



Normative values of the Rao's Brief Repeatable Battery in an Italian young adolescent population: the influence of age, gender, and education

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Abstract

Aim The Brief Repeatable Battery of Neuropsychological Tests (BRB) is frequently used to estimate cognitive function in adults with multiple sclerosis (MS), while it has been included in few studies on young MS, also because of the absence of normative values. We aim to evaluate the impact of age, gender, and education on BRB scores in a young adolescent population.

Methods We administered the BRB to 76, 14-to-17-year-old, healthy subjects. Linear regression models were used to assess the impact of age, gender, and education on sub-test scores. When statistically significant ($p < 0.05$), we used the regression coefficient to correct the raw scores.

Results Younger age was associated with better performance on SPART ($\beta = -2.54$; $p < 0.05$) and SPART-D ($\beta = -1.06$; $p < 0.05$). Male gender was associated with better performance on SPART ($\beta = 3.40$; $p < 0.05$), SPART-D ($\beta = 1.41$; $p < 0.05$), PASAT-3 ($\beta = 5.58$; $p < 0.05$), and PASAT-2 ($\beta = 5.07$; $p < 0.05$). Educational attainments were associated with better performance on SPART ($\beta = 3.23$; $p < 0.05$) and SPART-D ($\beta = 1.28$; $p < 0.05$). Cut-off points were suggested at the 5th lowest percentile.

Interpretation Age, gender, and education must be accounted for when applying the BRB to young population. Present results can prove useful for future clinical and research applications in adolescent MS patients.

Keywords Multiple sclerosis · Cognitive · Cognition · Rao · Pediatric

Introduction

Five percent people with multiple sclerosis (MS) have disease onset before 18 years-old, mainly in adolescence [1].

Cognitive symptoms are quite common in juvenile-onset MS, ranging from 55% in patients without any psychiatric comorbidity, to 80% among those suffering from anxiety or mood disorder [1, 2]. Cognitive performances deteriorate over time in both adult and young MS patients, but progression is more heterogeneous in pediatric patients, when compared with adults, and is frequently not related to progression of physical disability [3, 4]. Some young MS patients present with higher potential for compensation and improvement over time, compared with others whose cognitive impairment will affect them in the long term [5].

A number of neuropsychological batteries have been used to assess cognitive function in pediatric age (e.g., developmental NEUROPSYCHOLOGICAL assessment II and Brief Neuropsychological Battery for Children) [6, 7]. However, the main drawback is the lack of cut-off values in young population. Not least, the ideal neuropsychological battery should include reliable and reproducible tests, and should be used consistently during long-term follow-

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up (from pediatric to adult age). Among currently available neuropsychological batteries, the Brief Repeatable Battery of Neuropsychological Tests (BRB) was specifically developed for evaluating people with MS and is characterized by short duration (20–30 min) and high sensitivity (71%) and specificity (94%) in detecting cognitive impairment [8–10]. To date, the application of the BRB is limited to adult population where the impact of age, gender, and education has been assessed and cut-off points have been defined [11]. In pediatric MS, tests derived from the BRB have been frequently used [12–15], are associated with MS clinical features [12], and their psychometric properties are related to global cognitive functioning (IQ), as measured with the Wechsler Intelligence Scale [13]. As such, tests from the BRB would be potentially able to detect cognitive dysfunction in a relatively short time, when compared with IQ tests, but their use in young-onset MS is limited by the absence of normative values. Since “pediatric” age of onset of early MS is largely in adolescence, we aim (i) to assess the impact of age, gender, and education on cognitive performance assessed through the BRB, (ii) to provide raw score corrections with regard to such factors, and (iii) to estimate cut-off points for BRB in young adolescence.

Materials and methods

Study design and population

This is a cross-sectional observational study. The Federico II University of Naples ethics committee approved the study. Subjects were voluntarily recruited at three different high schools in Naples, Italy. Included subjects and their parents gave written informed consent to the research and to publication of the results.

We included 14-to-17-year-old healthy subjects. Exclusion criteria were the following: history of learning disabilities, serious head injury, visual/hearing dysfunction, concomitant neurological/psychiatric illness, or drug/alcohol abuse. Demographic characteristics of the recruited population are shown in Table 1.

Table 1 Demographic features of the study sample

	Total (n = 76)
Male/female	31/45
Age, years (mean ± SD)	15.81 ± 1.61
Education, years (mean ± SD)	10.61 ± 1.46

SD standard deviation

Neuropsychological test

Two neuropsychologists examined the subjects. They were trained together for data recording and scoring procedures, in order to uniform criteria of administration. We used a previously validated Italian translation of the BRB (version A) [16]. Administration of the whole battery took about 30 min.

Briefly, the BRB included neuropsychological tests evaluating the following:

Verbal learning, using the selective reminding test (SRT), which includes a measurement of long-term storage (SRT-LTS), its consistent retrieval (SRT-CLTS), and its delayed recall (SRT-D) [17];

Visuospatial learning, using 10/36 spatial recall test (SPART) and its delayed recall (SPART-D) [18];

Attention and processing speed, using the symbol digit modalities test (SDMT) [19], and the paced auditory serial addition test (PASAT) with a rate of number presentation of 3 (PASAT-3) and 2 s (PASAT-2) [20];

Verbal fluency, using the word list generation (WLG) [8].

Tests were administered in a standardized manner, during daytime, in a quiet room, and in a fixed order: SRT, SPART, SDMT, PASAT-3, PASAT-2, SRT-D, SPART-D, and WLG.

Statistical analysis

To evaluate factors impacting on cognitive performance, we used linear regression models using age, gender, and education in turn as possible predictors, and each test score as dependent variable, as previously done in adults [21]. When a significant association between test scores and each of the predictors was found ($p < 0.05$), the regression coefficients were used to calculate adjusted scores by applying the standard formula: corrected test score: raw score $- \beta$ age* (age—15.81) $- \beta$ education*(education—10.61) $- \beta$ gender, where β is the regression coefficient, 15.81 is the mean age, and 10.61 is the mean education.

After adjusting for the relevant demographic factors, we calculated the cut-off for each BRB score as [test score-(1.96*test standard deviation)], corresponding to the fifth percentile [11].

Considering the cross-sectional nature of the present study, conventional sample size/power calculation is impossible. Ninety-five percent confidence intervals (95% CI) were reported as an indirect measure of study power [22].

Results

Seventy-six healthy subjects were included in the study (Table 1). Raw scores on BRB are reported in Table 2.

Younger age was associated with better performance on SPART ($\beta = -2.54$; $p < 0.05$) and SPART-D ($\beta = -1.06$;

Table 2 BRB raw and adjusted scores and proposed cut-off points. The table shows BRB raw scores and scores adjusted for age, gender, and education (as necessary), with 95% confidence intervals (95% CI), and proposed cut-off points (at the lowest 5th percentile of adjusted scores)

Test	Raw score \pm SD [95% CI]	Adjusted score \pm SD [95% CI]	5th percentile
SRT-LTS	52.95 \pm 9.87 [50.73–55.17]	–	36.75
SRT-CLTR	44.84 \pm 12.41 [42.05–47.63]	–	25.50
SRT-D	9.86 \pm 1.87 [8.97–9.77]	–	7.00
SPART	24.29 \pm 4.56 [23.26–25.31]	20.90 \pm 4.35 [19.93–21.89]	14.36
SPART-D	8.76 \pm 1.82 [8.35–9.17]	7.36 \pm 1.75 [6.97–7.75]	3.99
SDMT	59.80 \pm 11.21 [57.28–62.32]	–	41.50
PASAT 3	43.42 \pm 10.33 [41.10–45.74]	40.35 \pm 9.73 [31.17–42.55]	24.27
PASAT 2	35.83 \pm 10.85 [33.39–38.27]	30.76 \pm 9.68 [28.58–32.94]	15.80
WLG	21.33 \pm 4.74 [20.26–22.40]	–	5.00

BRB, brief repeatable battery; SRT-LTS, selective reminding test long-term storage; SRT-CLTR, SRT consistent retrieval; SRT-D, SRT delayed recall; SPART, spatial recall test; SPART-D, SPART delayed recall; SDMT, symbol digit modalities test; PASAT, paced auditory serial addition test at 3 and 2 s; WLG, word list generation; SD, standard deviation; 95% CI, 95% confidence intervals

$p < 0.05$). Male gender was associated with better performance on SPART ($\beta = 3.40$; $p < 0.05$), SPART-D ($\beta = 1.41$; $p < 0.05$), PASAT-3 ($\beta = 5.58$; $p < 0.05$), and PASAT-2 ($\beta = 5.07$; $p < 0.05$). Educational attainments were associated with better performance on SPART ($\beta = 3.23$; $p < 0.05$) and SPART-D ($\beta = 1.28$; $p < 0.05$) (Table 3).

Table 2 shows mean scores and percentile values for BRB tests after correcting for relevant demographic factors; 95%CI are also reported as an indirect measure of study power [22].

Table 3 Significant predictors for BRB scores

Test	Significant predictors
SRT-LTS	–
SRT-CLTR	–
SRT-D	–
SPART	Age, $\beta = -2.54$ ($p < 0.05$) Male, $\beta = 3.40$ ($p < 0.05$) Education, $\beta = 3.24$ ($p < 0.05$)
SPART-D	Age, $\beta = -1.06$ ($p < 0.05$) Male, $\beta = 1.41$ ($p < 0.05$) Education, $\beta = 1.29$ ($p < 0.05$)
SDMT	–
PASAT 3	Male, $\beta = 5.58$ ($p < 0.05$)
PASAT 2	Male, $\beta = 5.07$ ($p = 0.02$)
WLG	–

β coefficients and p values are reported from statistically significant linear regression models using age, gender, and education in turn as possible predictors, and each test score as dependent variable

BRB, brief repeatable battery; SRT-LTS, selective reminding test long-term storage; SRT-CLTR, SRT consistent retrieval; SRT-D, SRT delayed recall; SPART, spatial recall test; SPART-D, SPART delayed recall; SDMT, symbol digit modalities test; PASAT paced auditory serial addition test at 3 and 2 s; WLG, word list generation

Discussion

The present study explored the impact of age, gender, and education on cognitive function, as measured with the BRB, in healthy adolescents under 18 years old. The BRB is increasingly used in the MS clinical practice but, to date, there are no normative data for young population. Juvenile-onset MS patients have a more unpredictable and, frequently, more aggressive disease course, when compared with adults [3]. Thus, identifying cognitive features of possible prognostic significance in early stages of the disease is extremely helpful for clinical and research purposes in pediatric MS [12, 23]. In particular, our findings underline that age, gender, and education significantly affect cognitive function in young adolescents, at different degree for each cognitive task. Also, we provided the first cut-off points for BRB in an Italian young adolescence population.

In our sample, gender was the most important variable affecting neuropsychological performance. In Italian adults, Amato and colleagues found a significant effect of gender on verbal fluency (for version A) and verbal learning (for version B), with females performing better than males [7]. In our study, as opposite to Amato and colleagues, males performed better on tasks that require spatial and attention abilities. This contrasting result might be explained by a different time of neurological maturation related to gender, with females generally outperforming males before the age of 10 years, but being overcome by males in young adulthood [24, 25]. Future studies will need to assess how the BRB is able to define trajectories in the developmental age, characterized by continuously-evolving cognitive function.

In our population, visuospatial learning was better in younger and more educated subjects. When compared with adults [11], age and education marginally influenced BRB scores in this young population. This is possibly due to the

homogenous age range (14–17 years) and educational background in our population that was recruited among high school students. In the future, young and adult populations could be included in the same study in order to obtain a full view on cognitive function throughout life and, not surprisingly, we could hypothesize a non-linear distribution of test scores [24, 25].

We need to acknowledge that the present study did not include neuropsychological tests other than those from the BRB; however, psychometric properties of the BRB have been previously explored, also in relation to the IQ [13]. We aimed to estimate normative values for an easy-to-administer battery, the BRB, that can be used to screen cognitive impairment in young MS patients, under 18 years old, and, then, can be used for monitoring of cognitive function through the life span. The sample was recruited from three schools within the same town (Naples, Italy), and the reproducibility of our results should be further evaluated in larger and more diverse Italian population; however, the students of the schools performed within the average, according to Italian rating agencies [26]. Sample size could be an issue, but was fairly larger than previous studies on similar topics [6]; more representative samples with larger age and educational span would allow to confirm normative values, avoiding the need for control groups when evaluating young MS patients' cognitive function.

In conclusion, we obtained cut-off scores through corrections for demographic variables, in an Italian adolescent population, for a widely used neuropsychological battery. In the future, the BRB could be used consistently in young and adult patients with MS for the clinical practice and research. More precise scoring of BRB might be helpful to evaluate cognitive function at diagnosis, and to monitor cognitive progression in relation to clinical variables and treatments.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

- Weisbrodt D, Charvet L, Serafin D, Milazzo M, Preston T, Cleary R, Moadel T, Seibert M, Belman A, Krupp L (2014) Psychiatric diagnoses and cognitive impairment in pediatric multiple sclerosis. *Mult Scler* 20:588–593. <https://doi.org/10.1177/1352458513504249>
- Goretti B, Portaccio E, Ghezzi A, Lori S, Moidola L, Falautano M, Viterbo R, Patti F, Vecchio R, Pozzilli C, Bianchi V, Cappiello S, Comi G, Trojano M, Amato MP, for the Multiple Sclerosis Study Group of the Italian Neurological Society (2012) Fatigue and its relationships with cognitive functioning and depression in paediatric multiple sclerosis. *Mult Scler J* 18:329–334. <https://doi.org/10.1177/1352458511420846>
- Yeh EA, Parrish JB, Weinstock-Guttman B (2011) Disease progression in pediatric multiple sclerosis: disparities between physical and neurocognitive outcomes. *Expert Rev Neurother* 11:433–440
- Hosseini B, Flora DB, Banwell BL, Till C (2014) Age of onset as a moderator of cognitive decline in pediatric-onset multiple sclerosis. *J Int Neuropsychol Soc* 20:796–804. <https://doi.org/10.1017/S1355617714000642>
- Nunan-Saah J, Paulraj SR, Waubant E, Krupp LB, Gomez RG (2015) Neuropsychological correlates of multiple sclerosis across the lifespan. *Mult Scler J* 21:1355–1364
- Ekmekci O (2017) Pediatric multiple sclerosis and cognition: a review of clinical, neuropsychologic, and neuroradiologic features. *Behav Neurol* 2017:1463570–1463511. <https://doi.org/10.1155/2017/1463570>
- Amato MP, Goretti B, Ghezzi A, Hakiki B, Niccolai C, Lori S, Moidola L, Falautano M, Viterbo RG, Patti F, Cilia S, Pozzilli C, Bianchi V, Roscio M, Martinelli V, Comi G, Portaccio E, Trojano M, On behalf of the MS Study Group of the Italian Neurological Society (2014) Neuropsychological features in childhood and juvenile multiple sclerosis: five-year follow-up. *Neurology* 83:1432–1438. <https://doi.org/10.1212/WNL.0000000000000885>
- Rao S, The Cognitive Function Study Group of the National Multiple Sclerosis Society (1990) A manual for the brief repeatable battery of neuropsychological tests in multiple sclerosis. Medical College of Wisconsin
- Rao SM, Leo GJ, Bernardin L, Unverzagt F (1991) Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology* 41:685–691. <https://doi.org/10.1212/WNL.41.5.685>
- Bever CT, Grattan L, Panitch HS, Johnson KP (1995) The brief repeatable battery of neuropsychological tests for multiple sclerosis: a preliminary serial study. *Mult Scler* 1:165–169. <https://doi.org/10.1177/135245859500100306>
- Amato MP, Portaccio E, Goretti B, Zipoli V, Ricchiuti L, de Caro MF, Patti F, Vecchio R, Sorbi S, Trojano M (2006) The Rao's brief repeatable battery and Stroop test: normative values with age, education and gender corrections in an Italian population. *Mult Scler* 12:787–793
- Lanzillo R, Chioldi A, Carotenuto A, Magri V, Napolitano A, Liuzzi R, Costabile T, Rainone N, Freda MF, Valerio P, Brescia Morra V (2016) Quality of life and cognitive functions in early onset multiple sclerosis. *Eur J Paediatr Neurol* 20:158–163. <https://doi.org/10.1016/j.ejpn.2015.08.005>
- Amato MP, Goretti B, Ghezzi A, Lori S, Zipoli V, Moidola L, Falautano M, de Caro MF, Viterbo R, Patti F, Vecchio R, Pozzilli C, Bianchi V, Roscio M, Martinelli V, Comi G, Portaccio E, Trojano M, For the Multiple Sclerosis Study Group of the Italian Neurological Society (2008) Cognitive and psychosocial features in childhood and juvenile MS: two-year follow-up. *Neurology* 70:1891–1897. <https://doi.org/10.1212/WNL.0b013e3181f4d821>
- Amato M, Goretti B, Ghezzi A et al (2010) Cognitive and psychosocial features of childhood and juvenile MS. *Neurology* 75:1134–1140. <https://doi.org/10.1212/01.wnl.0000346320.61178.56>
- Portaccio E, Goretti B, Lori S, Zipoli V, Centorrino S, Ghezzi A, Patti F, Bianchi V, Comi G, Trojano M, Amato MP, for the Multiple Sclerosis Study Group of the Italian Neurological Society (2009) The brief neuropsychological battery for children: a screening tool for cognitive impairment in childhood and juvenile multiple sclerosis. *Mult Scler* 15:620–626. <https://doi.org/10.1177/1352458508101950>
- Solari A, Mancuso L, Motta A, Mendozzi L, Serrati C (2002) Comparison of two brief neuropsychological batteries in people

- with multiple sclerosis. *Mult Scler* 8:169–176. <https://doi.org/10.1191/1352458502ms780aa>
17. Buschke H, Fuld PA (1974) Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology* 24:1019–1025
 18. Barbizet J, Cany E (1968) Clinical and psychometrical study of a patient with memory disturbances. *Int J Neurol* 7:44–54
 19. Smith A (1991) Symbol digit modalities test. Western Psychological Services
 20. Gronwall DMA (1977) Paced auditory serial-addition task: a measure of recovery from concussion. *Percept Mot Skills* 44:367–373. <https://doi.org/10.2466/pms.1977.44.2.367>
 21. Spinnler H, Tognoni G (1987) Standardizzazione e Taratura Italiana di Test Neuropsicologici. *Ital J Neurol Sci* 6:8–21
 22. Hoenig JM, Heisey DM (2001) The abuse of power: the pervasive fallacy of power calculations for data analysis. *Am Stat* 55(1–6): 19–24
 23. Moccia M, Lanzillo R, Palladino R, Chang KCM, Costabile T, Russo C, de Rosa A, Carotenuto A, Saccà F, Maniscalco GT, Brescia Morra V (2016) Cognitive impairment at diagnosis predicts 10-year multiple sclerosis progression. *Mult Scler* 22:659–667. <https://doi.org/10.1177/1352458515599075>
 24. Mous SE, Schoemaker NK, Blanken LME, Thijssen S, van der Ende J, Polderman TJC, Jaddoe VWV, Hofman A, Verhulst FC, Tiemeier H, White T (2016) The Association of gender, age, and intelligence with neuropsychological functioning in young typically developing children: the generation R study. *Appl Neuropsychol Child* 6:22–40. <https://doi.org/10.1080/21622965.2015.1067214>
 25. Rovio SP, Pahkala K, Nevalainen J, Juonala M, Salo P, Kähönen M, Hutri-Kähönen N, Lehtimäki T, Jokinen E, Laitinen T, Taittonen L, Tossavainen P, Viikari J, Rinne JO, Raitakari OT (2016) Cognitive performance in young adulthood and midlife: relations with age, sex, and education—the cardiovascular risk in young Finns study. *Neuropsychology* 30:532–542. <https://doi.org/10.1037/neu0000239>
 26. Fondazione Agnelli (2017) Eduscopio. <https://eduscopio.it/>. Accessed 3 Dec 2018