Cognitive reserve in the healthy elderly: cognitive and psychological factors

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ABSTRACT
Cognitive reserve (CR) helps explain the mismatch between expected cognitive decline and observed maintenance of cognitive functioning in older age. Factors such as education, literacy, lifestyle, and social networking are usually considered to be proxies of CR and its variability between individuals. A more direct approach to examine CR is through the assessment of capacity to gain from practice in a standardized challenging cognitive task that demands activation of cognitive resources. In this study, we applied a testing-the-limits paradigm to a group of 136 healthy elderly subjects (60–75 years) and additionally examined the possible contribution of complex mental activities and quality of sleep to cognitive performance gain. We found a significant but variable gain and identified verbal memory, cognitive flexibility, and problem-solving as important factors. This outcome is in line with our earlier study on CR in healthy mental aging. Interestingly and contrary to expectations, our analysis revealed that complex mental activities and sleep quality do not significantly influence CR. Best subset regression showed that better verbal memory and higher cognitive flexibility were related to high CR, which could also be seen when contrasting “high” and “low” cognitive performers; again, complex mental activities and sleep quality did not contribute to this measure of CR. In conclusion, the results of this study support and extend previous findings on CR in older age; further, they underline the need for improvements in existing protocols for assessing CR in a dynamic manner.

INTRODUCTION
The concept of cognitive reserve (CR) attempts to explain inter-individual variability in susceptibility to changes in brain function in pathological, but also normal aging of the brain [1,2]. In their model of CR, Satz et al. [3] proposed four factors (general intelligence (“g”), complex mental activity, processing resources, and executive function) as “potential reserve proxies” for CR in normal aging. Each of these factors encompasses one of several specific indicators that contribute to, or interact with CR. Examples of such factors include literacy and education, occupation, regular complex mental activities, and cohesiveness of social networks [4–8]. It is also plausible that other variables, such as mood [9] and quality of sleep [10] may also determine cognitive performance in older age. In addition, it should be noted that many of these putative CR-determining factors may be intercorrelated [11], and that they are influenced by individual life experiences and, thus, by developmental trajectories in early adulthood and middle age [12].

Since CR cannot be measured directly, the assessment of proxies is valuable; however, these proxies are likely to be static rather than dynamic representations of CR. From a conceptual and methodological perspective, it seems desirable to define and assess CR in a more direct fashion, e.g., by “forcing” subjects to activate their individual cognitive resources in a mentally challenging task. Such an approach would also fit into a model of task-related brain activity depending on the level of task demands, which helps to explain interindividual differences in the context of brain reserve and thus of the neural basis of CR [12]. Based on this framework, one would predict that subjects with higher functional brain reserve would also show higher performance in such a task because they can activate more cognitive resources in this condition. The gain in performance may thus represent a more valid proxy of CR because it is based on the dynamic use of implicitly existing CR, which cannot be determined validly in a one-trial assessment.
sensitive method to assess CR in this framework is the so-called testing-the-limits paradigm [14]. The use of the Digit Symbol Substitution Test (DSST), a multitasking cognitive measure [15], in a testing-the-limits paradigm with systematic repetition offers a way to assess CR in a dynamic way. In the following, we use the abbreviation CR to denote gains in the testing-the-limits paradigm, which serve as “intimate” proxies of CR. In our recent study that contrasted 140 younger with 140 older healthy subjects, all of whom had a similar level of education [16], we used such a paradigm to assess CR. The main outcome of that study was that systematic practice with DSST leads to significant gains in both age groups. Interestingly, although CR was significantly higher in the younger subjects, about 50% of older subjects showed similar CR values, suggesting that CR may, at least partly, represent an individual, age-independent factor. As predicted from the model of Satz et al. [3], CR was significantly associated with speed of information processing, verbal working memory, and problem-solving in the older group; no such associations were found in the younger group. Because DSST as a testing-the-limits paradigm has only been used in a few studies on mental aging research, and reproducibility is a “cornerstone of science” [17], we considered it important to demonstrate that this instrument is a valid and reliable measure of CR. In the current study, we therefore assessed CR with the same testing-the-limits paradigm in 136 healthy elderly subjects (age range: 60–75 years), all of whom had a similar high level of education (≥13 years of schooling). In addition, we examined the role of diverse cognitive and psychological variables in CR, i.e., cognitive architecture, mood, cognitive, social and physical activities, sleep quality, and well-being (quality of life and life satisfaction). According to the model of Satz et al. [3], complex mental activity, processing resources, and executive function represent core factors of CR. Complex mental activities (“cognitive lifestyle”) represent a significant factor for CR because they are associated with more favorable cognitive trajectories in older persons [4,6] and may even support reversal from mild cognitive impairment (MCI) to normal cognitive functioning [18]. Accordingly, our main hypotheses were that (1) subjects with higher processing resources and higher executive capacities will show higher CR, and (2) CR is positively correlated with cognitive lifestyles, mood, well-being, and sleep quality. To further elucidate the influence of these factors on CR, we performed linear best subset regression and contrasted high and low performers using an extreme-group comparison analysis.

MATERIALS AND METHODS

Participants

A total of 138 healthy elderly subjects aged between 60 and 75 years with at least 13 years of education (range: 13–21 years) participated in this study. Older subjects were recruited from senior university students enrolled at Ludwig-Maximilians-Universität (Munich); their relatives and friends served as further participants. Before admittance to the study, subjects were given a detailed telephone interview to screen for exclusion criteria, in particular neurological and mental disorders as well as non-correctable visual or auditory impairments and motor limitations of the dominant (right or left) hand. According to the Edinburgh handedness inventory [19], 97% of subjects were right-handed, three were left-handed, and three were ambidextrous. Two subjects were excluded due to incomplete data sets; thus, 136 participants (68 female, 68 male; age: M = 68.71 years, SD = 3.60 years) were studied in detail. All subjects had at least 14 years of education; thus, the influence of the level of education on cognitive architecture and CR was minimal. Each participant was tested with the Mini-Mental State Examination (MMSE of the CERAD-Plus; [20]) to exclude subjects with global cognitive impairment (MMSE ≤ 26 points). No subject scored lower than this cut-off due to prior verbal screening. In addition, detailed information on education and occupation, medical history, medication, smoking, and alcohol use was collected.

Assessment of cognitive and psychological variables

Cognitive measures: Cognitive architecture was assessed using standard one-time measurements in the following cognitive domains: cognitive multitasking (DSST; German version [21], number of correct symbols), verbal learning and long-term memory (word list memory and recall of the CERAD-Plus [20], number of correctly recalled items in three consecutive trials and after delay), verbal short-term and working memory (Digit Span forward and backward; WAIS-III, German version [21], number of correctly recalled digits), information processing speed/attention and cognitive flexibility (Trail Making Test, TMT, Parts A and B, of the CERAD-Plus [20], response time), interference (Stroop Color and Word Test, German Version [22], hits per 45 s for word and color conditions and for interference condition), verbal fluency (Regensburger Word Fluency Test, RWT [23], total number of correctly produced words for letters S, K, and M, within 1 min), visual problem-solving (matrix reasoning of the WAIS-III, German version [21], number of correct items), and reading performance (standard text of 200 words, measured in words per minute, wpm).

Psychological measures: The above-mentioned cognitive tests were complemented by assessments of mood (Geriatric Depression Scale, GDS, a 15-items short form, German version [24]), sleep quality (Pittsburgh Sleep Quality Index, PSQI; German translation [25]), quality of life (World Health Organization Quality of Life assessment instrument, short form, WHOQOL-BREF, German version [26]), and life satisfaction (Satisfaction with Life Scale, SWLS; German translation [27]), as well as leisure activities (self-generated questionnaire of physical, social, and cognitive activities).

Measurement of CR: To determine improvement after systematic practice, a modified version of the DSST was used. In the original DSST, subjects are required to assign nine different symbols to the digits “1–9” based on a previously introduced
combinations. The modified test was identical to the original DSST, except that different symbols were introduced which subjects had to match to digits. In the testing-the-limits-paradigm, participants were required to fill in the missing symbols with a pencil as fast and accurately as possible in each of 10 consecutive trials using the identical version of the modified DSST (30-s inter-trial intervals were used to avoid motor fatigue of the hand). To avoid ceiling effects, the time for the trials was limited to 90 s (standard: 120 s). The number of correctly assigned symbols was used as a measure of performance. Test-retest reliability of the DSST is known to be high (0.82–0.84 [28]), indicating uniformity of changes in performance. Further, performance in the DSST is sufficiently sensitive to mental aging and is independent of years of education [29].

Procedure
All test sessions were carried out between 9 am and 1 pm and, including adequate breaks, lasted approximately 3 h. Tests were administered by three well-trained psychologists. The study design conformed to the principles outlined in the latest version of the Declaration of Helsinki and was approved by the Ethical Committee of the Medical Faculty of Ludwig-Maximilians-Universität. Written informed consent was provided by each participant in the study; participants received a small financial compensation (€30).

Data analysis
Calculation of indexes of CR: Given the usefulness of simple gain scores [30], we used the following formula as an index for CR [16]:

\[
CR = \sum_{i=1}^{n} (1 + x_1 x_{\text{max}}) \times x_i - x_1 x_{\text{max}}
\]

Where the gain in every trial is divided by the population maximum and multiplied by the quotient of the baseline and population maximum. The sum of these products provides the area under the curve of the relativized gain function (=CR). This product is set at 0 in the first trial and may increase (positive values) or decrease (negative values) with relative increments or decrements in DSST performance during successive trials.

Statistical analysis of data: Data were analyzed using R [31]. Pure performance gain, i.e., difference between correctly assigned symbols in the first and in the best trial of the 10 consecutive trials, was calculated with a dependent samples t-test of maximum vs. initial score in the modified DSST. Relationships within measures of cognitive architecture and psychological factors, and between these measures and CR, were analyzed using bivariate correlation analysis. Pearson correlations were also used to test relationships between age and CR, and cognitive as well as psychological variables. In addition, differences in CR, cognitive architecture, and psychological factors were tested with respect to gender by applying two-tailed independent samples t-tests. To account for the correlations between our variables, we performed linear best subset regression, thus investigating which variables from cognitive architecture and psychological factors were jointly able to predict CR. Best subsets were selected by the Bayesian Information Criterion (BIC) and delete-d cross-validation [32], as implemented in the bestglm package [33]. For delete-d cross-validation, the default settings of the bestglm package were used. Linear best subset regression automatically estimates an optimal linear regression model out of a possibly large pool of predictor variables. This is done by computing linear models for all possible predictor combinations and choosing the best fitting model, with regard to a certain model choice criterion. Thirteen measures for cognitive architecture, 11 psychological factors (see Table 1), sex,

Table 1. Cognitive architecture and psychological factor outcomes and their correlation with CR.

<table>
<thead>
<tr>
<th>Cognitive architecture</th>
<th>Descriptives</th>
<th>Correlation with CR</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSST</td>
<td>M 67.20</td>
<td>SD 14.01</td>
<td>.12</td>
<td>.99</td>
</tr>
<tr>
<td>WL learning</td>
<td>M 22.89</td>
<td>SD 3.29</td>
<td>.32*</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>WL delay</td>
<td>M 7.97</td>
<td>SD 1.65</td>
<td>.35*</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>DS forwards</td>
<td>M 5.76</td>
<td>SD 1.04</td>
<td>.14</td>
<td>.99</td>
</tr>
<tr>
<td>DS backwards</td>
<td>M 4.48</td>
<td>SD 1.07</td>
<td>.19</td>
<td>.75</td>
</tr>
<tr>
<td>TMT A</td>
<td>M 39.19</td>
<td>SD 12.50</td>
<td>.06</td>
<td>.99</td>
</tr>
<tr>
<td>TMT B-A</td>
<td>M 44.40</td>
<td>SD 21.45</td>
<td>-.31*</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Stroop</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Words</td>
<td>M 100.45</td>
<td>SD 13.43</td>
<td>.09</td>
<td>.99</td>
</tr>
<tr>
<td>Colors</td>
<td>M 69.02</td>
<td>SD 10.40</td>
<td>.18</td>
<td>.88</td>
</tr>
<tr>
<td>Interference</td>
<td>M 50.52</td>
<td>SD 5.87</td>
<td>.14</td>
<td>.99</td>
</tr>
<tr>
<td>RWT</td>
<td>M 45.10</td>
<td>SD 9.80</td>
<td>.20</td>
<td>.44</td>
</tr>
<tr>
<td>MR</td>
<td>M 18.89</td>
<td>SD 4.58</td>
<td>.28*</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Reading</td>
<td>M 169.16</td>
<td>SD 26.83</td>
<td>.17</td>
<td>.99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychological factors</th>
<th>Descriptives</th>
<th>Correlation with CR</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDS</td>
<td>M 1.31</td>
<td>SD 1.61</td>
<td>-.12</td>
<td>.99</td>
</tr>
<tr>
<td>PSQI</td>
<td>M 5.01</td>
<td>SD 3.05</td>
<td>-.10</td>
<td>.99</td>
</tr>
<tr>
<td>WHOQOL-BREF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>M 79.41</td>
<td>SD 11.54</td>
<td>.10</td>
<td>.99</td>
</tr>
<tr>
<td>Physical</td>
<td>M 83.43</td>
<td>SD 11.77</td>
<td>.02</td>
<td>.99</td>
</tr>
<tr>
<td>Psychological</td>
<td>M 77.17</td>
<td>SD 11.46</td>
<td>.12</td>
<td>.99</td>
</tr>
<tr>
<td>Social</td>
<td>M 70.68</td>
<td>SD 16.22</td>
<td>-.06</td>
<td>.99</td>
</tr>
<tr>
<td>Environmental</td>
<td>M 88.08</td>
<td>SD 9.73</td>
<td>.12</td>
<td>.99</td>
</tr>
<tr>
<td>SWLS</td>
<td>M 12.80</td>
<td>SD 4.55</td>
<td>.01</td>
<td>.99</td>
</tr>
<tr>
<td>Leisure activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>M 31.25</td>
<td>SD 9.40</td>
<td>&lt;.01</td>
<td>.99</td>
</tr>
<tr>
<td>Social</td>
<td>M 34.82</td>
<td>SD 7.75</td>
<td>&lt;.10</td>
<td>.99</td>
</tr>
<tr>
<td>Cognitive</td>
<td>M 49.71</td>
<td>SD 9.86</td>
<td>&lt;.05</td>
<td>.99</td>
</tr>
</tbody>
</table>

DSST, Digit Symbol Substitution Test; WL, CERAD-Plus word list; DS, digit span; TMT, Trail Making Test; Stroop, Stroop color and word test; RWT, Regensburger word fluency test; MR, matrix reasoning; GDS, Geriatric Depression Scale; PSQI, Pittsburgh sleep quality index; WHOQOL-BREF, WHO quality of life (short form); SWLS, Satisfaction with Life Scale.

*p < .05, two-tailed. P-values were Bonferroni-corrected by a factor of 24 to account for multiple comparisons.
and age were considered as possible predictors for CR. Especially with small sample sizes relative to the high number of predictor variables, over fitting can become a problem [34]. By choosing delete-d cross-validation and BIC to select the best subsets, we favored sparse models with few predictors, which can be expected to predict CR not only in our sample, but in future studies as well. In a final analysis using extreme best subsets, we favored sparse models with few predictors, over fitting can become a problem [34].

Relationship between cognitive architecture and psychological factors: Correlations between measures in subtests of cognitive architecture for cognitive multitasking (DSST), verbal memory (CERAD-Plus, word list delayed), information processing speed/attention (TMT A), cognitive flexibility (TMT B-A), visual problem-solving (Matrix Reasoning), and reading performance, with mood (GDS), sleep quality (PSQI), and leisure activities (combined) are shown in Table 2. Considerable correlations were only found between mood and information processing speed/attention (r = .27). No significant correlation was found between reading performance and any psychological factor.

Cognitive reserve
Analysis of the effect of systematic practice on the modified DSST (10 trials) is illustrated in Figure 1. On average, participants correctly assigned 49.32 (SD = 9.70) symbols in the first trial and showed a 15-item improvement in performance in the last trial (M = 64.85, SD = 10.73). Despite the large variability in performance, the increase in performance was highly significant (t(135) = 30.06, p < .001, d = 1.52). There were no significant differences in CR between males and
females (t(134) = .56, p = .58, d = .10). Moreover, CR did not correlate with age (r = -.09, p = .32).

Relationship between cognitive architecture and CR: Results of correlational analyses between CR and domains of cognitive architecture are displayed in Table 1. Significant correlations with moderate effect sizes were only found for verbal learning (CERAD-Plus word list, learning trials: r = .32, p < .01) and verbal memory (CERAD-Plus wordlist, delay: r = .35, p < .01), cognitive flexibility (TMT, B-A: r = -.31, p < .01), and visual problem-solving (Matrix Reasoning, WAIS-III: r = .28, p < .05). Interestingly, no significant correlation was found between CR and reading performance (r = .17, p = .99).

Relationship between CR and psychological factors: Furthermore, as can be seen in Table 1, correlations between CR and psychological measures all failed to reach significance. Coefficients indicate only weak (e.g. GDS, PSQI) or negligible relations (e.g. SWLS, physical engagement) between CR and subjective well-being.

Best subset regression: Both delete-d cross-validation and BIC selected the linear model which included only verbal memory (CERAD-Plus wordlist, delay) and cognitive flexibility (TMT, B-A) as important predictors for CR. Results of this model are summarized in Table 3. The model explained about 17% of the observed variance in CR ($R^2_{adj} = .17$). Visual problem-solving (Matrix Reasoning, WAIS-III) and verbal learning (CERAD-Plus word list, learning trials) were not selected for the final model. Considering the correlations between visual problem-solving and cognitive flexibility ($r = -.35$) as well as between verbal learning and verbal memory ($r = .77$), these two measures seem to carry no additional information to predict CR. Notably, no psychological factor was selected in the final model, which is in line with the low correlations between psychological factors and CR.

![Figure 1. Mean score in the modified DSST in 10 consecutive trials of the testing-the-limits paradigm for the assessment of CR. Vertical bars indicate ±1 SD.](image)

Table 3. Results of the best subset linear regression model.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>b</th>
<th>β</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>.88</td>
<td></td>
<td>.32</td>
</tr>
<tr>
<td>WL delay</td>
<td>.12</td>
<td>- .30</td>
<td>.03</td>
</tr>
<tr>
<td>TMT B-A</td>
<td>-.01</td>
<td>-.24</td>
<td>.01</td>
</tr>
</tbody>
</table>

$R^2_{adj} = .17$.

WL, CERAD-Plus word list; TMT, Trail Making Test; b, unstandardized coefficient; β standardized coefficient; SE, standard error.

Differences between high and low performers of CR in cognitive architecture and psychological factors: To test for differences between high and low performers, CR scores were separated into the upper (n = 34) and lower (n = 34) quartiles of the distribution, respectively. The mean CR was 2.48 (SD = .44) in high performers and .73 (SD = .23) in lower performers. Cognitive architecture differed in terms of verbal learning (CERAD-Plus word list: t(66) = 3.69, p < .001, d = .90), verbal memory (CERAD-Plus word list, delay, t(66) = 4.02, p < .001, d = .98), and cognitive flexibility (TMT B-A: t(66) = 3.63, p < .001, d = .88). Reading performance differed by 15 wpm between high and low performers, (t(66) = 2.13, p < .05, d = .52). No significant differences were found in psychological measures obtained from low and high performers (largest difference for sleep quality, PSQI: t(66) = 1.87, p = .07, d = .45).

DISCUSSION

A major finding to emerge from this study is that repeated practice by healthy subjects, aged between 60 and 75 years, can result in considerable improved performance in a complex cognitive task such as the DSST; this was seen despite considerable within-group variation in CR. The improvements were not confined to one gender and did not depend on age (in the range examined). Importantly, significant correlations between measures of cognitive architecture and CR were found for verbal memory, cognitive flexibility, and visual problem-solving, whereas psychological variables (e.g. mood, sleep quality, quality of life, life satisfaction, and leisure activities) did not significantly correlate with CR. Best subset regression complemented these findings by selecting a sparse best fitting model, which included only verbal memory and cognitive flexibility. Better performance in the verbal memory test and in the cognitive flexibility task was related to higher CR. Notably, complex mental activity and sleep quality did not play a significant role in CR, neither alone nor together with cognitive architecture. This finding was unpredicted. An extreme group comparison method again revealed better verbal learning, verbal memory, and cognitive flexibility in high vs. low performers. However, high performers also did not differ from low performers in terms of complex mental activities and sleep quality or any of the psychological measures.
Overall, the present results are consistent with those of our previous study [16] and favor the evidence that activation of cognitive resources is well preserved in the healthy elderly, notwithstanding individual differences in performance gains. In this study, performance gain in the DSST testing-the-limits paradigm was 15.53 items ($SD = 6.03$), as compared to 18.94 items ($SD = 7.30$) in our earlier study [16]. Interestingly, the younger group (20–30 years) in our earlier study [16] showed a higher gain (25.52), but variability was in a similar range ($SD = 10.10$). This supports the idea that CR is not a quality of older age alone [36], and that inter-individual variability is already apparent at earlier ages; therefore, aging is not the main or only determinant of CR variability in older age.

In addition, we found a significant association between CR, verbal memory, and executive function, but no association between CR and gender, in both studies. Apart from three measures of cognitive architecture (verbal learning, verbal memory, and cognitive flexibility), high performers did not differ significantly from low performers, indicating that CR may depend on particular, rather than general, components of cognitive architecture. It is likely that this interpretation may not apply to other dynamic measures of CR in which other components of cognitive architecture may be a prerequisite for achieving high gain. Nevertheless, the positive relationship between verbal learning, verbal memory, executive function, and CR indicates that these cognitive capacities play a crucial role in determining performance in the DSST. Roldán-Tapia et al. [37] found a significant contribution of speed of information processing, verbal memory, and executive function to CR (defined as a proxy for verbal intelligence, educational level, and profession). Notably, Santos et al. [9] reported memory and executive function as the main cognitive dimensions that separate high and low performers in cognitive architecture. Together, these results support the idea of a "central circuit of the mind" in which brain structures underlying declarative memory and executive function that serve as basic modules of cognitive architecture [38].

In contrast to earlier studies [39,40], we did not find evidence that years of education (educational level) and reading performance play an essential role for CR in our group. This discrepancy is possibly explained by the fact that all subjects in the present study had an above-average (high) level of education and reported high cognitive engagement in leisure activities as well as regular reading. As Reed et al. [41] and Kávé et al. [42] have shown, cognitive leisure activities and regular reading are more important than level of formal education for later cognitive functioning and CR proxies. This view is supported by the finding that, although education is related to CR, it does not necessarily slow cognitive decline in older age [43], while active cognitive lifestyle does [4,6]. Interestingly, this also holds true for premorbid cognitive activities and CR proxies in subjects with multiple sclerosis [44] and MCI [18,45].

Mood and sleep quality of our subjects did not have significant effects on their CR; this finding is not surprising given that all subjects in this study reported good mood and sleep quality. Murphy and O’Leary [46] found an association between depressive symptoms and poor verbal memory, with higher education levels contributing to higher performance. Zimmermann et al. [47] reported that only older adults with lower education suffer from the negative effects of difficulties in sleep onset and maintenance on CR. Thus, pathological states of mood and sleep quality may have a significant impact on cognitive architecture; higher education may serve as a protective factor in both cases. Interestingly, however, comparison of high and low performers in their study revealed higher performance in measures of cognitive architecture in subjects with higher mood scores and higher engagement in leisure activities, supporting the view that mood and cognitive lifestyle are key determinants of cognitive performance in healthy older individuals [6,9,18].

The present data contribute to the CR model proposed by Satz et al. [3] by confirming the assumption that processing resources, verbal memory, executive function, and complex cognitive activities promote CR. We only studied direct effects of cognitive architecture and psychological factors on CR. Verbal memory and cognitive flexibility explained about 17% of the variance of CR in our sample. It should be noted that this estimate of the explained variance in the population can be rather optimistic because its computation was based on the same sample also used for finding the best subset solution [34]. We did not investigate if psychological factors influence the relationship between cognitive architecture and CR, by conducting moderation or mediation analyses. This choice was made considering the negligible correlations of psychological factors with CR and our limited sample size compared to the high number of predictors and possible moderators. However, with a bigger sample this could be an important endeavor to strengthen the claims in the CR model by Satz et al. Interestingly, despite narrow selection criteria, the subjects in this study showed high variability in CR, indicating that CR may be influenced strongly by subject-specific characteristics. This question must be addressed in future tests of the CR model proposed by Satz et al. [3], where CR is assessed in subgroups of healthy older subjects by considering demographic variables, educational level, cognitive lifestyle, including reading and mood. Investigations of large groups will help to reveal the effect of these variables on a large continuum. Although such studies will not permit unequivocal conclusions about their specific role(s) on CR, they will help better define more valid "proxies." Individual differences in CR may mirror individual differences in the interplay between genetics and environment and thus, brain function (phenotypes; [48]). Furthermore, biological variables, such as hormonal profiles [49], brain morphology [50], and individual resting state activity [51], may potentially contribute to interindividual differences in "cognitive plasticity" and thus, CR. However,
part of the differences in the high and low performers may be attributed to age-independent interindividual differences in cognition and cognitive plasticity [36]; the outcome of our earlier study [16] would also support such an assumption. In conclusion, the results of this study support the model proposed by Satz et al. [3] and suggest the need for a more dynamic standardized assessment of CR; such assessment should consider that “cognitive reserve is not fixed but continues to evolve across life span” [52]. Our results confirm the validity of measures of gain in performance in a cognitively challenging testing-the-limits paradigm as an essential measure of CR in healthy mental aging; such an approach aligns with the theoretical research model proposed by Steffener and Stern [13], which attempts to unify the notion of neural vs. CR. In addition, this paradigm may be also helpful in the differential diagnostic assessment of potentially existent vs. absent cognitive resources, especially in subjects with suspected or proven cognitive impairments.

REFERENCES


COMPETING INTERESTS
The authors declare no competing interests.