<td>76/98 (77.5%)</td>
</tr>
</tbody>
</table>
Graph 5 – ROC curve of the NINDS-CSN 5 Minutes Protocol screening test compared to test associated with the Wire Cube Drawing Test.
Figure 2 – Traffic light model to address the probabilities of dementia occurrence and the need for further neuropsychological approaches in patients with Parkinson's Disease, based on the results obtained in the NINDS-CSN 5 minutes protocol cognitive screening test.

<table>
<thead>
<tr>
<th>Cortes</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS &lt;= 8 (Sample Median)</td>
<td>35/42 (83.3%)</td>
<td>39/56 (69.6%)</td>
<td>74/98 (75.5%)</td>
</tr>
<tr>
<td>NINDS &lt;= 7 (ROC Curve cutoff)</td>
<td>33/42 (78.7%)</td>
<td>48/56 (85.7%)</td>
<td>81/98 (82.5%)</td>
</tr>
<tr>
<td>NINDS &lt;= 9 (ROC Curve cutoff)</td>
<td>37/42 (88.1%)</td>
<td>30/56 (53.5%)</td>
<td>67/98 (68.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scale</th>
<th>Area (95%)</th>
<th>: p Cutoff</th>
<th>[50] ROC curve</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>PPV</th>
<th>NPV</th>
<th>Kappa</th>
<th>p-value</th>
<th>mean time (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS</td>
<td>0.86 (0.78 - 0.94)</td>
<td>&lt; 0.001</td>
<td>s 7.5</td>
<td>(78.6 %, 85.7%)</td>
<td>33/42 (78.5%)</td>
<td>48/56 (85.7%)</td>
<td>81/98 (82.5%)</td>
<td>33/41 (80.4%)</td>
<td>48/57 (84.2%)</td>
<td>0.64</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

>9 Low Probability of Parkinson's disease dementia.

=8 Possible Dementia – Further assessment if possible.

<=7 Probable Dementia – Always further dementia assessment.
**Graph 6** - Comparison between tests among patients with educational level of less than 4 years.

**Table 7** – Comparison between tests among patients with educational level of less than 4 years.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Area (IC95%) ; p</th>
<th>Cutoff</th>
<th>(S;S Roc Curves</th>
<th>Sens</th>
<th>Spec</th>
<th>Acc</th>
<th>PPV</th>
<th>NPV</th>
<th>Kappa (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS</td>
<td>0.66 (0.74 - 0.88); &lt; 0.001</td>
<td>≤ 6.5</td>
<td>76.6% ; 80.0%</td>
<td>75.9</td>
<td>80.0</td>
<td>78.0</td>
<td>87.0</td>
<td>65.7</td>
<td>0.54 (&lt;0.001)</td>
</tr>
<tr>
<td>MOCA</td>
<td>0.29 (0.73 – 0.99); &lt; 0.001</td>
<td>≤ 15.5</td>
<td>76.5% ; 80.0%</td>
<td>75.9</td>
<td>80.0</td>
<td>78.0</td>
<td>87.0</td>
<td>65.7</td>
<td>0.54 (&lt;0.001)</td>
</tr>
<tr>
<td>MEEM</td>
<td>0.80 (0.67 - 0.93); &lt; 0.001</td>
<td>≤ 22.5</td>
<td>73.1% ; 73.3%</td>
<td>73.1</td>
<td>73.3</td>
<td>62.5</td>
<td>61.1</td>
<td>73.1</td>
<td>0.44 (0.004)</td>
</tr>
<tr>
<td>NINDC11</td>
<td>0.85 (0.74 – 0.93); &lt; 0.001</td>
<td>≤ 6.5</td>
<td>73.9% ; 80.0%</td>
<td>75.9</td>
<td>80.0</td>
<td>77.0</td>
<td>66.7</td>
<td>73.0</td>
<td>0.54 (&lt;0.001)</td>
</tr>
<tr>
<td>NINDC33</td>
<td>0.84 (0.70 - 0.97); &lt; 0.001</td>
<td>≤ 6.5</td>
<td>69.2% ; 80.0%</td>
<td>69.2</td>
<td>80.0</td>
<td>73.1</td>
<td>85.7</td>
<td>50.4</td>
<td>0.46 (0.002)</td>
</tr>
</tbody>
</table>
Graph 7 - Comparison between tests among patients with educational level between 5 and 8 years.

Table 8 – Comparison between tests among patients with educational level between 5 and 8 years.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Area (IC95%) ; p</th>
<th>Cutoff</th>
<th>(S:S) ROC Curves</th>
<th>Sens</th>
<th>Spec</th>
<th>Acc</th>
<th>PPV</th>
<th>NPV</th>
<th>Kappa (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS</td>
<td>0.75 (0.54 - 0.96); 0.041</td>
<td>≤ 8.5</td>
<td>(96.0% ; 69.2%)</td>
<td>60.0%</td>
<td>69.2%</td>
<td>65.2%</td>
<td>60.0%</td>
<td>69.2%</td>
<td>0.29 (0.161)</td>
</tr>
<tr>
<td>MOCA</td>
<td>0.62 (0.37 - 0.87); 0.306</td>
<td>≤ 26.5</td>
<td>(50.0% ; 61.5%)</td>
<td>50.0%</td>
<td>61.5%</td>
<td>56.5%</td>
<td>50.0%</td>
<td>61.5%</td>
<td>0.11 (0.550)</td>
</tr>
<tr>
<td>MEEM</td>
<td>0.64 (0.32 - 0.95); 0.264</td>
<td>≤ 33.5</td>
<td>(50.0% ; 64.1%)</td>
<td>50.0%</td>
<td>64.1%</td>
<td>58.5%</td>
<td>50.0%</td>
<td>64.1%</td>
<td>0.11 (0.550)</td>
</tr>
<tr>
<td>NINDC11</td>
<td>0.72 (0.49 - 0.94); 0.672</td>
<td>≤ 9.5</td>
<td>(50.0% ; 53.4%)</td>
<td>60.0%</td>
<td>53.4%</td>
<td>59.5%</td>
<td>50.0%</td>
<td>63.6%</td>
<td>0.13 (0.510)</td>
</tr>
<tr>
<td>NINDC33</td>
<td>0.74 (0.51 - 0.97); 0.051</td>
<td>≤ 10.5</td>
<td>(60.0% ; 61.5%)</td>
<td>60.0%</td>
<td>61.5%</td>
<td>60.6%</td>
<td>54.5%</td>
<td>66.7%</td>
<td>0.21 (0.365)</td>
</tr>
</tbody>
</table>
Graph 8 - Comparison between tests among patients with educational level of more than 8 years.

Table 9 - Comparison between tests among patients with educational level of more than 8 years.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Area (IC95%) ; p</th>
<th>Cutoff</th>
<th>(S:S) Roc Curves</th>
<th>Sens</th>
<th>Spec</th>
<th>Acc</th>
<th>PPV</th>
<th>NPV</th>
<th>Kappa (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS</td>
<td>0,63 (0,65 – 1,00); 0,011</td>
<td>≤ 8,5</td>
<td>(66,7%; 75,0%)</td>
<td>66,7%</td>
<td>75,0%</td>
<td>73,5%</td>
<td>36,4%</td>
<td>91,3%</td>
<td>0,31 (0,048)</td>
</tr>
<tr>
<td>MOCA</td>
<td>0,66 (0,73 – 1,00); 0,005</td>
<td>≤ 21,5</td>
<td>(63,3%; 78,6%)</td>
<td>83,3%</td>
<td>78,6%</td>
<td>79,4%</td>
<td>45,5%</td>
<td>95,7%</td>
<td>0,46 (0,003)</td>
</tr>
<tr>
<td>MEEM</td>
<td>0,64 (0,59 – 0,99); 0,009</td>
<td>≤ 26,5</td>
<td>(66,7%; 78,6%)</td>
<td>66,7%</td>
<td>78,6%</td>
<td>76,4%</td>
<td>40,0%</td>
<td>91,7%</td>
<td>0,35 (0,027)</td>
</tr>
<tr>
<td>NINDC11</td>
<td>0,65 (0,69 – 1,00); 0,008</td>
<td>≤ 8,5</td>
<td>(66,7%; 78,6%)</td>
<td>66,7%</td>
<td>78,6%</td>
<td>76,4%</td>
<td>40,0%</td>
<td>91,7%</td>
<td>0,35 (0,027)</td>
</tr>
<tr>
<td>NINDC33</td>
<td>0,63 (0,66 – 1,00); 0,011</td>
<td>≤ 10,5</td>
<td>(66,7%; 71,4%)</td>
<td>66,7%</td>
<td>70,5%</td>
<td>70,5%</td>
<td>33,3%</td>
<td>90,9%</td>
<td>0,27 (0,076)</td>
</tr>
</tbody>
</table>
List of abbreviations, acronyms and symbols

PD – Parkinson’s disease.
NC5MPA - National Institute of Neurological Disorders and Stroke - Canadian Stroke Network (NINDS-CSN) - 5 Minute Protocol Assessment.
MoCA – Montreal Cognitive Assessment.
MMSE – Mini-Mental State Examination.
PDD – Parkinson’s disease dementia.
CDT – Clock Drawing Test.
PPV – Positive predictive value.
NPV – Negative Predictive value.
AUC – Area under curve.
MDS – Movement Disorders Society.
PD-CRS - Parkinson's Disease-Cognitive Rating scale.
SCOPA-COG - Scales for Outcomes of Parkinson’s disease–Cognition.
MDRS - Mattis Dementia Rating Scale.
BDS – Beck depression scale.
MCI – Mild Cognitive Impairment.
GBA – Glucocerebrosidase.
SNCA – Synuclein.
ACE-R – Adembrook cognitive examination revised.
GPOCG – General Practicioner Assessment of Cognition.
MIS – Memory Impairment Screen test.
CDR – Clinical dementia rating scale.
CDR – SB – Clinical dementia rating scale – sum of boxes
CDR-GS – Clinical dementia rating scale – global score.
LEDD – Levodopa equivalente dose of dopaminergic drugs.
mH&Y – Modified Hoehn & Yahr scale.
S&E – Schwab & England scale.
UPDRS - Unified Parkinson's disease rating scale.
NINDS - National Institute of Neurological Disorders and Stroke - Canadian Stroke Network (NINDS-CSN) - 5 Minute Protocol Assessment.
UKPDS – United Kingdom Parkinson’s disease Society.
Introduction
Introduction

Parkinson’s disease (PD) is a progressive, chronic and neurodegenerative disorder affecting about 1-2 per 1000 of the population, according to a 2005 epidemiological study carried out in some European countries, such as Austria, Czech Republic, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden and the United Kingdom\(^1\); additionally, it occurs in more than 1% of the population with over 60 years of age\(^2\). It is one of the most frequent neurodegenerative diseases in the world and has an economic impact - in direct medical estimate costs of $25.4 billion and indirect and non-medical costs of $26.5 billion. Such direct costs derive from some health services. Among them are: hospital care (28.4%), non-acute institutional care (28.2%) and outpatient care (21.7%), and indirect medical and non-medical costs derive from $7.7 billion in lost productivity, $7.5 billion in non-medical costs, $4.8 billion in disfunction, and $6.6 billion in lost productivity from partners and unpaid caregivers. However, the economic impact of PD will tend to increase in the coming years, as well as the number of patients, especially due to an increasing number of people aging, with an economic burden exceeding $79 billion per year in 2037, in the United States. Some experts consider that these numbers may be even higher\(^3\).

Its pathophysiology is the brain deposition of a protein called alpha-synuclein (1990), formerly called perfectine (alpha-synuclein) and imperfectine (beta-synuclein), being the alpha isomer of synuclein - a protein encoded by the long arm of chromosomes 4 and 5. Bearing this in mind, Parkinson's disease dementia (PDD) is part of a family of diseases called synucleinopathies including: Lewy’s body dementia, PD, PDD, multiple system atrophy and pure autonomic failure.
The aggregation of these mutated proteins leads to the formation of the so-called “Lewy bodies,” which are the pathological biomarker of PDD and Lewy body dementia. This synuclein mutation and its deposition in the brain both occur in the most common sporadic forms of PD, as well as in other forms of genetic causes. Another major pathophysiological biomarker of this disease is the death of dopaminergic cells, although the disease can compromise the function of several other neurotransmitters such as acetylcholine, serotonin and noradrenaline. However, the role of these substances in the clinical syndrome is still being better explained in more recent studies.

The location of these brain changes in PD is very broad, with the most involved areas being thalamus, hypothalamus, limbic cortex, neocortex, locus coeruleus, raphe nucleus, Meynert's basal nucleus and the autonomic nervous system. However, the most important and early affected areas are the substantia nigra pars compacta and locus coeruleus, which proved to be largely responsible for the motor symptoms, and for the onset of clinical motor phase of the disease. In addition to its cardinal motor characteristics, PD presents a combination of many other nonmotor symptoms, such as mood alterations, dysautonomia and sleep disorders. However, one of the main nonmotor complications of PD is the cognitive impairment with a more-than-six-times risk of occurrence in PD individuals in comparison with healthy ones. Cognitive impairment can seriously affect the quality of life of PD patients and their daily functionality, and it has been shown to have substantial economic consequences both for the patient and the family, as well as for the health system. Cognitive impairments, especially PDD, specifically when not diagnosed or not well treated, leads to a significant drop in response to the treatments received and in the subjective well-being of the
patient. This leads to an increase in morbidity and mortality rates of these patients, thereby, representing a high priority for its identification and diagnosis not only by physicians, but by patients and caregivers as well.\textsuperscript{11-12}

An important step in the diagnostic suspicion of cognitive disorders in PD is the initial neuropsychological assessment. After the cognitive complaint of patients, caregivers or attending physician observation, two important steps have to be considered: the first step is the use of validated diagnostic screening tests, which have the function to improve the sensitivity of the diagnosis, at the expense of an often much lower specificity. By doing so, it will much exclude the possibility of a patient with cognitive disorders not to be properly evaluated or diagnosed; the second step is a more extensive neuropsychological assessment, with the evaluation of all cognitive domains in details, increasing the specificity and accuracy of the diagnosis. According to the Movement Disorders Society (MDS), the screening tests that should be considered in clinical practice for the diagnosis of cognitive impairment in PD, are the Montreal Cognitive Assessment (MoCA), the Parkinson’s Disease-Cognitive Rating scale (PD-CRS), the Scales for Outcomes of Parkinson’s disease–Cognition (SCOPA-COG) and the Mattis Dementia Rating Scale (MDRS), due to their effectiveness and evidence of good sensitivity, specificity and accuracy from previous studies. However, some of these screening tests can be quite difficult to perform because their performance times are especially high, the fastest being around more than 10 minutes in total, which can often be difficult to be performed by a physician and arduous to perform by patients with PD motor symptoms in clinical practice routines.\textsuperscript{13,11}

For this reason, the Mini-Mental State Examination (MMSE) is a screening test that is still widely used in clinical practice - perhaps the most used in the world
since it is easier and faster to be performed; however, it has already been proven in other studies that it lacks specificity and, especially, sensitivity to be used as a cognitive screening tool in PDD\textsuperscript{13:14}.

More effective, faster and easier-to-perform screening tests to make sure that PD patients can have cognitive assessments more routinely are needed. This will enable physicians to make diagnoses of PDD earlier and more effectively, especially because dementia associated with the disease are evidence-based drug treatments that can relieve symptoms and improve quality of life. So, with easier and faster screening protocols, the complications associated with non-diagnosis, misdiagnosis or late-diagnosis of cognitive disorders associated with PD are likely to be reduced.
Objectives:

The objectives of the study are:

**Main Objectives:** To attest if, in a Brazilian population with PD, there is a good correlation between PDD and the NINDS-CSN 5-Minutes Protocol Screening Test (NC5MPA), so as to compare if this screening “mini-test” is comparable for specificity, sensitivity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) to the two most used tests in the screening analysis of cognitive impairment in PD: the MMSE and the MoCA. In addition to this main objective, we compared the test performance times, analyzing whether the NC5MPA screening test is easier and faster to perform, compared to the other tests used in this study.

**Secondary objectives:** To compare whether the association of the NC5MPA with the Cube Drawing Test (CDT), using both qualitative (0 to 1 points) and quantitative (0 to 3 points) analyses, leads to an advantage over the use of the test solely in the screening for PD-related dementia, as well as to assess if there is any interference of the educational level in the interpretation of the NC5MPA test.
Literature Review
Literature Review

PD was first described as a clinical syndrome in 1817 by Dr. James Parkinson, although there are many descriptions of symptoms that suggest PD symptoms in earlier descriptions, by Sylvius de la Boe (1680), Sauvages (1768) and other millennial traditional Indian and Chinese literature that also had descriptions of sick patients with symptoms that strongly appeared to be PD\textsuperscript{15}. His short 66-page monograph entitled “Essay on Shaking Palsy” includes an academic literature review and a clinical description of six patients (all male, ages ranging from 50 to 72 years), three of whom were his patients, two of whom he had seen on the streets and then examined, and one he had observed from distance walks through the streets of Hoxton, UK. In chapter one (Definitions-History-Illustrative Cases), Parkinson reports a programme at the beginning of the chapter, which he considers to encompass the main features of “Paralysis Agitans”: “Involuntary tremulous movements, with decreased muscular strength, in parts out of action and even when supported; with a tendency to bend the trunk forward and change from a walking pace to a running pace: the senses and intellects being uninjured.” In this description, we can see that the doctor believed that cognitive functions were preserved in PD\textsuperscript{16}. It was the great French neurologist, considered the father of Modern Neurology, Jean Martin Charcot at the Pitié-Salpetrière Hospital School of Medicine, who described in details (as was his common practice) various other aspects of the disease, such as the arthritic deformations of the limbs, dysautonomia, micrography, the definition of bradykinesia and postural instability (2 of the 4 cardinal signs of the disease), dysarthria, better characterization of classic anteroflexed posture of gait, definition of limb rigidity,
characterization of parkinsonian face, and even the institution of a treatment for the disease based on a precursor of the belladonna alkaloids, the hyoscinamidé\(^{17-18-19}\).

Charcot also made the first description of the cognitive changes that occur in PD, especially dementia, when he says in one of his reports about the symptoms that occurred in the period he called the “\textit{période terminale}”: “\textit{A un moment donné, l’intelligence s’obscurcit, la mémoire se perd}.”, contradicting what James Parkinson himself said, who claimed in his reports that the “mind” of the patients he reported in this disease was not affected, as he himself describes it and its symptoms on page 34: “… and by the absence of any injury to the senses and to the intellect, that the morbid state does not extend to the encephalon”. Charcot came up with the idea of naming the disease, formerly called “\textit{Paralisie Agitans}” from “\textit{Parkinson’s Disease}” (“\textit{Maladie de Parkinson}”), in honor of the great doctor from Hoxton. And so, it remains known as so to this day\(^{16-20}\).

Later, the Uzbek neuropathologist Konstantin Nicolaevich Tretiakoff dedicated himself to the identification of the neuropathology of PD, relating parkinsonian motor symptoms to evidence of degeneration of the substantia nigra, in 1919\(^{21-22}\). The American neurologist Fritz Jacob Heinrich Lewy was the first to describe the eosinophilic inclusion bodies in certain brain nuclei, later known as Lewy bodies, the pathological signature of the Lewy body diseases, in 1912\(^{23}\). But it was just in 1997 that Mihael H. Polymeropoulos published a study describing the first specific genetic aberration linked to PD in some Italian and Greek families, a G209A substitution in the \textit{SNCA} gene linked to the metabolism of the synuclein protein - one located in the presynaptic terminals of the neurons, concluding that synuclein is linked to both familial and sporadic forms of PD\(^{24-25}\).
PD, due to its degenerative nature, has a slow progression and the onset of its pathological process may precede the parkinsonian motor symptoms by more than 10 years\textsuperscript{26}. Thus, there are different stages of PD since the onset of the pathological process. Based on Braak's theories, the synuclein pathology progresses through cell-to-cell contact from the periphery to the olfactory medulla, then infiltrating further into the brainstem and striatal regions, causing the onset of early motor symptoms, and later affecting the limbic system and neocortical regions, leading to behavioral/cognitive impairment and motor/nonmotor symptoms in advanced stages. This theory, which helped to explain the progression of the disease and the onset of symptoms, is recently known as Braak's Hypothesis\textsuperscript{27}. PD has three distinct clinical phases in its evolution: the preclinical, the prodromal and the clinical, which is divided, in turn, into early, intermediate and advanced phases. In the preclinical phase, there is deposition of pathological material in the brain tissue, but without evidence of symptoms related to PD, being only possible to make the diagnosis through biological markers of the disease. In the prodromal phase, there is the onset of nonmotor symptoms that precede the motor symptoms of the disease, often not being recognized as symptoms related to the PD pathology. The most frequent being: REM sleep behavioral disorder, depression/anxiety, hyposmia/anosmia, excessive daytime sleepiness, constipation, erectile dysfunction, and urinary dysfunction\textsuperscript{26-28}.

In the early motor phase, the traditional motor symptoms of PD appear. These are called "cardinal" because they must be present for the diagnosis, and can appear in different combinations, but bradykinesia always must be present. According to one of the most classic criteria for PD - the United Kingdom
Parkinson's Disease Society Brain Bank Criteria for the diagnosis of PD, bradykinesia must be present and associated with one or more of the other three motor symptoms: tremors of 4 to 6 hertz, muscular rigidity and postural instability. The tremors in PD have the characteristic of being at rest, generally asymmetrical and more evident in the upper limbs, classically called "coin-counting" or "pill-rolling" tremors. The stiffness in PD has a hallmark feature called "plastic-type," "lead-pipe" or "cogwheel-type" stiffness, occurring evenly throughout the joint movement path, unlike the "elastic-type" rigidity, related to upper motor neuron lesions. As the last "cardinal" symptom of PD, postural instability occurs as a result of the other associated hypokinetic symptoms (bradykinesia and rigidity), leading to poor postural adaptation and loss of balance during posture and gait, leading to an increase of imbalances and falls.

After the progression of PD, about 5 to 6 years after the onset of motor symptoms, some characteristics are very common to happen in the disease, such as the motor fluctuations, the emergence of nonmotor symptoms, and the decline in symptoms responsiveness to antiparkinsonian medications. The initial phase of PD (the first 4 to 5 years) is called the "honeymoon-phase" of the treatment, due to the very important responsiveness to the treatment. However, over the years and with the decrease in dopaminergic cells, the metabolism of dopamine in the synaptic cleft becomes increasingly difficult and oscillating, leading to the so-called motor fluctuations called "off" periods. The 'Storage Hypothesis' advocates that, with the loss of dopaminergic cells, there is a loss of presynaptic dopaminergic terminals, which reduces the striatal capacity to store dopamine and to prevent large fluctuations in levodopa levels in the synaptic cleft. Furthermore, alterations in postsynaptic channels and proteins may help to
explain the pathophysiological mechanism of motor fluctuations, among other more complex mechanisms. In this phase of the disease, it is often the difficulty to manage dopaminergic and antiparkinsonian drugs and to maintain the degree of improvement obtained previously with the treatments, compared to that of earlier stages of the disease, requiring the combination of various medications and different pharmacological and nonpharmacological treatment techniques.

Finally, in the advanced or late stage of the disease, which Charcot once called “periode terminale,” alpha synuclein deposits spread even further, especially over the cerebral cortex and also in extracerebral structures. Such complications, when occurring in extracerebral structures, lead to dysautonomic alterations, such as cardiac conduction alterations, intestinal constipation, urinary alterations (especially urinary incontinence), postural hypotension, salivary and swallowing alterations, and those in sweating, piloerection and temperature control, as a result of changes in autonomic systems, also mediated by dopaminergic cells. Other very frequent non-motor symptoms that are a result of the accumulation of proteins in some regions of the cerebral cortex, are: depression and/or anxiety disorders, chronic fatigue, sleep alterations, and one of the most important non-motor alterations - the behavioral/cognitive impairment and dementia associated with PD.

PDD is one of the major and prevalent complications of the disease. In a study carried out in Italy with 139 PD patients, 55 (39.6%) reached the diagnosis of mild cognitive impairment (MCI) at the onset of the study. In the 84 patients with normal cognition, during a mean follow-up of 23.5±10.3 months, 28 patients (33.3%) developed MCI and 4 (4.8%) developed symptoms of dementia. The
incidence rate of dementia was 24.3/1000 per year (95% CI 7.7–58.5). Some studies estimated that cognitive impairments and dementia may occur in up to 80% of PD patients, in a long-term evaluation\textsuperscript{13-36}. Another European study showed PD patients with a risk of 5.9-fold for developing dementia, compared to controls without PD, after adjusting for age, sex, and education\textsuperscript{37}. In 2016, there was an estimate of 6.1 million PD patients, compared to 2.5 million in 1990 around the world. Thus, it is estimated that not only PD but also PDD will become an enormous public health concern over the years, especially with the aging of the population in the coming decades\textsuperscript{38}.

The pathophysiology of the cognitive impairments of PD is still widely studied and is still a subject of great controversy. Classically, it is due to the spread of alphasynuclein and progressively greater deposition of Lewy bodies, in cortical structures, especially in those of the parietal and frontal lobes, as well as in the subcortical regions of these cerebral topographies. However, several theories have emerged to try to explain this pathophysiology, precisely because of its complexity, its characteristics of occurrence and its impact during the disease. One of these emerging theories is called “Dual Syndrome Hypothesis,” which differentiates between the two distinct cognitive syndromes found at different stages of PD: (1) a neuropsychological profile in nondemented PD patients with mild cognitive impairment leading to deficits in planning, working memory and executive function reflecting striatal dysfunctions, being amenable with dopaminergic drugs for the treatment of PD, and (2) a profile with gait disturbance and akinetic-predominant clinical changes, demonstrating early deficits in visuospatial functions and semantic fluency which indicates posterior cortical involvement and temporal lobe dysfunction, with faster cognitive decline for
dementia and in which cholinergic treatment may offer greater clinical benefits. In this last cognitive profile, dopaminergic drugs for the PD treatment do not generate great clinical benefits, unlike in the MCI profile, which leads to the thought that only the degeneration of dopaminergic structures would not be sufficient to explain this phenotypic distinction, despite showing some degree of overlap\textsuperscript{39-40-41}. In some cross-sectional studies, global amyloid deposition was found to be related to cognitive performance within groups diagnosed with PDD; in addition, other studies showed that patients had greater cognitive decline the greater the deposition of amyloid bodies in cortical cerebral tissues, showing a direct relationship with the velocity of cognitive decline. This and other studies have shown that the deposition of amyloid bodies may play an important role in elucidating the pathophysiology of PDD\textsuperscript{42}.

As for risk factors for developing dementia, PD patients are more susceptible when: (1) they are older at the onset of motor symptoms, (2) they have the disease for a longer period of time since the onset of motor symptoms, (3) there are more severe parkinsonian symptoms, (4) they present a rigid-akinetic profile, (5) there are atypical symptoms (such as symmetrical disease, more evident and early autonomic dysfunction, early speech disorders, unsatisfactory response to levodopa and gait and posture instability phenotype), (6) cognitive disorder since the onset of the disease, especially with changes in verbal fluency, (7) there is an early occurrence of hallucinations (especially visual), mental confusion or psychosis with the use of dopaminergic drugs, (8) they experience excessive daytime sleepiness, (9), they present history of REM sleep behavior disorder, (10) depression, (11) low levels of beta-amyloid in the cerebrospinal fluid analysis, and (12) white matter lesions with hyperintensities on brain MRI.
Smoking was associated with up to a 2-fold increased risk of developing dementia, despite being considered a protective factor for PD, and hormone replacement treatment with estrogen was associated as a protective factor\textsuperscript{43-44}.

From the point of view of the genetic risk of developing dementia in PD patients, some genes are more related to the development of earlier and more severe dementia. Mutations in the MAPT gene (H1/H1 haplotype) and especially in patients with heterozygous mutations in the glucocerebrosidase (GBA) gene, are shown to have a high risk of developing dementia in PD patients. Glucocerebrosidase (GBA) mutations have a 5.8 times greater chance of developing dementia. Mutations by duplication or even triplication of the synuclein gene (SNCA) have a high rate of conversion to dementia, in addition to being closely related to early familial PD. The mutations of PINK 1 (PARK6) and DJ-1 (PARK7) genes, present low rates of the development of dementia related to PD. Genetic mutations of the APOE E2 and E4 genes are not yet robustly associated with the development of dementia in PD patients, but some studies attest that it may represent an important risk factor\textsuperscript{45}.

Clinically, a PD cognitive disorder should be suspected in patients with a well-established PD diagnosis, through the currently most used criteria, the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria or the Movement Disorders Society Parkinson's Disease Criteria and presenting, after 1 year of the onset of PD, symptoms and signs of cognitive dysfunction with neurodegenerative characteristics (chronic and progressive evolution), where such cognitive deficits must significantly interfere with basic, instrumental and daily activities of the patients (the so-called major cognitive disorder by the Diagnostic and Statistical Manual of Mental Disorders 5th Edition or DSM-5, or
dementia), or not (called MCI), associated with a compatible cognitive profile featuring a decline in the following functions: (1) executive: with difficulties in planning and executing tasks, conceptualization of ideas and decreased speed of thought, (2) attentional: with difficulty in concentration and focus and may have fluctuations in attention during the course of the day, (3) visuospatial: with difficulty in spatial orientation, visuo-construction and/or visuo-perception, and (4) memory: greater difficulty in short-term memory and learning, but benefiting from phonemic or semantic cues, generally with relative preservation of recognition. Language is much less affected. There may be difficulties in mentally locating and searching specific words or memories, often with spontaneous later retrieval with benefits from clues and hints, not to mention difficulty in understanding long and complex sentences. Some behavioral changes are more frequent in PDD and should be investigated, as they can help to reinforce the diagnosis; these include apathy, mood and personality changes (such as depression and/or anxiety), hallucinations, delusions (especially paranoid ones, such as infidelity) and excessive daytime sleepiness.\textsuperscript{13-46-47}

The efficiency in the diagnosis of dementia is essential for the early treatment of a patient, as its delay can significantly have an impact on the prognosis of a PD patient. It is estimated that the number of PD patients reaches 80% at 80 years and 90% at 90 years, with a substantial decrease in the patient's life expectancy and quality of life, with a drop in survival to 3 years after diagnosis of dementia related to PD.\textsuperscript{12-48-49} In clinical practice, patients with signs and symptoms suggestive of cognitive impairment or PDD must be evaluated not only from a clinical point of view by the neurologist, but also from a neuropsychological point of view, through validated neuropsychological tests that can specifically
track the most affected cognitive domains of the patient, being able to obtain a more accurate clinical diagnosis as well as leading to a most appropriate treatment\textsuperscript{13}. However, it is quite difficult in daily clinical practice to obtain an adequate neuropsychological assessment for all these patients.

Neuropsychological assessment in our country and in many other countries is often difficult to access, largely because of the lack of specialized professionals in our country, or because of the costs that are often difficult to access for the majority of the Brazilian population. Neuropsychology is a relatively new discipline in science, having emerged in the early 20th century as a field of knowledge. The term neuropsychology was suggested by both psychologist Donald Olding Hebb (1904-1985) and physician William Osler (1849-1919). As it is a new field of knowledge, despite being an extremely important interface between neurology and psychology and being fundamental for the diagnosis of the cognitive impairment, there are still few places dedicated to the training of these professionals, both in our country and in the world. For this reason, there is a huge difference between the number of patients who need this evaluation and the number of those who effectively manage to be properly evaluated and diagnosed\textsuperscript{50}. For this reason, the so-called “cognitive screening tests” were created and are necessary.

Cognitive screening tests aim, as the name implies, to rapidly and efficiently “track” patients who have possible cognitive impairments that deserve a more detailed cognitive assessment. This is because the majority of screening tests (at least those most used in our clinical practice) are not capable of providing accurate neuropsychological diagnoses, as they are often made from subtests - each assessing several cognitive domains together, and cannot assess each
domain in detail, which leads to an unsatisfactory diagnostic specificity for dementia in these patients. Some of the main goals of screening tests are: to be quick and easy to perform, to be easy to administer and, above all, to be very sensitive to cognitive alterations. Thus, the main role of a cognitive screening test is to detect the majority of patients at risk of having cognitive decline and thus, ideally, to conduct them to more elaborate and specific tests that can attest with greater certainty if this patient has a cognitive impairment or dementia. The most recommended screening tests for PDD, according to the Movement Disorders Society, are: the PD-CRS, the SCOPA-COG, the MoCA and the ACE-R13.

The MMSE is one of the most used for cognitive screening in Brazil, probably in all the world, and some studies have shown that it has good sensitivity in detecting dementia and PD-related cognitive impairments. It is a quick exam, taking about 5 to 10 minutes to be performed, and easy to administer, as it does not need many instruments for such assessment, just a pen and paper. However, despite being very easy to perform, it does not present great specificity and sensitivity in the detection of cognitive impairments. In a 2009 study, using the optimal screening cut-offs for the diagnosis of MCI (26/27 and 29/30 respectively for the MMSE and the MoCA) the sensitivity for the MoCA was 0.83 and specificity 0.53. In the case of the MMSE, the sensitivity was 0.91 and the specificity was 0.38. In the PDD screening analysis, the optimal screening cut-offs were 24/25, with a sensitivity of 0.82 and specificity of 0.75 for MoCA, as well as, in the 28/29 cut-off for the MMSE, the sensitivity was 0.82 and the specificity was 0.63, respectively. The ideal diagnostic breakpoints for dementia, for the MoCA and MMSE, respectively, were 17/18 and 24/25, with maximum specificity related to the maximum possible sensitivity51. The study performed by Brucki et al., which
is used by the Brazilian Ministry of Health as a parameter of the alterations in the scores of MMSE considering educational level interference, took into consideration the cut-offs for cognitive impairments and dementia in different levels of education in our population, where for illiterate patients, the cut-off should be around 20 and for patients with more than 11 years of education, the cut-off of 29 should be considered.

The MoCA and ACE-R are screening tests that are also widely used around the world, including Brazil, with greater sensitivity and specificity. In a 2015 study carried out in Brazil with PD patients, the best cut-off score for MoCA to differentiate patients with no cognitive impairment from those with MCI was 26 with a sensitivity of 84% and specificity of 27%, while for the ACE-R test, the best score was 89 with a sensitivity of 84% and a specificity of 20%. The area under the ROC curve (AUC) for the MoCA to diagnose dementia was 0.86 (CI=95%) and for the ACE-R it was 0.84 (95% CI = 0.74-0.94). The best cut-off score for the MoCA to differentiate patients with dementia from the others was 21, with a sensitivity of 94% and specificity of 68%, while for the ACE-R test it was 76, with a sensitivity of 88% and specificity of 68%. However, the MoCA, when performed in a Brazilian population with PD, in a 2016 study, showed that some of the MoCA subtests can be very difficult to be performed by patients with low educational levels, through analysis of data obtained in the LARGE-PD study (Latin American Research consortium on the GEnetics of PD). Sixty-six patients were assessed at the end, after exclusion of patients who presented incomplete data or who had signs of dementia through the UPDRS phase 1 questionnaire. In this study, it was observed that at least 5 of the 10 subtests presented a floor effect, and test performance showed a strong correlation with educational level.
(correlation coefficient of 0.66; p=0.0001). 34 of the 66 patients had less than 21 points on the test, a cut-off that was considered indicative of dementia in the study. The main tests where the "floor" effect was detected in the study were: concentration and calculation test, repetition, phonemic verbal fluency, abstraction and memory\textsuperscript{54}.

Thus, it became questionable if the MoCA test can be reliably administered in the Brazilian population with PD. Data from the Ministry of Health Portal (portal.mec.gov.br) attest that until approximately the year of 2014, the Brazilian's average education level was 7.7 years, with 7.5 years for men and 8 years for women. Despite the growing increase in schooling reported in the last years (an average of 9.3 years), the average years of schooling obtained a few years ago is worrying, given the analysis that this population will probably age more and in greater proportion in the coming years and, given the conditions of preventive health care in Brazil, which invests little in public policies for the prevention of diseases and the treatment of comorbidities, leading to an increase of PD and PDD risk factors, such as hypertension, diabetes, dyslipidemia, obesity and a sedentary lifestyle\textsuperscript{5}. We can believe that these facts will increasingly expose patients to risk factors for developing PD and PDD, if such health policies do not change.

Due to the growing search for more efficient cognitive screening tests, in recent decades, several studies have searched for faster and more accurate ways to assess such patients. The so-called “mini-tests” were built to be performed in less than 5 minutes. Such tests have sought to reduce the time required for evaluation, without compromising too much the sensitivity and specificity of the diagnosis. (\textsuperscript{55}) Some of these are the Mini-Cog test, the Codex (Cognitive Disorders
Examination), the Memory Impairment Screening (MIS) and the General Practitioner Assessment of Cognition (GPCOG). With different groupings of several other tests used in other cognitive assessments as in a screening test, each subtest in these tests usually assesses more than one cognitive domain in order to optimize the patient's evaluation time.56

Thus, in a 2006 study published in the Stroke journal, a screening test called the National Institute of Neurological Disease and Stroke-Canadian Stroke Network (NINDS-CSN) 5-minute Protocol was created, which was an initiative aimed to seek better assessments to analyze the cognitive profiles of patients with cognitive impairments of vascular etiology. With this initiative, a group of experts was asked to create a 60-minute analysis protocol to be used in studies that would require a division of cognitive skills by domain, with an emphasis on 4 main domains: executive, language, visuospatial and memory. Then, a 30-minute protocol was used as a clinical screening test for patients with suspected vascular cognitive impairment, and finally, a 5-minute protocol was created to be used by primary care physicians, nurses, and other associated healthcare professionals, since they needed faster screening in the office or at bedside. This 5-minute protocol consists of selected MoCA subtests, including a 5-word immediate and delayed memory test, a 6-item orientation task, and a letter phonemic fluency test done in sixty minutes (with the letter F). In addition, the 5-minute protocol was designed so that it could be administered over the phone, thus seeking a greater number of patients and providing more patient comfort.57 Subsequent studies showed good correlations of the 5-minute screening test with cognitive impairment of vascular etiology, with a sensitivity of about 82% and a specificity of 67% when using a cut-off of 6/7 points. The test was considered very useful
for this diagnosis and easy to administer, and it managed to differentiate very well between dementia after stroke and patients without dementia after stroke.\textsuperscript{58}

Then, a 2015 study published by Singapore Universities showed an analysis through this screening test, with PD patients, using a fluency of animals in place of a fluency of letters. A total of 101 PD patients were analyzed, and in the initial analysis, 60 had cognitive impairments and 41 did not. AUC were similar between the MoCA and the NC5MPA, whereas they were statistically better than in the MMSE analysis. The sensitivity and specificities when comparing the NC5MPA (with a cut-off of 9) and the MoCA (cut-off of 22) were statistically similar (77\% and 85\%, respectively) and superior to the MMSE (52\% with cut-off of 24). Although the test performance times were not computed in this study, the opinion is that the NC5MPA test was shorter, faster and easier to perform than the other tests and with very promising results. The same study confirms that other studies and a larger analysis of patients would be necessary for such results to be confirmed.\textsuperscript{59}

Until nowadays, when analyzing PubMed databases (https://pubmed.ncbi.nlm.nih.gov) there are no records of new studies that analyze the accuracy, sensitivity and specificity of the NC5MPA for the screening of PD-related cognitive impairment and PDD.
Methods
Methods

Participants and procedures.

The present study is a multicenter observational study that was carried out at the Neurology Movement Disorders Clinics of the Escola Paulista de Medicina – Federal University of São Paulo – UNIFESP/Brazil, which is headed by Doctors Henrique Ballalai Ferraz and Vanderci Borges, and at the Neurology Movement Disorders Clinics of the Botucatu Medicine College – São Paulo State University – UNESP/Brazil, which is headed by Dr. Arthur Oscar Schelp. The universities are 2 of the largest medical schools in Brazil and have Neurology sectors that cover a large number of patients. The study was conducted from November, 2019, to December, 2021. Based on the populations of both regions and on the values of incidence and prevalence of PDD in Brazil, we calculated that a total sample of 120 patients would be sufficient to answer the main questions of this study, with a confidence interval above 95%.

With diagnoses based on United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank criteria, we analyzed PD patients with diagnoses made by movement disorders expert neurologists, with more than 4 years after the onset of the motor symptoms of the disease. Demographical data were collected regarding the patients' medical records as well as personal interview, such as: age at the time of assessment, age at the onset of motor symptoms, gender and educational level, as well as the medication dose measured by LEDD.

Cognitive screening tests assessments

These patients were analyzed using the scales NC5MPA, using the score of 0 to 12 (version using the respective tests of the MoCA translated into Portuguese),
the MoCA, using scores of 0 to 30 (version translated into Portuguese\textsuperscript{62}) and the MMSE, using scores of 0 to 30 (version translated into Portuguese\textsuperscript{52}). They were also assessed using the CDT, at the end of the analysis made by the NC5MPA, using 2 types of analysis of the results - one qualitative analysis based on Kobayashi et al. (0 when inaccurate drawing and 1 when accurate drawing\textsuperscript{63}) and one quantitative analysis, adapted from the study of Strub et al., ranging from 0 to 3 points (0 when totally inaccurate drawing, 1 when drawing one face, 2 when drawing two “parallel” faces and 3 when drawing a totally correct 3-D figure), as this facilitates the binarization of the results obtained (from 0 or 1 - bad, to 2 or 3 - good), to improve the accuracy of the analysis results after evaluating the association of this test with the NC5MPA\textsuperscript{64}.

The analysis of the impact of the cognitive symptoms in the instrumental and daily life activities were performed using the validated Clinical Dementia Rating (CDR) scale, using the global scores (CDR-GS) of 0 to 3, in the rule-based analysis, proposed by Hughes et al. in 1982\textsuperscript{65} and adapted by Morris et al. in 1993\textsuperscript{66}, and the “sum of boxes” (CDR-SB) analysis, using a 0 to 18 score, based on the sum of all the fulfilled categories (Portuguese version\textsuperscript{67}). Beyond the accomplishment between the three screening tests, the performance times of the three tests were recorded for later comparisons, including recording of patients' performance times of NC5MPA screening test with and without addition of the performance time in the CDT.

In addition, patients were analyzed based on the modified Hoehn & Yahr (mH&Y) scale, a scale of PD severity of symptoms (Portuguese version\textsuperscript{68-69}), by the functionality scale of Schwab & England (S&E - Portuguese version\textsuperscript{70}), and
by the motor scale (part 3) of the Unified Parkinson's disease rating scale (UPDRS) (Portuguese version71).

All tests were performed during the patient's medication “on” period. If the patient was in “off” state of the antiparkinsonian medication, he was asked to take it at the usual dose and was waited until he reported that he was in the medication action period to start the tests, hoping that patients did not have interference of motor symptoms in the performance of the tests.

Inclusion Criteria

Patients were included in this study after diagnosed with PD by a neurologist specialist in movement disorders, based in UKPDS Brain Bank Criteria for the PD diagnosis with duration disease > 4 years. Patients were assessed by screening tests just after cognitive complaint by the patients themselves, caregivers or neurologists and after excluding other neurological, psychiatric or systemic diseases that could mimic cognitive conditions. Finally, patients were included after signing a consent form.

Exclusion Criteria

Beck Depression Score (BDS - version translated into Portuguese) > 28 (patients with severe depression) were excluded, as well as patients with comorbidities that could make the analysis difficult for screening tests, such as visual problems, or severely impaired motor conditions.

The study was previously approved by the Ethics Committee of the Federal University of Medicine of São Paulo/Escola Paulista de Medicina – UNIFESP, as well as by the Ethics Committee of the Júlio Mesquita Filho University - UNESP, where the collection of study data was started only after approval by both committees.
Statistical Analysis.

All statistical analyses were performed using the SPSS version 21 software. A comparison between the two groups was based on the CDR-GS scores (<1 e ≥1), analyzing the epidemiological data collected from the patients, and scores obtained from screening tests was performed by the t test between the two samples and Mann-Whitney U techniques. After the correlation comparisons between groups, z score was used to evaluate p-value regarding significance between these correlations. Additionally, a relationship between the screening test scores and epidemiological data with global scores in CDR-GS scales ≥ 0.5 (MCI related to dementia) and ≥ 1 (PDD), was made by simple Poisson regression.

The comparison between the NC5MPA, MoCA, MMSE, a combination between NC5MPA and CDT (both qualitative and quantitative), was performed by estimating the AUC via the ROC curve and the Kappa test. In addition, the tests were compared through estimates of accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) based on the cut-off points that maximize sensitivity and specificity through the ROC curve. Similarly, the analysis of the interference of educational level in the tests was made, estimating the AUC via the ROC curve and the Kappa test in the population studied, dividing them into 3 samples based on schooling (≤4, 4 to 8 and >8 years of education).
Results
Results

A total of 133 patients were analyzed, 35 of them were excluded patients, as they had a BDS ≥ 28 (severe depression) or any of the other contraindications, leaving 98 patients in the final sample (Figure 1). Of these 98 patients collected, 69 (70.4%) were men and the mean age of the patients during the interview was 65.4 years (37 to 84 years - SD ± 9.6), with the mean age at the time of disease onset of 53.7 years (18 to 78 years - SD ± 10.8) and the mean disease duration of the patients was 11.6 years (4 to 33 years - SD ± 5.8), with the mean LEDD of 892.8 mg (0-2000 mg – SD ± 441.3). The mean educational level was 7.2 years (0-19 years - SD ± 4.2), with the mean functionality by the analysis of the S&E scale of 61.1% (10-90% - SD ± 20.7), and a severity staging of disease according to the mH&Y scale of 2.8 points (1-5 points – SD ± 0.8). The mean of measurements on the BDS was 12 points (0-20 points – SD ± 6.0). Of the 98 patients, 11 (11.2%) had a CDR-GS of 0, 45 (45.9%) of the patients had a CDR-GS of 0.5, 42 (42.9%) of the patients had a CDR-GS ≥ 1, being 27 (27.6%) patients with CDR-GS of 1, 11 (11.2%) had CDR-GS of 2 and 4 (4.1%) patients had CDR-GS of 3. The mean of the “sums of the boxes” of the CDR scale was of 4.4 (0-15 points – SD ± 3.4) (Table 1).
Figure 1 – Flowchart of the study sample.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean (Minimum-Maximum)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (N)</td>
<td>69 (70.4%)</td>
<td></td>
</tr>
<tr>
<td>Age during the interview (in years)</td>
<td>65.4 (37-84)</td>
<td>66.0</td>
</tr>
<tr>
<td>Disease onset age (in years)</td>
<td>53.7 (18-78)</td>
<td>53.0</td>
</tr>
<tr>
<td>Disease Duration (in years)</td>
<td>11.6 (04-33)</td>
<td>10.0</td>
</tr>
<tr>
<td>Schooling level (in years)</td>
<td>07.2 (00-19)</td>
<td>05.0</td>
</tr>
<tr>
<td>Loevooda Daily Dose (LEDD – in mg/day)</td>
<td>892.8 (100-2000)</td>
<td>800.0</td>
</tr>
<tr>
<td>CDR score-Global Score (in points)</td>
<td>00.9 (00-03)</td>
<td>00.5</td>
</tr>
<tr>
<td>CDR - Sum of Boxes (in points)</td>
<td>04.4 (00-15)</td>
<td>03.5</td>
</tr>
<tr>
<td>Modified Hoehn-Yahr Scale (in points)</td>
<td>02.8 (01-05)</td>
<td>02.5</td>
</tr>
<tr>
<td>Schwab-England Scale (in percentage)</td>
<td>61.1 (10-90)</td>
<td>60.0</td>
</tr>
<tr>
<td>Beck Depression Scale (in points)</td>
<td>12.0 (00-28)</td>
<td>11.0</td>
</tr>
<tr>
<td>Mini Mental Status Examination (MMSE-in points)</td>
<td>23.3 (05-30)</td>
<td>24.0</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment (MOCA-in points)</td>
<td>18.8 (01-29)</td>
<td>20.0</td>
</tr>
<tr>
<td>NINDS-CSN 5 Minutes Protocol (in points)</td>
<td>07.8 (00-12)</td>
<td>08.0</td>
</tr>
<tr>
<td>UPDRS – part 3 (in points)</td>
<td>40.2 (11-97)</td>
<td>46.0</td>
</tr>
</tbody>
</table>

Table 1 – Profile of the selected patients with PD
The average score of the patients' assessments by the MMSE was 23.3/30 points (5-30 points - SD ± 5.7), with the scores in the individual test parameters: 8.6/10 in Temporal and Spatial Orientation, 2.9/3 in immediate memory register, 2.7/5 in arithmetic exercise, 1.5/3 in recent memory, 2.9/3 in language (naming and repetition), 2.5/3 in verbal order, 0.8/1 in written order, 0.7/1 in spontaneous writing of a sentence and an average of 0.5/1 in the drawing of pentagons (Graphic 1). In the case of the analysis of patients using the MoCA screening test, the average of the scores was 18.8/30 points (1-29 points SD ± 6.3), and the scores of the individual analyzes of the scale in these patients were: 2.5/5 in Visuospatial/Executive assessment, 2.2/3 in naming, 3.9/6 in attention, 1.5/3 in language, 0.7/2 in abstraction, 1.9/5 in delayed recall and 5.2/6 in orientation (Graphic 2). The mean times of patients in the MMSE and the MoCA were respectively 5.8 (3.2-13.7) and 10.8 (6.4-19.7) in minutes (Graphic 4).

Graph 1 - Analysis of the MMSE subtests in patients with PD
In the case of the results of the NC5MPA assessments, the average score of the patients analyzed in this study was 7.8/12 (0-12 points SD ± 2.8), and the analysis of the subtests contained in the test showed average scores of: 5.2/6 in...
orientation, 0.4/1 in animal semantic fluency (with an average of 12.3 words in the test, {1 – 24}) and 2.3/5 in delayed recall. In the CDT, patients averaged scores of 0.3/1 points (0-1 points) when analyzed by scores ranging from 0 to 1 and average scores of 1.3/3 points (0-3 points) when analyzed by the score ranging from 0-3 points. Regarding the test performance times, the NC5MPA had an average of 3.2 minutes of execution (1.9 - 5.1 minutes) when performed without the cube test and an average of 4.5 minutes (2.7- 7.6 minutes) when performed in conjunction with the CDT.

Table 3 presents the data on the analysis of bivariate associations by simple Poisson regression for the prevalence for patients who presented CDR-GS ≥ 0.5. All parameters included in the study and their relationship with the detection of CDR-GS ≥ 0.5, were assessed. However, none of the parameters assessed (location of data collection, gender, age of the patient, age at the onset of illness, duration of illness, education level, mH&Y, S&E, LEDD, side of symptom onset, and severity of depressive symptoms), was found not having an important association with CDR-GS ≥ 0.5 (p-values between 0.502 and 0.993). The same was found when the associations of the NC5MPA, MMSE and MoCA scales were analyzed, where no important relationships were found between them, as well as no associations were found with the CDT, both in the qualitative and quantitative analysis performed (p values between 0.387 and 0.962). This was due to the small number of patients with CDR-GS = 0 in our study population (11 patients – 11.2%), in relation to the number of patients with CDR-GS ≥ 0.5 (87 patients – 88.8%).
Table 3 - Bivariate Associations by Simple Poisson Regression for CDR prevalence $> 0.5$.

Table 4 presents the data based on the analysis of bivariate associations by simple Poisson regression for the prevalence of CDR-GS $\geq 1$ (CDR-GS 1, 2 or 3). Regarding the location where data were obtained (Movement Disorders Outpatients Department in Neurology UNIFESP/EPM or Movement Disorders Outpatient Department in Neurology HC-FMB/UNESP), the side of the onset of symptoms (left side onset), LEDD, BDS and male gender good correlation were not found with the detection of CDR-GS $\geq 1$. For the values obtained in the bivariate analysis by Poisson regression of age at diagnosis, age during assessment, disease duration, educational level, disease severity scores by the mH&Y scale and scores by the S&E showed good correlation with CDR-GS values $\geq 1$ ($p$-values between 0.000 and 0.025). Also, in table 3, the association values between the analyzed screening tests were very promising, with $p$-values, all of them demonstrating $p= 0.000$, which demonstrates a strong correlation between these scales and values of CDR-GS $\geq 1$. In the case of the CDT...
performed alone, p-values were > 0.05, not demonstrating good correlation with the primary objective (CDR-GS ≥ 1).

Table 4 – Bivariate Associations by Simple Poisson Regression for CDR Prevalence ≥ 1,0.

These epidemiological findings were compared after segregation of the total sample between two subgroups (Table 2), based on CDR-GS (CDR-GS < 1 and ≥ 1). All the patients in the CDR-GS ≥ 1 presented lower average scores in MMSE, MoCA and NC5MPA (19.15, 14.15, 05.75, respectively) in comparison CDR-GS < 1 group (25.83, 22.33, 09.41, respectively), all of them presenting good significance (p-value=0.00000). Such results remain similar when comparing the NC5MPA scores summed with scores of the CDT in qualitative (0 to 1) and quantitative (0 to 3) analyses, respectively 05.74 and 06.34 in CDR-GS ≥ 1 group, with 09.59 and 11.15 in the CDR-GS < 1 group (p-value=0.00000).

The CDR-GS ≥ 1 group also presented higher age at onset of motor symptoms, disease duration, age at interview, as so as higher mH&Y scale scores than CDR-GS <1 group patients. Also, the CDR-GS ≥ 1 group revealed lower mean education level and S&E scale scores. All these parameters presented p-value <
0.001 (good significance) in these comparisons. However, the differences found in LEDD between the two groups, with higher mean doses in the CDR-GS ≥ 1 group, was not statistically significant (p=0.12507, CI=95%).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean Score (Maximum -Minimum)</th>
<th>p-value</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CDR &lt; 1 (57.1%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-Mental State Examination (in points)</td>
<td>25.83 (30-19) m = 26</td>
<td>(p=0.00000)</td>
<td>19.15 (30-02) m = 20</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment (in points)</td>
<td>22.33 (29-14) m = 23</td>
<td>(p=0.00000)</td>
<td>14.15 (25-01) m = 14</td>
</tr>
<tr>
<td>NINDS-CSN 5 minutes protocol (in points)</td>
<td>09.41 (12-05) m = 10</td>
<td>(p=0.00000)</td>
<td>05.75 (12-00) m = 06</td>
</tr>
<tr>
<td>NINDS-CSN 5 minutes protocol +</td>
<td>09.59 (13-05) m = 10</td>
<td>(p=0.00000)</td>
<td>05.74 (12-00) m = 06</td>
</tr>
<tr>
<td>Cube Drawing Test – qualitative (in points)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NINDS-CSN 5 minutes protocol +</td>
<td>11.15 (15-05) m = 12</td>
<td>(p=0.00000)</td>
<td>06.34 (12-00) m = 06</td>
</tr>
<tr>
<td>Cube Drawing Test – quantitative (in points)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schooling (in years)</td>
<td>08.49 (19-02) m = 08</td>
<td>(p=0.00001)</td>
<td>04.91 (13-00) m = 04</td>
</tr>
<tr>
<td>Age at disease onset (in years)</td>
<td>51.13 (74-35) m = 51</td>
<td>(p=0.00006)</td>
<td>57.35 (78-18) m = 59</td>
</tr>
<tr>
<td>Disease duration (in years)</td>
<td>10.03 (18-04) m = 08</td>
<td>(p=0.00060)</td>
<td>13.64 (28-05) m = 13</td>
</tr>
<tr>
<td>Age at interview (in years)</td>
<td>61.21 (74-37) m = 61</td>
<td>(p=0.00000)</td>
<td>71.24 (84-52) m = 71</td>
</tr>
<tr>
<td>Schwab&amp;England (in percentage)</td>
<td>70.83 (90-20) m = 75</td>
<td>(p=0.00000)</td>
<td>48.66 (90-10) m = 50</td>
</tr>
<tr>
<td>Hoehn&amp;Yahr (in points)</td>
<td>02.61 (05-01) m = 2.5</td>
<td>(p=0.00002)</td>
<td>03.21 (05-02) m = 03</td>
</tr>
<tr>
<td>LEDD (in mg/day)</td>
<td>882.66 (2000-200) m = 762.5</td>
<td>(p=0.12507)</td>
<td>947.64 (1800-100) m = 900</td>
</tr>
<tr>
<td>UPDRS - part 3 (in points)</td>
<td>41.55 (11-83) m = 41</td>
<td>(p=0.02222)</td>
<td>59.47 (18-97) m = 59.5</td>
</tr>
<tr>
<td>CDR - Sum of Boxes (in points)</td>
<td>02.01 (00-06) m = 02</td>
<td>(p=0.00000)</td>
<td>07.37 (01-15) m = 06</td>
</tr>
</tbody>
</table>

Table 2 – Epidemiological data comparison analysis between CDR-GS scale groups separated in ≥1 point and <1 point.

In graphic 3 and table 5, which relates the sensitivities and specificities of the tests, we presented the ROC curves between the screening tests analyzed. In the comparison between the AUC, the NC5MPA area (0.86) under the cut-off point of 7.5 points was greater than the area representing the MoCA test (0.85) under the cut-off score of 19.5 points and the MMSE (0.81) under the cut-off score of 24.5 points. At this point where the points of greatest sensitivity and specificity of the tests are selected, the sensitivity and specificity of the NC5MPA test were
78.5% and 85.7%, respectively, in MoCA these values were 76.1% and 76.7% and in the case of the MMSE they were 76.1% and 67.8%. Regarding the accuracy of the tests, in the NC5MPA test, the result was 82.6% (with a PPV of 80.4% and a NPV of 84.2%), against an accuracy of 76.5% of the MoCA (with PPV of 71.1% and NPV of 81.1%) and 71.4% of the MMSE (with PPV of 64% and NPV of 79.1%). The Kappa concordance coefficient was strong (0.64) on the NC5MPA, moderate on the MoCA, and fair on the MMSE (all p<0.001).

**Graphic 3** – ROC curve of the screening tests analyzed.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Area (AUC); (IC5%)</th>
<th>p</th>
<th>Cutoff</th>
<th>(Sen,Spe)</th>
<th>ROC curve</th>
<th>Sen</th>
<th>Spe</th>
<th>Ac</th>
<th>VPP</th>
<th>VPN</th>
<th>Kappa (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MNI85</td>
<td>0.65 (0.78 - 0.94); p &lt; 0.001</td>
<td>≥ 7.5</td>
<td>33/42</td>
<td>(78.5%)</td>
<td>43/56 (85.7%)</td>
<td>45/98 (82.6%)</td>
<td>33/41 (80.4%)</td>
<td>43/57 (84.2%)</td>
<td>0.64 (p &lt; 0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOCA</td>
<td>0.85 (0.77 - 0.93); p &lt; 0.001</td>
<td>≥ 19.5</td>
<td>32/42</td>
<td>(76.1%)</td>
<td>43/56 (76.7%)</td>
<td>75/98 (76.5%)</td>
<td>32/45 (71.1%)</td>
<td>43/53 (81.1%)</td>
<td>0.52 (p &lt; 0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEEM</td>
<td>0.81 (0.73 - 0.90); p &lt; 0.001</td>
<td>≥ 24.5</td>
<td>32/42</td>
<td>(76.1%)</td>
<td>38/56 (67.8%)</td>
<td>70/98 (71.4%)</td>
<td>32/50 (64.0%)</td>
<td>38/48 (79.1%)</td>
<td>0.43 (p &lt; 0.001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 5** – Analysis of screening tests ROC curves compared in the best ROC scores.
Table 6 and Graphic 5 shows the comparisons between the sensitivity, specificity and accuracy values found in the analyzes of the different cut-off points of the NC5MPA test. For the cut-off = 8 points, which corresponds to the sample median found in the values obtained in the test, the sensitivity and specificity were, respectively, 83.3% and 69.6%, with 75.5% of accuracy. In the cut-off points based on the ROC curve of 7 and 9 points, the accuracy rates were, respectively, 82.6% and 68.3%, being for the cut-off = 7 points, 78.7% of sensitivity and 85.7% of specificity and for the cut-off = 9, 88.1% of sensitivity and 53.5% of specificity. Trying to improve the sensitivity and specificity of the NC5MPA test, associations were made between the test results performed on the study patients and the CDT, both qualitative and quantitative analyses. In the qualitative analysis, the accuracy value was 58.1%, with sensitivity of 88.1% and specificity of 35.7%. Regarding the quantitative analysis, the accuracy was 70.4%, with a sensitivity of 85.7% and specificity of 58.9%. The CDT, in the qualitative interpretation, presented accuracy of 58.1%, with sensitivity of 88.1% and specificity of 35.7%; in the binarized qualitative interpretation showed an accuracy of 70.4%, with a sensitivity of 85.7%, with a specificity of 58.9%.

Patients were also assessed based on the summed scores of the NC5MPA test with CDT scores, both the qualitative and the quantitative, performing the ROC curve analysis and AUC. In this analysis, in association with the qualitative score, the sensitivity was 83.3%, specificity was 73.2% and accuracy was 77.5%, PPV was 70% and NPV was 85.4%, with an average performance time of 4.46 minutes (4.28-4.65 minutes). And, in the analysis with the association of the qualitative score of CDT, sensitivity was 83.3%, specificity was 73.2%, accuracy was 77.5%,
PPV was 70% and NPV was 85.4%. The AUC was similar to the NC5MPA (p-value < 0.01).

**Graphic 5** – ROC curve of the NINDS-CSN 5 Minutes Protocol screening test compared to test associated with the Wire Cube Drawing Test.

**Table 6** - Sensitivity, Specificity and Accuracy of the NC5MPA test analyzed with and without association with the Cube Drawing Test.
We immediately proceeded the analysis of the test parameters after dividing the initial sample of the patients based on educational levels in order to measure the interference of schooling on test scores (Tables 7, 8 and 9 / Graphs 6, 7 and 8). The ranges into which the patients were divided, were: less than 4 years, 5 to 8 years and more than 8 years of education. In the range of less than 4 years, in the NC5MPA, sensitivity is 76.9%, specificity of 80% and accuracy of 78%, with a PPV of 87% and a NPV of 66.7 %, with an AUC of 0.86 and p-value < 0.001, with a confidence interval of 95%. In the educational level range of 5 to 8 years, sensitivity was 60%, specificity was 69.2%, accuracy was 65.2%, with a PPV of 60%, and a NPV of 69.2%, with an AUC of 0.75 and p-value < 0.041 (p < 0.05). Finally, in the age group over 8 years of education, sensitivity is 66.7%, specificity is 75% and accuracy is 73.5%, with a PPV of 36.4% and a NPV of 91.3%, with an AUC of 0.83 and a p-value < 0.011.

Still in the analysis of the results dividing the initial sample by education levels (Tables 7, 8 and 9 / Graphs 6, 7 and 8), in the MoCA test analysis, sensitivity was 66.7%, specificity was 75% and accuracy was 73.5%, with a PPV of 36.4% and NPV of 91.3%, with AUC of 0.83, with a p-value < 0.011. Education level between 5 to 8 years, sensitivity was 50%, specificity was 61.5%, accuracy was 56.5%, with a PPV of 50% and NPV of 61.5%, with an AUC of 0.62, but with a p-value of 0.306 (> 0.05); in the group with more than 8 years of education, sensitivity was 83.3%, specificity was 78.6%, accuracy was 79.4%, with PPV of 45.5 and NPV of 95.7%, with an AUC of 0.86 and p-value = 0.005. When analyzing the MMSE screening test, in the range of less than 4 years, sensitivity was 73.1%, specificity was 73.3% and accuracy was 82.6%, with a PPV of 61.1% and a NPV of 73.1%, with an AUC of 0.80 and a p-value < 0.001. In the 5 to 8 years group, sensitivity
was 50%, specificity was 61.5% and accuracy was 56.5%, with a PPV of 50% and a NPV of 61.5%, with an AUC of 0.64, but with a p-value = 0.264. And, finally, in the educational level group of more than 8 years, sensitivity was 66.7%, specificity was 78.6% and accuracy was 76.4%, with PPV of 40% and a NPV of 91.7%, with an AUC of 0.84 and with a p-value = 0.009.

**Graphic 6 -** Comparison between tests among patients with educational level of less than 4 years.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Area (IC95%) ; p</th>
<th>Cutoff</th>
<th>(S;S) Roc Curves</th>
<th>Sens</th>
<th>Spec</th>
<th>Acc</th>
<th>PPV</th>
<th>NPV</th>
<th>Kappa (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS</td>
<td>0.86 (0.74 - 0.95); &lt; 0.001</td>
<td>≤ 6.5</td>
<td>(76.5%; 80.0%)</td>
<td>75.9%</td>
<td>80.0%</td>
<td>78.0%</td>
<td>87.0%</td>
<td>66.7%</td>
<td>0.54 (&lt;0.001)</td>
</tr>
<tr>
<td>MOCA</td>
<td>0.89 (0.79 - 0.99); &lt; 0.001</td>
<td>≤ 15.5</td>
<td>(76.5%; 80.0%)</td>
<td>75.9%</td>
<td>80.0%</td>
<td>78.0%</td>
<td>87.0%</td>
<td>66.7%</td>
<td>0.54 (&lt;0.001)</td>
</tr>
<tr>
<td>MEEM</td>
<td>0.80 (0.67 - 0.99); &lt; 0.001</td>
<td>≤ 22.5</td>
<td>(73.1%; 73.3%)</td>
<td>73.1%</td>
<td>73.1%</td>
<td>73.1%</td>
<td>61.1%</td>
<td>73.1%</td>
<td>0.44 (0.004)</td>
</tr>
<tr>
<td>NNDC11</td>
<td>0.86 (0.74 - 0.98); &lt; 0.001</td>
<td>≤ 5.5</td>
<td>(76.9%; 80.0%)</td>
<td>75.9%</td>
<td>80.0%</td>
<td>87.0%</td>
<td>65.7%</td>
<td>70.0%</td>
<td>0.54 (&lt;0.001)</td>
</tr>
<tr>
<td>NNDC33</td>
<td>0.84 (0.70 - 0.97); &lt; 0.001</td>
<td>≤ 6.5</td>
<td>(85.2%; 80.0%)</td>
<td>69.2%</td>
<td>80.0%</td>
<td>73.1%</td>
<td>85.7%</td>
<td>60.0%</td>
<td>0.46 (0.002)</td>
</tr>
</tbody>
</table>

**Table 7 -** Comparison between tests among patients with educational level of less than 4 years.
Graphic 7 - Comparison between tests among patients with educational level between 5 and 8 years.

Table 8 – Comparison between tests among patients with educational level between 5 and 8 years.
**Graphic 8** - Comparison between tests among patients with educational level of more than 8 years.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Area (IC95%)</th>
<th>p</th>
<th>Cutoff</th>
<th>(S;S) Roc Curves</th>
<th>Sens</th>
<th>Spec</th>
<th>Acc</th>
<th>PPV</th>
<th>NPV</th>
<th>Kappa (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MINDS</td>
<td>0.83 (0.65 - 1.00) ; 0.011</td>
<td>&lt; 3.5</td>
<td>66.7%</td>
<td>75.0%</td>
<td>66.7%</td>
<td>75.0%</td>
<td>73.5%</td>
<td>35.4%</td>
<td>91.3%</td>
<td>0.31 (0.043)</td>
</tr>
<tr>
<td>MOCA</td>
<td>0.86 (0.73 - 1.00) ; 0.005</td>
<td>&lt; 21.5</td>
<td>63.3%</td>
<td>83.6%</td>
<td>83.3%</td>
<td>78.6%</td>
<td>79.4%</td>
<td>45.5%</td>
<td>95.7%</td>
<td>0.46 (0.003)</td>
</tr>
<tr>
<td>MEEM</td>
<td>0.84 (0.69 - 0.95) ; 0.039</td>
<td>&lt; 26.5</td>
<td>66.7%</td>
<td>78.6%</td>
<td>66.7%</td>
<td>78.6%</td>
<td>76.4%</td>
<td>40.0%</td>
<td>91.7%</td>
<td>0.35 (0.027)</td>
</tr>
<tr>
<td>MINDC11</td>
<td>0.85 (0.69 - 1.00) ; 0.038</td>
<td>&lt; 3.5</td>
<td>66.7%</td>
<td>79.6%</td>
<td>66.7%</td>
<td>78.6%</td>
<td>76.4%</td>
<td>40.0%</td>
<td>91.7%</td>
<td>0.35 (0.027)</td>
</tr>
<tr>
<td>MINDC33</td>
<td>0.83 (0.65 - 1.00) ; 0.011</td>
<td>&lt; 10.5</td>
<td>66.7%</td>
<td>71.4%</td>
<td>56.7%</td>
<td>70.5%</td>
<td>70.5%</td>
<td>33.3%</td>
<td>90.9%</td>
<td>0.27 (0.070)</td>
</tr>
</tbody>
</table>

**Table 9** - Comparison between tests among patients with educational level of more than 8 years.
Discussion
Discussion

The diagnosis of PDD is of uttermost importance in the evolution of the treatment of a PD patient, as it is a very frequent complication in these patients, reaching 30% in PD patients and being 4 to 6 times more prevalent in PD patients when compared to the population without the disease. Furthermore, it is known that patients with cognitive impairment and/or dementia in Parkinson's disease have a lower quality of life, associated with greater disability and worsening of functionality, as well as greater complications in the relationship with the caregivers due to greater burden. Another important detail to emphasize about the diagnosis of PDD is that, in treating the PDD in these patients, especially with the acetylcholinesterase inhibitors and drugs to control behaviors and neuropsychiatric conditions, the quality of life of patients and family members, as well as the functionality and daily living activities can be improved.

In epidemiological terms, the study did not show major statistical differences between the populations studied, one in metropolitan São Paulo city and the other in the São Paulo state upcountry region of Botucatu, Brazil. The mean age of onset of the patients symptoms in our sample was above 50 years (53.7 years), which is consistent with the current literature, as well as the mean age of disease of patients estimated at over 10 years (11.6 years of disease) is also quite congruent with the literature findings; these attest that cognitive impairments occur more frequently in later stages of the disease, especially after 10 years of disease, the advanced stage of the disease, when the Lewy bodies dissemination through areas of the cerebral cortex lead to the characteristic symptoms of the disease, although milder cognitive conditions can be found even in earlier stages.
of the disease\textsuperscript{74-75}, especially restricted to executive and attentional domains\textsuperscript{39}. The mean “disease duration” (years with disease) of patients being over 10 years of disease may partly explain the finding of a small number of patients with CDR-GS = 0 (no cognitive impairment). This detail probably had a great impact on the findings in relation to the study of the sensitivity and specificity of the test for patients with cognitive disorders (CDR-GS \geq 0.5; MCI or dementia), as explained in more details later in this literature, but showed no relevant impact on the patients’ findings in relation to the occurrence of dementia (CDR-GS \geq 1).

The average schooling of patients was considered low in relation to studies carried out in other locations on the planet\textsuperscript{76}. Currently in Brazil, the mean time of schooling, according to a recent survey, is 11.8 years. However, in the 1990s, it was estimated to be between 4.9 and 5.1 years, and in this study the mean time of schooling of our sample was 7.2 years, in patients with a mean age of over 50 years, congruent with the probable mean education level of these patients corrected by ages\textsuperscript{77}. It is known from several previous studies that lower educational level is a risk factor for the development of cognitive impairments and dementia syndromes, such as Alzheimer's Disease and PDD\textsuperscript{78-79}.

The diagnosis of PD-related cognitive decline has been widely discussed in recent years. The MDS, in 2012, released a guideline for the diagnosis of MCI in PD. In this task-force, it was decided that two points are extremely important for the diagnosis: the first is the establishment of a cognitive impairment and the second necessary criterion is to exclude any interference of this cognitive impairment in the activities of daily living and functionality of the patient. The first stage in the process of diagnosing a cognitive impairment is the use of cognitive screening tests, followed by the use of more specific screening tests\textsuperscript{13}. In the
case of a possible or probable dementia condition, the core factors are: the diagnosis of an impairment in more than one cognitive domain, representing a decline from premorbid level and if cognitive these cognitive alterations are severe enough to impair the daily life activities (social, occupational, or personal care)\textsuperscript{46}. In both cases, patients must have a well-defined PD diagnosis, according to validated criteria. In our study, the establishment of a PD diagnosis was made through the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria, and in the diagnosis of cognitive impairments, there was no need to establish a larger protocol of cognitive analysis through more specific diagnostic tests because there are already numerous studies in the literature that give strength to a very satisfactory sensitivity and specificity for the MoCA as a screening test for cognitive disorders and especially for dementia in PD. Thus, the comparison with the MoCA test, in our view, is enough to attest whether a screening test is good enough to be used as a screening test for cognitive impairments in PD.

Likewise, in the establishment of a dementia syndrome, in our study, the CDR was used - one of the most used scales in the world for the analysis of impairments in activities of daily living and functionality. The CDR scale, a global instrument for staging dementia, was developed by the Memory and Aging Project at Washington University School of Medicine and was primarily designed for its use in people with dementia of the Alzheimer type; however, it has been researched for assessment of cognitive conditions in other degenerative diseases. The CDR rates six domains associated with dementia: memory; orientation; judgment and problem solving; community affairs; home and hobbies; and personal care. For dementias in general, the scale has a very satisfactory sensitivity and specificity in studies carried out with Brazilian populations,
presenting sensitivities between 86 and 91.2% and specificity of 100%, showing a PPV of 100% and NPV of 97.6%. Despite presenting satisfactory values, there is a substantial decrease in sensitivity and specificity when the objective is to evaluate patients with MCI, with sensitivity of 80 to 93% of and specificity of 97% to 100%\textsuperscript{67-80-85}. When specifically talking about Parkinson's disease-related dementia, a 2015 Movement Disorders Clinical Practice study by Wyman-Chick et al. found a sensitivity of 79% and specificity of 96%, with an AUC of 0.92 (CI=0.95) when using a dementia cut-off of CDR-GS $\geq 1$, but with a sensitivity of 0.88 and a specificity of 0.82 for MCI, with AUC of 0.51, not being an acceptable value to have sufficient diagnostic certainty to relate the values of the scales with MCI, but in relation to PD-related dementia, the specificity values found give us the possibility to evaluate the relationship of the scales with dementia (CDR-GS $\geq 1$)\textsuperscript{81} and have been used for the stratification of healthy groups with MCI and dementia in several studies\textsuperscript{86}. Thus, in our study, we found it is sufficient and more advantageous use the CDR-GS for the establishment of patients with probable dementia (CDR-GS $\geq 1$) and with probable non-dementia cognitive impairment (CDR-GS $< 1$) in order to obtain a larger number of patients\textsuperscript{80-81}.

In the comparison between epidemiological data of our sample of two groups of patients presenting CDR-GS $\geq 1$ (probable dementia group) and CDR-GS $< 1$ (probable non-demented patients) (table 2), patients in the CDR-GS $\geq 1$ group presented higher age at the onset of the motor symptoms, disease duration of the motor symptoms, age at the interview and mH&Y scale scores, the same way that presented lower education level and S&E scale scores, in comparison with the CDR-GS $< 1$ group. All these differences in the parameters showed significant correlations between the two groups, showing p-value $< 0.005$. These findings,
assuming that $\text{CDR-GS} \geq 1$ would be a group of patients likely to have dementia, are congruent with the literature, which show that the PD patients that are more prone to develop dementia are older, with more duration of the motor disease and higher mH&Y scale scores, not to say that they present lower education levels and S&E functionality scale scores. However, in comparing the LEDD, our study showed higher doses of medication in “probably demented” group, but this difference was not statistically significant ($p$-value = 0.12507).

On this same analysis (table 2), we compared the two groups regarding the scores of the screening cognitive scales used in this study to assess cognitive disorders in the PD patients. Comparing the scores obtained in the study, the CDR-GS $\geq 1$ (probably demented group) presented lower scores in the three screening tests used, with statistical significance between these differences ($p$-values = 0.00000; CI=95%). There is abundant evidence in literature that in the case of the MMSE and MoCA the scores of the PD patients are lower the greater the severity of the cognitive impairments associated with the disease, and PDD patients tend to have much lower scores on these screening tests when compared to those without dementia. In addition, these comparisons also prove that the differences in the scores found in the two groups in the NC5MPA are significantly important ($p$-value = 0.0000), when “probably demented” patients presented lower scores than the “nondemented” ones. These differences remain significantly relevant when comparing the summed scores obtained in the NC5MPA and CDT, both in qualitative and quantitative analyses, presenting in both cases lower scores in the “probably demented” group.

Regarding one of the main objectives of the study, as evidenced, the small number of patients in the sample with CDR-GS = 0 made it impossible to carry
out an analysis of the sensitivity and specificity of the tests performed about the occurrence of MCI (CDR-GS ≥0.5) in PD patients, as much for the NC5MPA, for the MoCA or the MMSE. Several factors may have contributed to this aspect of the study: the patients collected, in order to avoid the risk of collecting data from patients who might not have PD, patients selected had more than 4 years from the onset of motor symptoms of the disease. According to the most recent studies, PD patients present cognitive alterations since the earlier stages of the disease, even being able to present MCI, leading to a minority of the patients having the diagnosis of not having cognitive disorders, as attested by CDR-GS = 0.39-83. Additionally, patient data were collected, in large part, during the COVID-19 pandemic, where many clinics restricted the number of patients. Also, generally, more severely affected patients had a lower rate of missed appointments than those less compromised, where, in this case, the literature corroborates that the risk of PD patients to present cognitive alterations, especially dementia, is directly proportional to the patients' motor impairment and disease severity84.

Regarding the relationship between the analyzed parameters and the probability of patients presenting CDR-GS ≥1, meaning the occurrence of PDD, most of the analyzed parameters had a positive correlation with the probability of PDD, with p-values < 0.05 (CI= 95%), including: age at interview, age at diagnosis, disease duration, educational level, mH&Y scale score, S&E scale score, where such correlations are similar to other previous studies showing that the risk for the development of dementia is directly proportional to the worsening of functional parameters and the progression of the disease48. However, certain parameters did not present a good correlation with PDD, such as: LEDD and
male gender. About these last parameters assessed, they were described in the literature as presenting a positive relationship to PDD. Table 3 also shows that, in this study, the correlation presented between the NC5MPA test and PDD was similar to one between the other tests analyzed, showing a good correlation as a screening test for PDD.

The CDT was included in the study because it showed in previous studies a good correlation with dementia, such as Alzheimer's Disease, as well as showing good sensitivity and specificity in some studies for the detection of cognitive impairments in PD, being even an important part of one of the analyzed scales, the MoCA, being a test that presents a great demand in cognitive domains, especially planning, three-dimensional analysis and visuospatial perception, analyzing subcortical brain structures with good accuracy. That means it can be assessed qualitatively or quantitatively.

Despite this, as shown in table 3, the analyzes proposed for the CDT, both qualitative and quantitative, did not show a good correlation with the occurrence of CDR-GS > 1, when used as isolated analyses, in the present study. This does not allow us to state that, in this case, the CDT in isolation is a good screening test for PDD.

When directly analyzed (graph 3 and table 4), the sensitivities, specificities and accuracies of the three tests involved, using an analysis through ROC curve and AUC, the sensitivities of the tests were very similar among them, with a slightly higher sensitivity of the test NC5MPA; however, this difference is not statistically significant with all, showing great sensitivity when we think about a screening test, where the main screening instruments used vary around 80% in sensitivity. In the specificity analyses, the NC5MPA test showed a significant superiority in
relation to the tests to which it was compared, which also happened when the
tests were compared in terms of accuracy. Statistically speaking, the NC5MPA
test also showed superiority in the PPV, in comparison to the others, in addition
to presenting a NPV similar to the MoCA test, by the current literature that shows
greater specificity and accuracy for PDD\cite{51}, where both show significant
superiority in these items in relation to the MMSE test. As a consequence, the
AUC (CI=95%) within the analyzed screening tests were statistically quite similar,
indicating that the NC5MPA showed to be good for PDD screening, presenting
some advantages at some points of the analysis.

In addition, in the analysis of the performance times (graphic 4) of the tests, the
NC5MPA presented itself faster in relation to the screening tests with which it was
compared, with the MMSE being the second fastest exam, followed lastly by the
MoCA. It is quite evident from the analysis of the graphic - the times within the
tests, establishing the average, maximum and minimum times performed, show
that the NC5MPA does not have an intersection with those the other tests
performed, testing that the test is much faster to carry out than the other
screening tests, proving to be a great tool in clinical practice for the diagnosis of
PDD. Regarding the times of the other screening tests with which the test
analyzed in this study was compared, they were similar to those seen in literature,
with the MoCA having times around 10 to 15 minutes and the Mini Mental State
Examination of around 5 to 10$^{13-90}$.

In the analysis of the parameters of the NC5MPA test and its correlation with
dementia (CDR-GS $\geq$ 1), the best cut-offs of the scores analyzed in terms of
accuracy, sensitivity and specificity (table 5) were 8 (sample median found), 7
and 9 (found through the ROC curves). The cut-offs showed a sensitivity
relationship directly proportional to the scores presented, but all the cut-offs showed satisfactory results. In the analysis of specificity and accuracy, values decreased as scores increased, showing an inversely proportional relationship, but specificity decreases significantly, being moderate in the cut-off below 8 and poor in the cut-off below 9. Assessing accuracy, the cut-off of 8 and 7 presented good results; however, in the cut-off of 9, it presented a substantial decrease, but with moderate accuracy. Thus, being used as a screening test, the cut-off of 9 would lead to a very low number of false negatives, but a greater possibility of false positives. This would indicate that a patient with scores $\geq 9$ to have a very small possibility to present dementia. Based on the accuracies and specificities analyzed, the best cut-off to be considered would be $\leq 7$, as it has satisfactory accuracy and specificity, without presenting a significant drop in sensitivity that would compromise the tests as a screening test for dementia, avoiding many false negatives, in addition to presenting the best accuracy among the analyzed values.

The characteristics of the data found allow us to make some considerations. When the patients present NC5MPA $\geq 9$, theoretically, there is a very small chance that these patients present PDD, whereas, when a cut-off $\leq 8$, the patient has a moderate chance of actually having dementia. However, in this case, it would deserve a more detailed investigation, as it has a lower sensitivity than the cut-off of 9 points, but still showing good sensitivity in terms of screening tests. Finally, when presenting a cut-off $\leq 7$, all patients should be referred to an assessment to diagnose a possible dementia, and start treatment if confirmed. This is because they have a low probability of presenting false positives, with good sensitivity, which is still acceptable for a screening test in clinical practice.
Therefore, it is possible to trace three “alert stages” for the studied cut-offs: (1) “green” alert stage with a cut-off greater than or equal to 9, with a low chance of presenting dementia; (2) “yellow” alert stage, with a cut-off of 8, deserving greater attention for a more detailed assessment in an attempt to exclude dementia; and (3) a “red” alert stage, with a cut-off \( \leq 7 \) where the patient must be referred to a detailed assessment of this dementia condition. In the case of a score equal to 8, one of the screening tests reported here can be used, previously associated with the MMSE, the MoCA even the MDRS (figure 2 – “traffic light model”).

<table>
<thead>
<tr>
<th>Cortes</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS ( \leq 8 )</td>
<td>35/42 (83.3%)</td>
<td>39/56 (69.6%)</td>
<td>74/98 (75.5%)</td>
</tr>
<tr>
<td>NINDS ( \leq 7 )</td>
<td>33/42 (78.7%)</td>
<td>46/56 (85.7%)</td>
<td>81/98 (82.6%)</td>
</tr>
<tr>
<td>NINDS ( \leq 9 )</td>
<td>37/42 (88.1%)</td>
<td>30/56 (53.5%)</td>
<td>67/98 (68.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scale</th>
<th>Area (CMH)</th>
<th>( \cdot \ p )</th>
<th>Cutoff</th>
<th>(5) ROC curve</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>PPV</th>
<th>NPV</th>
<th>Kappa (p-value)</th>
<th>mean time (ICEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS</td>
<td>0.84 (0.78 - 0.94)</td>
<td>( p = 0.001 )</td>
<td>( \leq 7 )</td>
<td>( 70 )</td>
<td>( 93 )</td>
<td>( 59 )</td>
<td>( 84 )</td>
<td>( 82 )</td>
<td>( 84 )</td>
<td>( 0.84 )</td>
<td>( 0.84 )</td>
</tr>
</tbody>
</table>

Figure 2 – Traffic light model to address the probabilities of dementia occurrence and the need for further neuropsychological approaches in patients with Parkinson's Disease, based on the results obtained in the NINDS-CSN 5 minutes protocol cognitive screening test.

Thinking that the CDT would be a good option when associated with the NC5MPA test increasing the specificity and/or sensitivity of the test, two types of analyses were performed, one of them starting from a bivariate analysis transforming quantitative tests into qualitative data, as well as transforming them into summed quantitative data and assessing the specificity, sensitivity and
accuracy (table 5). The analysis did not show significant advantages in using the CDT associated with NC5MPA, because, despite having increased sensitivity, but not significantly, the test led to a substantial decrease in specificity, accuracy and PPV, with no significant change in the NPV, when compared to the NC5MPA test, in isolated administration. Additionally, the analysis of the test associated with the CDT significantly increased the test performance time. However, even so, it was below the times of the other screening tests to which it was compared (graph 5).

Also, in many previous studies carried out in Brazil, educational level had substantial interference in the results of cognitive screening tests, which can interfere with the sensitivity, specificity and accuracy of the tests (54). The results of our study (graphs 6, 7 and 8 and tables 7, 8 and 9), after dividing our sample by three education levels, were significantly affected by the substantial decrease in the number of patients, especially in the range between 5 to 8 years of schooling, where there were only 10 patients of the 98 patients in this analysis range. This led to a great instability of the ROC curve, making it not possible to safely consider this sample for the analysis. Nevertheless, the curves for the ranges of \( \leq 4 \) years of schooling and of \( \geq 8 \) years of schooling remained stable for all tests administered, making it possible to assess the interference of schooling on the tests performed. Comparing groups with \( \leq 4 \) years of schooling to those with \( \geq 8 \), there was a significant decline in sensitivity, but no changes in specificity or accuracy, with a significant decline in PPV and an improvement in NPV. However, we reiterate that, in this study, this analysis was greatly affected by the number of patients in each sample and we consider, therefore, that we cannot draw us to a safe conclusion about whether the accuracy of the analyzed
test would be affected by the education level of the patients. Previous studies have already been proven for the other tests with which the NC5MPA was compared\textsuperscript{91-92,54-93}.

Another important point to consider is that the NC5MPA test does not have an assessment where the patient needs to perform motor tasks, such as drawing, writing or other manual exercises, which is something that can also be quite advantageous for the assessment of patients with dementia. It is known that PDD patients generally have more evident motor impairment and reduced functionality, often with UPDRS phase 3 scale scores higher than the population without dementia and lower scores on the S&E functional scale. Therefore, patients with dementia are more likely to be in an advanced stage of disease, to have less schooling, to have more severe motor conditions during assessment, to have predominantly rigid-akinetic motor conditions and less responsive to levodopa, and to have functionality more impaired\textsuperscript{48-94}. For this reason, having a scale that is easier to understand, quicker and easier to perform and that does not require motor activity during the assessment, seems to be quite advantageous for clinical practice.

The population of the present study, which was 98 patients at the end, as a whole, suffered major setbacks due to the COVID-19 pandemic which began in Brazil in March, 2020. However, the decrease in the circulation of people and even the closure of outpatient clinics for face-to-face consultations at the beginning of the pandemic and even the very important decrease in the number of circulating patients led to a decrease in the prospective number of patients for the study, which predicted more than 100 patients. This had a greater impact on some statistics and conclusions that were expected from the study. Despite that,
many of the conclusions drawn appear to be statistically satisfactory and to support our initial suspicions.
Conclusions
Conclusions

The NC5MPA test shows sensitivity comparable to other cognitive screening tests and shows superior accuracy and specificity to the other tests to which it has been compared for the detection of PDD. In addition, the study also showed that the NC5MPA is faster and easier to apply than the other proposed tests, which takes longer to perform and some exercises may be affected by the severity of the patient's motor condition.

However, it was not possible to reach the conclusion that the test is satisfactory for the detection of MCI in Parkinson's disease. Neither was it possible to reliably detect whether the test is influenced by educational level in the detection of dementia and the MCI in PD, due to the sample size in this study. Furthermore, the addition of the CDT did not appear to increase the sensitivity, specificity, and accuracy of the test, and it did unnecessarily increase the time to administer the test.

Thus, the NC5MPA test appeared to be a good one in the detection of PDD. However, other tests with larger populations should be performed in order to specifically investigate the efficiency of this screening test for the detection of patients with MCI in PD, as well as to elucidate whether the educational level can substantially interfere in the accuracy of the test for detection of MCI and PDD.
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Appendix

Appendix 1- Approval of ethics committees via Plataforma Brasil of both Universities included in the study - Federal University of São Paulo – UNIFESP / São Paulo State University - UNESP.

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Titulo da Pesquisa: Comparação entre as ferramentas de avaliação National Institute of Neurological Disease and Stroke-Canadian Stroke Network (NINDS-CSN) 5-minute protocol, Montreal Cognitive Assessment (MoCA) e Mini Exame do Estado Mental como rápido rastreio cognitivo para Demência na Doença de Parkinson na população brasileira.

Pesquisador: Igor de L. Teixeira
Área Temática: 
Versão: 5
CAAE: 13388919.9.1001.5505
Instituição Proponente: Escola Paulista de Medicina
Patrocinador Principal: Universidade Federal de São Paulo
Conclusões ou Pendências e Lista de Inadequações:
Emenda aprovada.
Situacao do Parecer:
Aprovado
PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Comparação entre as ferramentas de avaliação National Institute of Neurological Disease and Stroke-Canadian Stroke Network (NINDS-CSN) 5-minute protocol, Montreal Cognitive Assessment (MoCA) e Mini Exame do Estado Mental como rápido rastreio cognitivo para Demência na Doença de Parkinson na população brasileira.

Área Temática:
Versão: 1
CAAE: 13388919.9.2001.5411
Instituição Proponente: Departamento Neurologia, Psicologia e Psiquiatria
Patrocinador Principal: Universidade Federal de São Paulo
Pesquisa apresentado.

Considerações Finais a critério do CEP:
Conforme deliberação do Colegiado, em REUNIÃO ORDINÁRIA do Comitê de Ética em Pesquisa FMB/UNESP, realizada em 04/10/2021, do PROJETO de Pesquisa apresentado encontra-se APROVADO.
Appendix 2- Free and informed consent form given to patients to be signed before data collection.
4 - O paciente terá assistência permanente durante o estudo, ou mesmo após o término ou interrução do estudo, como paciente do Ambulatório de Neurologia - Transtornos do Movimento - UNIFESP/EPM.

5 - Caso ocorra qualquer problema ou dano pessoal comprovadamente decorrente dos procedimentos ou tratamentos aos quais o paciente será submetido, lhe será garantido o direito a tratamento gratuito na Unidade do e o paciente terá direito a Indenização do determinada pelo leilão.

6 - O paciente não receberá nenhuma compensação financeira relacionada à sua participação neste estudo. Da mesma forma, o paciente não terá nenhuma despesa pessoal em qualquer fase do estudo, incluindo exames e consultas.

7 - A qualquer momento, se for de seu interesse, o paciente poderá ter acesso a todas as informações obtidas a seu respeito nesta pesquisa, ou a respeito dos resultados gerais do estudo.

8 - Quando o estudo for finalizado, o paciente será informado sobre os resultados gerais e conclusões obtidas no estudo.

9 - Em qualquer etapa do estudo, o paciente terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventualidades. O principal Investigador é o Dr. Igor de Lima e Telles, que pode ser encontrado no endereço: Rua Pedro de Toledo 65a, Vila Clementino, SBo Paulo/SP, Telefone (11) 50B9-9200. Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o C. M. de Etica em Pesquisa da Unifesp - Rua Prof. Francisco de Castro, 55 - CEP: 04020-050 - Vila Clementino - Telefone: (11) 5571-1062, Fax: (11) 5535-7162 - E-mail: cceo4unifesp edu br A.

DECLARAÇÃO DO PARTKIPAMTE

DECLARO, POR MEIO DESTE TERMO, QUE CONCORDEI EM SER ENTREVISTADO (A) E/OU PARTICIPAR NA PESQUISA DE CAMPO REFERENTE À PESQUISA INTITULADA "COMPARA ENTRE AS FERRAMENTAS DE AVALIAÇÃO, CNS-FVFI/OS S MINUTES PROTOCOL, MOCA/TREAT COGNITIVE A:SESs sENT (MOCA) E MINI EXAME DO ESTADO MENTAL COMO SUÍPIDO RASTREIO COGNITIVO PARA DEMÊNCIA NA DÉNCEA DE PARKINSON (DP) NA POPULAR BRASILEIRA", DESENVOLVIDA POR SETOR DE TRANSTORNOS DO MDVIMENTO - NEUROLOGIA UNIFESP/EPM.

Fui ardentemente(a), ainda, de que a pesquisa é coordenada por Dr. Igor de Lima e Teixeira, a quem poderei comatar / consultar a qualquer momento que julgar necessário através do e-mail IPortelxelranerro@tpmall.com.

Afirmo que aceitei participar por minha própria vontade, sem receber qualquer Incenlvido financiado ou ter qualquer Onus e com a finalidade exclusiva de colaborar para o sucesso da pesquisa.
Fui informado(a) dos objetivos estritamente acadêmicos do estudo, que foram acima esclarecidos. Fui também esclarecido(a) de que os usos das informações por mim oferecidas estão submetidos às normas éticas destinadas à pesquisa envolvendo seres humanos, da Comissão Nacional de Ética em Pesquisa (CONEP) do Conselho Nacional de Saúde, do Ministério da Saúde. Minha colaboração se fará de forma anônima, por meio entrevistas e emprego de escalas de rastreio cognitivo. O acesso e a análise dos dados coletados se farão apenas pelo(a) pesquisador(a) e/ou seu(s) orientador(es) / coordenador(es).

Fui ainda informado(a) de que posso me retirar desse(a) estudo a qualquer momento, sem prejuízo para meu acompanhamento ou sofrer quaisquer sanções ou constrangimentos. Atesto recebimento de uma cópia assinada deste Termo de Consentimento Livre e Esclarecido, conforme recomendações da Comissão Nacional de Ética em Pesquisa (CONEP).

São Paulo, ___ de ________________ de ______

NOME DO(A) PESquisador(A): ______________________________

Assinatura do(a) pesquisador(a): ______________________________

NOME DO(A) PARTICIPANTE: ______________________________

Assinatura do(a) participante: ______________________________

NOME DO(A) TESTEMUNHA(A): ______________________________

Assinatura do(a) testemunha(a): ______________________________

UNIFESP

Universidade Federal de São Paulo

1933
Appendix 3- Beck Depression Scale – Portuguese Version.

Inventário de Depressão de Beck

Nome: ____________________________  Idade: ______  Estado Civil: __________
Profissão: ______________________  Escolaridade: ______  Data de aplicação: ________  Pontuação: ______

Instruções

Neste questionário existem grupos de afirmações. Por favor leia cuidadosamente cada uma delas. A seguir selecione a afirmação, em cada grupo, que melhor descreve como se sentiu NA SEMANA QUE PASSOU, INCLUINDO O DIA DE HOJE. Desenhe um círculo em torno do número ao lado da afirmação selecionada. Se escolher dentro de cada grupo várias afirmações, faça um círculo em cada uma delas. Certifique-se que leu todas as afirmações de cada grupo antes de fazer a sua escolha.

1. 0 Não me sinto triste.
                1 Sinto-me triste.
                2 Sinto-me triste o tempo todo e não consigo evitá-lo.
                3 Estou tão triste ou infeliz que não consigo suportar.

6. 0 Não me sinto que esteja a ser punido(a).
                1 Sinto que posso ser punido(a).
                2 Sinto que mereço ser punido(a).
                3 Sinto que estou a ser punido(a).

2. 0 Não estou particularmente desencorajado(a) em relação ao futuro.
                1 Sinto-me desencorajado(a) em relação ao futuro.
                2 Sinto que não tenho nada a esperar.
                3 Sinto que o futuro é sem esperança e que as coisas não podem melhorar.

7. 0 Não me sinto desapontado(a) comigo mesmo(a).
                1 Sinto-me desapontado(a) comigo mesmo(a).
                2 Sinto-me desgostoso(a) comigo mesmo(a).
                3 Eu odeio-me.

3. 0 Não me sinto fracassado(a).
                1 Sinto que falhei mais do que um indivíduo médio.
                2 Quando analiso a minha vida passada, tudo o que vejo é uma quantidade de fracassos.
                3 Sinto que sou um completo fracasso.

8. 0 Não me sinto que seja pior que qualquer outra pessoa.
                1 Crítico-me pelas minhas fraquezas ou erros.
                2 Culpo-me constantemente pelas minhas falhas.
                3 Culpo-me de todas as coisas más que acontecem.

4. 0 Eu tenho tanta satisfação nas coisas, como antes.
                1 Não tenho satisfações com as coisas, como costumava ter.
                2 Não consigo sentir verdadeira satisfação com alguma coisa.
                3 Estou insatisfeito(a) ou entediado(a) com tudo.

9. 0 Não tenho qualquer ideia de me matar.
                1 Tenho ideias de me matar, mas não sou capaz de as concretizar.
                2 Gostaria de me matar.
                3 Matar-me-ia-se tivesse uma oportunidade.

5. 0 Não me sinto particularmente culpado(a).
                1 Sinto-me culpado(a) grande parte do tempo.
                2 Sinto-me bastante culpado(a) a maior parte do tempo.
                3 Sinto-me culpado(a) durante o tempo todo.

10. 0 Não costumo chorar mais do que o habitual.
                1 Choro mais agora do que costumava fazer.
                2 Actualmente, choro o tempo todo.
                3 Eu costumava conseguir chorar, mas agora não consigo, ainda que queira.
i 1.
0 Não me viiTio mars do que costuiuva.
1 Fico abon'écido(a) ou irritado(a) iuais facilriante du do que costiuua.
2 Actualiuente, sinto-me peniamenteiuente iimtado(a).
3 Ja mo consiigo ficar iin4tado(a) cout as coisas que antes me iintavaui.

12.
0 Não perdi o interesse nas outras pessoas.
1 Iteresso-me inenos do que costuiuva pelas outras pessoas.
2 Perdi a maior parte do meu interesse nas outras pessoas.
3 Perdi todo o meu interesse nas outras pessoas.

13.
0 Toimo decisões coimo antes.
1 Adio as minhas decisões inais do que costuiuva.
2 Tenho maior dificuldade em toinhar decisões do que antes.
3 Ja náo consiigo toinhar qualquer decisão.

14.
0 Não sinto que a minha aparência seja pior do que costuiuva ser.
1 Preocupo-me porque estou a parecer velho(a) ou nada atraente.
2 Sinto que ha liudan9as penneuete na niin9ia aparência que rue tomain nada atraente.
3 Considero-rue feio(a).

15.
0 Não sou capaz de trabalhar tao bem coimo antes.
1 Preciso de uin esfor9o extra para coiu9ar qualquer coisa.
Tenho que me for9ar iuuito para fazer quialquer coisa.
3 Náo consiigo fazer nenhum trabalho.

16.
0 Diuwo tño bein coimo habitualmente.
1 Não daivo tao beui conio costuiuiava.
2 Acordo 1 ou 2 horas antes que o habitual e teiemo dificuldade em viuotar a adonnecer.
3 Acordo várias vezes inais cedo du que costuiuva e uao cousigo viuotar a donnir.

Total: ______  Classificação: ____________________________
Appendix 4- Schwab & England Scale of Functionality in Parkinson’s Disease.

Escala de Atividades Diárias de Schwab e England

100% - Completamente independente. Capaz de realizar todas as atividades diárias sem lentidão, dificuldade ou comprometimento. Essencialmente normal.


80% - Completamente independente na maioria das atividades. Demora o dobro. Consciente da dificuldade e lentidão.

70% - Não completamente independente. Maior dificuldade em algumas atividades. Três a quatro vezes mais demorado em algumas. Pode gastar uma grande parte do dia com elas.

60% - Alguma dependência. Pode realizar a maioria das atividades, mas é excessivamente lento e faz muito esforço. Algumas impossíveis.

50% - Mais dependente. Metade das atividades com auxílio, mais lento. Dificuldade com tudo.

40% - Muito dependente. Participa de todas as atividades, mas poucas sozinho.

30% - Com esforço consegue realizar poucas atividades, ou iniciá-las sozinho. Necessita de muito auxílio.

20% - Nada realiza só. Pode ser auxiliado em algumas atividades. Invalidez severa.

10% - Totalmente dependente, desamparado. Completamente inválido.

0% - Ausência de controle de funções vegetativas como deglutição, micção e evacuação.
Appendix 5- Modified Hoehn & Yahr Scale of Disability in Parkinson's Disease.

Escala de Estadiamento de Hoehn e Yahr Modificada

- Estágio 0 = Nenhum sinal da doença.
- Estágio 1 = Doença unilateral.
- Estágio 1,5 = Envolvimento unilateral e axial.
- Estágio 2 = Doença bilateral, sem comprometimento do equilíbrio.
- Estágio 2,5 = Doença bilateral leve, com recuperação no teste de puxar o paciente pelas costas.
- Estágio 3 = Doença bilateral leve a moderada; alguma instabilidade postural; fisicamente independente.
- Estágio 4 = Incapacidade severa; ainda capaz de andar ou permanecer em pé sem assistência.
- Estágio 5 = Restrito a cadeira de rodas ou ao leito. Necessita de ajuda.
**Appendix 6**- National Institute of Neurological Disease and Stroke-Canadian Stroke Network (NINDS-CSN) – 5 Minute Protocol Assessment (NC5MPA) – translated to Portuguese.

### National Institute of Neurological Disease and Stroke-Canadian Stroke Network (NINDS-CSN) 5-minute protocol

1. **Memória** – "Repita as palavras que eu lhe disser":

<table>
<thead>
<tr>
<th>Memória</th>
<th>Rosto</th>
<th>Voluto</th>
<th>Igreja</th>
<th>Margarida</th>
<th>Vermelho</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leia a lista de palavras, o sujeito de repetição, faça duas tentativas. Evocar após 5 minutos</td>
<td>1ª tentativa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2ª tentativa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Orientação** (número de pontos é igual ao total de acertos):

<table>
<thead>
<tr>
<th>Dia do mês</th>
<th>Mês</th>
<th>Ano</th>
<th>Dia da semana</th>
<th>Lugar</th>
<th>Cidade</th>
</tr>
</thead>
</table>

3. **Flúência verbal – animais** – "Fale o máximo de nomes de animais que você souber em 1 minuto (mínimo 13 – 1 ponto):

   - 15 seg –
   - 30 seg –
   - 45 seg –
   - 60 seg –

4. **Evolução tardia**

   - Geração: [ ]
   - Nome: [ ]
   - Data: [ ]
   - Ponto total: [ ]

   **Pontuação final** [ ]/12

5. **Teste do Desenho do Cubo** – "Desenhe esta figura o mais parecido que você conseguir":

   ![Cubo]{}

   **Pontuação:**
Appendix 7- Montreal Cognitive Assessment (MoCA).
### Mini-Exame do Estado Mental

**Orientação Temporal Espacial** – questão 2.a até 2.j pontuando 1 para cada resposta correta, máximo de 10 pontos.

**Registros** – questão 3.1 até 3.d pontuação máxima de 3 pontos.

**Atenção e cálculo** – questão 4.1 até 4.f pontuação máxima 5 pontos.

**Lembrança ou memória de evocação** – 5.a até 5.d pontuação máxima 3 pontos.

**Linguagem** – questão 5 até questão 10, pontuação máxima 9 pontos.

### Identificação do cliente

Nome: 
Data de nascimento/idade: 
Sexo: 
Escolaridade: Analfabeto ( ) 0 à 3 anos ( ) 4 à 8 anos ( ) mais de 8 anos ( )
Avaliação em: ____/____/____ Avaliador: 

<table>
<thead>
<tr>
<th>Pontuações máximas</th>
<th>Pontuações máximas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Orientação Temporal Espacial</strong></td>
<td><strong>Linguagem</strong></td>
</tr>
<tr>
<td>1. Qual é o (a) Dia da semana?</td>
<td>5. Aponte para um lápis e um relógio. Faça o paciente dizer o nome desses objetos conforme você os aponta</td>
</tr>
<tr>
<td>Dia do mês?</td>
<td>______</td>
</tr>
<tr>
<td>Mês?</td>
<td>1</td>
</tr>
<tr>
<td>Ano?</td>
<td>1</td>
</tr>
<tr>
<td>Hora aproximada?</td>
<td>1</td>
</tr>
<tr>
<td>Local?</td>
<td>______</td>
</tr>
<tr>
<td>Instituição (casa, rua)?</td>
<td>1</td>
</tr>
<tr>
<td>Bairro?</td>
<td>1</td>
</tr>
<tr>
<td>Cidade?</td>
<td>1</td>
</tr>
<tr>
<td>Estado?</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Registros</strong></th>
<th><strong>(Ignore erros de ortografia ao marcar o ponto)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mencione 3 palavras levando 1 segundo para cada uma. Peça ao paciente para repetir as 3 palavras que você mencionou. Estabeleça um ponto para cada resposta correta.</td>
<td>8. Faça o paciente ler e obedecer ao seguinte: FECHOS OLHOS.</td>
</tr>
<tr>
<td>-Vaso, carro, tijolo</td>
<td>9. Faça o paciente escrever uma phrase de sua própria autoria. (A frase deve conter um sujeito e um objeto e fazer sentido).</td>
</tr>
<tr>
<td>______</td>
<td>______</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Atenção e cálculo</strong></th>
<th><strong>(Ignore erros de ortografia ao marcar o ponto)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sete seriado (100-79=3-7=86-7=79-7=72-7=65) Estabeleça um ponto para cada resposta correta. Interrumpa a cada cinco respostas. Ou soletar apalavra MUNDO de trás para frente.</td>
<td>10. Copie o desenho abaixo. Estabeleça um ponto se todos os lados e ângulos forem preservados e se os lados da interseção formarem um quadrilátero.</td>
</tr>
<tr>
<td>______</td>
<td>______</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Lembranças (memória de evocação)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pergunte o nome das 3 palavras aprendidos na questão 2. Estabeleça um ponto para cada resposta correta.</td>
</tr>
<tr>
<td>______</td>
</tr>
</tbody>
</table>
# Appendix 9 – Clinical Dementia Rating Scale (CDR) – Portuguese Version.

**AVALIAÇÃO CLÍNICA DA DEMÊNCIA – CLINICAL DEMENTIA RATING (CDR)**

<table>
<thead>
<tr>
<th>NOME:</th>
<th>DATA DA AVALIAÇÃO:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>SAUDÁVEL</th>
<th>DEMÊNCIA QUESTIONÁVEL</th>
<th>DEMÊNCIA LEVE</th>
<th>DEMÊNCIA MODERADA</th>
<th>DEMÊNCIA GRAVE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEMÓRIA</strong></td>
<td>CDR 0</td>
<td>CDR 0.5</td>
<td>CDR 1</td>
<td>CDR 2</td>
<td>CDR 3</td>
</tr>
<tr>
<td></td>
<td>Sem perda da memória, ou apenas esquecimento discreto e inconsistente</td>
<td>Esquecimento leve e consistente; lembrança parcial de eventos; esquecimento &quot;benigno&quot;</td>
<td>Perda de memória moderada, mais acentuada para fatos recentes, o déficit interfere com atividades do dia-a-dia</td>
<td>Perda de memória grave; apenas material muito aprendido é retido; materiais novos são rapidamente perdidos</td>
<td>Perda de memória grave; apenas fragmentos permanecem</td>
</tr>
<tr>
<td><strong>ORIENTAÇÃO</strong></td>
<td>Plenamente orientado</td>
<td>Plenamente orientado</td>
<td>Dificuldade moderada com as relações do tempo; orientação no espaço, no exame, mas pode ter desorientação geográfica em outros locais</td>
<td>Geralmente desorientado</td>
<td>Orientação pessoal apenas</td>
</tr>
<tr>
<td><strong>JULGAMENTO E SOLUÇÃO DE PROBLEMAS</strong></td>
<td>Resolve bem problemas do dia-a-dia, julgamento crítico é bom em relação ao desempenho passado</td>
<td>Leva comprometimento na solução de problemas, semelhanças e diferenças</td>
<td>Dificuldade moderada na solução de problemas, semelhanças e diferenças; julgamento social geralmente mantido</td>
<td>Gravemente comprometido para solução de problemas, semelhanças e diferenças; julgamento social geralmente comprometido</td>
<td>Incapaz de resolver problemas ou de ter qualquer julgamento crítico</td>
</tr>
<tr>
<td><strong>ASSUNTOS DA COMUNIDADE</strong></td>
<td>Função independente nas atividades de trabalho, compras, negócios, finanças e grupos sociais</td>
<td>Leva dificuldade nas atividades</td>
<td>Incapaz de funcionar independentemente nas atividades, embora ainda possa desempenhar algumas; pode parecer normal na avaliação inicial</td>
<td>Sem possibilidade de desempenho fora de casa; parece suficientemente bem para ser levado a atividades fora de casa</td>
<td>Sem possibilidade de desempenho fora de casa; parece muito doente para ser levado a atividades fora de casa</td>
</tr>
<tr>
<td><strong>LAR E PASSATEMPOS</strong></td>
<td>Vida em casa, passatempos e interesses intelectuais mantidos</td>
<td>Vida em casa, passatempos e interesses intelectuais levemente afetados</td>
<td>Comprometimento leve mais evidente em casa; abandono de tarefas mais difíceis; passatempos e interesses mais complicados são abandonados</td>
<td>Só realiza tarefas mais simples, interesses muito limitados e pouco mantidos</td>
<td>Sem qualquer atividade significativa em casa</td>
</tr>
<tr>
<td><strong>CUIDADOS PESSOAIS</strong></td>
<td>Plenamente capaz</td>
<td>Plenamente capaz</td>
<td>Necessita de assistência ocasionais</td>
<td>Requer assistência no vestir e na higiene</td>
<td>Requer muito auxílio nos cuidados pessoais. Geralmente incapaz</td>
</tr>
</tbody>
</table>

**Escore final:**

Assinatura e carimbo do médico

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