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Cognitive reserve modulates ERPs associated with verbal working memory in healthy younger and older adults

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Abstract

Although many epidemiological studies suggest the beneficial effects of higher cognitive reserve (CR) in reducing age-related cognitive decline and dementia risk, the neural basis of CR is poorly understood. To our knowledge, the current study represents the first electrophysiological investigation of the relationship between CR and neural reserve (i.e., neural efficiency and capacity). Specifically, we examined whether CR modulates event-related potentials (ERPs) associated with performance on a verbal recognition memory task with three set sizes (1, 4, or 7 letters) in healthy younger and older adults. Neural data showed that as task difficulty increased, the amplitude of the parietal P3b component during the probe phase decreased and its latency increased. Notably, the degree of these neural changes was negatively correlated with CR in both age groups, such that individuals with higher CR showed smaller changes in P3b amplitude and less slowing in P3b latency (i.e., smaller changes in the speed of neural processing) with increasing task difficulty, suggesting greater neural efficiency. These CR-related differences in neural efficiency may underlie reserve against neuropathology and age-related burden.

Keywords

Cognitive reserve; Verbal working memory; Neural efficiency; Event-related potentials (ERPs); P3; Cognitive aging

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Disclosure Statement

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1. Introduction

The concept of cognitive reserve (CR) has been proposed as an explanation for why individuals with similar levels of brain pathology or injury can differ markedly in the clinical manifestation of that pathology, with some individuals being symptom free and others showing cognitive and/or functional impairment. CR is a theoretical construct that postulates that certain lifetime experiences, including education, occupational breadth and complexity, and engagement in activities that are cognitively, socially, and physically stimulating increase the efficiency, capacity, and flexibility of brain networks. As a result, individuals with higher levels of CR are thought to be able to sustain greater levels of brain pathology or damage before showing clinically significant levels of impairment (for a review see Stern, 2009).

In support of the concept of CR, many studies have shown that higher levels of educational and occupational attainment, as well as greater pre-morbid intelligence are associated with better clinical outcomes across a variety of conditions, such as a reduced risk of mild cognitive impairment or dementia (Pettigrew et al., 2013; Soldan et al., 2013; Wilson et al., 2002), better recovery from traumatic brain injury (Fay et al., 2010; Levi et al., 2013), and less cognitive impairment in multiple sclerosis (Sumowski et al., 2013) or Parkinson's disease (Perneczky et al., 2008).

Despite the strong evidence for the beneficial effects of CR, the neural mechanisms by which it operates are poorly understood. It has been proposed that there are two different ways in which CR is implemented in the brain: neural reserve and neural compensation (Stern, 2009). Neural compensation refers to the reliance on alternative brain networks that are not normally used by healthy individuals to maintain or improve cognitive performance in the face of age or pathology-induced changes. Neural reserve, by comparison, refers to individual differences in the efficiency and capacity of brain networks underlying task performance in unimpaired individuals that provide reserve against the impact of brain injury. Such individual differences in neural efficiency and capacity are thought to be present before the onset of pathology or injury and therefore exist in both young and older individuals.

In support of the concept of neural compensation, functional neuroimaging studies have reported CR-related activation of brain regions among cognitively normal older adults that are not typically activated by young subjects (Scarmeas et al., 2003; Springer et al., 2005; Steffener et al., 2011; Stern et al., 2008). Likewise, high performing older individuals (who presumably have higher CR) often recruit additional brain regions (usually in the contralateral hemisphere) when engaging in strategies associated with better task performance (reviewed in Reuter-Lorenz and Park, 2010). There is also some evidence for greater neural efficiency among cognitively normal young and older adults, such that subjects with high CR show less task-related activation as a function of increasing task load than subjects with lower CR (Habeck et al., 2003; Habeck et al., 2005; Steffener et al., 2011; for similar evidence also see Bosch et al., 2010).

To our knowledge, prior investigations that have directly examined the neural basis of CR have been conducted using $H_2{}^{15}O$ positron emission tomography (PET) or functional magnetic resonance imaging (fMRI). Although these methods are very useful for identifying mechanisms of neural compensation (due to their high spatial resolution), they are less useful for addressing another potentially important aspect of CR, neural processing speed, owing to their poor temporal resolution. That is, to the extent that CR is associated with neural efficiency (e.g., higher CR, greater neural efficiency), one would predict not only a relationship between CR and the magnitude of neural activation, but also between CR and the speed of neural processing (e.g., higher CR, greater neural speed). Therefore, the primary aim of the current study was to investigate the association between CR and neural reserve (as indexed by neural efficiency and capacity) in young and older adults using event-related potentials (ERPs), which have excellent temporal resolution. We did not examine neural compensation because of the poor spatial resolution of ERPs. ERPs, which measure synchronized post-synaptic potentials of pyramidal cortical neurons, have the additional advantage that unlike the fMRI BOLD response and $H_2{}^{15}O$ PET, they are not influenced by potentially confounding neurovascular-coupling mechanisms that change with aging (Ances et al., 2008; Ances et al., 2009; Fabiani et al., 2014; Fleisher et al., 2009; Hutchison et al., 2012).

Our investigation focused on the central-parietal P3b (or P300b) ERP component because both its amplitude and latency are modulated by the cognitive demands of a task (e.g., Kok, 2001; Polich, 2007). In particular, P3b amplitude is often thought of reflecting cognitive resource allocation (Donchin and Coles, 1988; Kok, 2001; Linden, 2005; Polich, 2007), whereas P3b latency appears to be related to information processing speed (i.e., stimulus evaluation time), independent of motor response preparation and execution processes (McCarthy and Donchin, 1981; Walhovd and Fjell, 2003). Moreover, a number of studies have reported associations between intelligence and P3b amplitude and/or latency (Gevins and Smith, 2000; Houlihan et al., 1998; Jausovec and Jausovec, 2000; Liu et al., 2011; Pelosi et al., 1992; e.g., Wronka et al., 2013) as well as between intelligence and neural efficiency as measured by EEG alpha-band desynchronization (ERD, reviewed in Neubauer and Fink, 2009), which is functionally related to the P3b (Peng et al., 2012), suggesting that the P3b would also be related to CR.

The current study used a Sternberg verbal working memory paradigm to measure individual differences in neural reserve (i.e., neural efficiency and capacity). Task load was manipulated parametrically by varying the number of items participants had to encode and retain in memory (e.g., 1, 4, or 7 letters). Varying task difficulty is advantageous for studying the neural basis of CR because CR is hypothesized to modify how the brain copes with increasing task demands, as could be the case following brain insult: tasks that are easy when an individual is healthy may be difficult following brain damage or pathology (Stern, 2009). Previous work using the Sternberg paradigm with letters has shown that P3b amplitude and latency during the encoding phase increase with the number of letters to be encoded, reflecting extra stimulus processing at higher set sizes (Houlihan et al., 1998). Moreover, longer P3b latencies during encoding, particularly at higher set sizes, have been associated with higher intelligence scores and better task performance (Houlihan et al., 1998). This suggests that greater load-related increases in P3b latency and amplitude at

encoding may be beneficial to task performance and be associated with CR. By comparison, during the probe phase P3b amplitude decreases with increasing memory load, whereas latency increases, reflecting more resource-demanding memory search processes for the higher set sizes (Houlihan et al., 1998; Morgan et al., 2008; Pinal et al., 2014).

Similar to the definitions provided by Stern (2009), we defined greater neural efficiency as smaller changes in P3b amplitude or latency with increasing memory load given the same or better behavioral performance. Greater neural capacity was defined as a larger change in P3b amplitude or latency with increasing memory load, coupled with better performance. The following hypotheses were tested. First, higher CR is associated with better task performance, particularly at the higher set sizes. Second, P3b amplitude and latency during the encoding phase increase with set size and the amount of this load-related increase is positively correlated with CR. If the first and second hypotheses were confirmed, this would provide evidence for greater neural capacity among individuals with higher CR. Third, P3b amplitude during the probe phase decreases with memory load, whereas P3b latency during the probe phase increases with memory load and the amount of these load-related changes is negatively correlated with CR (i.e., smaller change with higher CR, in line with the results of an fMRI study using the same task, Habeck et al., 2005). If the first and the third hypotheses were both confirmed, this would provide evidence for greater neural efficiency among high CR individuals. In addition, we calculated neural inefficiency indexes to more directly relate load-related changes in P3b amplitude to behavioral performance measures and tested whether these indexes correlate with CR. Lastly, we tested the hypothesis that the relationships between CR, behavior, and load-related changes in P3b amplitude and latency are the same across age groups, which would support the view that neural reserve operates similarly in young and older adults.

2. Methods

2.1 Participants

Twenty-five healthy young adults and 21 non-demented healthy older adults participated in this study. Two older participants performed at chance-level in the high load condition and were excluded from analyses because their poor performance may have reflected disengagement from the task, which cannot be interpreted meaningfully with respect to CR. Thus, analysis was performed on 25 young adults and 19 older adults. See Table 1 for participant characteristics. All were right-handed with normal or corrected-to-normal vision (visual acuity cut-off of 20/50 as assessed by a Snellen chart), and none reported any history of neurological or psychiatric diseases that would affect the central nervous system. The older participants were recruited from the community surrounding North Dartmouth, MA, and received monetary compensation at a rate of $15/ per hour. All older adults were screened for dementia via the dementia rating scale (DRS; all scored at or above 137; Mattis, 1988). Young adults were students at the University of Massachusetts, Dartmouth, and received partial course credit for their participation. Written informed consent was obtained prior to participation.

2.2 Cognitive Reserve Composite Score

We created a CR composite score based on measures thought to reflect CR: the National Adult Reading Task (NART; Nelson, 1982), the vocabulary subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981), and years of education. Measures of intelligence, particularly verbal intelligence, are commonly included when attempting to model CR (Alexander et al., 1997). Supporting this approach, a prospective study by Richards and Sacker (2003) found that intelligence at age 53 was uniquely influenced by adult occupation, educational attainment, and childhood cognition. Accordingly, basing a measure of CR on variables such as verbal intelligence means that CR is not inflexible, but rather can change over the course of one's lifetime. Educational attainment, on the other hand, is the most commonly used proxy for CR, and is often combined with other predictors into a composite variable as in the present study. Because education is a strong determinant of future employment and income level (Beckles et al., 2011), educational attainment directly correlates with other CR proxies such as socioeconomic status and occupational attainment.

All three proxy measures of CR were correlated with one another for the older adults (all $p < 0.05$). For the young adults, who had not yet completed their education, the CR measure was based on the NART and WAIS-R vocabulary scores only, which were also correlated ($p < 0.05$). To calculate the composite CR score, these individual measures were transformed to z-scores and then averaged. Use of CR composites such as these has been shown to have construct validity (Siedlecki et al., 2009).

2.3 Stimuli and Procedures

All participants performed a delayed item recognition task measuring verbal working memory (Sternberg, 1966) on a computer in a sound attenuated booth. Each trial began with the presentation of a variable inter-stimulus interval lasting 2.25 s to 2.75 s. A memory set of one, four, or seven uppercase letters was presented for 2.5 s. Regardless of set size, the stimulus geometry was a two-row array with one row containing three stimuli and the other four stimuli. For set size one and four, each absent letter in the array was replaced with an asterisk to keep the geometric array consistent for each set size. This way, differences in neural responses to different set sizes at encoding cannot be attributed to differences in the amount of visual information presented, but must reflect the active processing of this information. The memory set was followed by a 5 s delay that served as a retention period in which only a blank screen was shown. Then, a probe stimulus was presented for 2 s that consisted of a single lowercase letter. Participants were instructed to press a key indicating whether or not the probe was part of the memory set. Memorizing uppercase letters and then responding to a lowercase letter forced participants to base their decision on the phonological or pre-lexical representation of the letters rather than simply on the shape of the letters. The total length of one trial was 12 s (see Figure 1).

A total of 240 trials were divided into eight blocks, each containing 10 trials of each set size (1, 4, 7) for a total of 80 trials at each set size. Within each block, there were 5 targets (i.e., the probe letter was in the memory set) and 5 non-targets (i.e., the probe was not in the memory set) at each set size. Each block contained a different list of stimuli. The order of

block presentation was counterbalanced across participants and each block's contents were randomized. Participants were given a 1-minute break between each block in order to help prevent fatigue. The first two blocks served as training and were excluded from analysis to minimize the effects of task-related skill learning on performance and neural responses. The last six blocks (i.e. 60 trials of each set size) were included in data analysis. Participants were instructed to answer as quickly and accurately as possible. They were not given feedback about their performance.

2.4 Behavioral Data Analysis

The behavioral accuracy data was analyzed in terms of the signal-detection theory measure of sensitivity, d_L, a measure of accuracy without response bias, (Snodgrass and Corwin, 1988). The measure of d_L can be thought of as standardized hits minus standardized false alarms. It is based on logistic distributions and is functionally equivalent to *d*' (d-prime), which is based on normal distributions. Both d_L and mean reaction time (RT) were assessed for effects of set size, age group, and group by set size interaction via repeated measures analysis of variance (ANOVA). Incorrect trials were excluded from the RT analysis. For each subject, linear regression analysis was used to calculate the slope of RT across set size, the RT intercept (i.e., imputed value at set size = 0), the slope of d_L across set sizes, and the d_L intercept. The slope of performance variables measures how well one adapts to the changes in task difficulty, whereas the intercept of performance variables measures the baseline performance level when there is no memory load (i.e., at set size = 0). These measures were used to calculate the neural inefficiency scores (see below).

2.5 EEG Recording and Analysis

Brain electrical activity was recorded from 32 scalp sites (ActiveTwo electrodes, Biosemi) using an elastic cap with mounted active electrodes positioned according to the International 10/20 System. The electrode offset was kept below 40 mV. Electrodes were initially referenced to the common mode sense (CMS) electrode and then converted to an average reference offline. EEG was amplified and continuously sampled at 512 Hz with a bandpass filter of 0.05–100 Hz. The electrooculogram (EOG) was recorded by means of electrodes placed approximately 1 cm below each eye as well as lateral to the outer canthi of each eye. Eye movements were modeled and compensated for using 2–4 ocular source components (BESA; MEGIS Software GmbH, Grafelfing, Germany). Incorrect trials, as well as trials with muscle or skin artifacts were excluded from analysis. For each participant, baseline-corrected, artifact-free trials, time locked to the onset of a stimulus (memory set or probe), were averaged separately for each set size (1, 4, or 7) from 100 ms before stimulus onset until 1,000 ms thereafter. A low-pass filter of 40 Hz was applied after averaging.

For the encoding phase, the mean number of trials for set size 1 was 43.0 (SD = 7.5, Min = 25, Max = 57), for set size 4 it was 43.7 trials (SD = 8.0, Min = 25, Max = 59), and for set size 7 it was 37.1 trials (SD = 7.1, Min = 22, Max = 57). For the probe phase, the mean number of trials for set size 1 was 48.0 (SD = 7.4, Min = 31, Max = 59), for set size 4 it was 47.3 trials (SD = 7.0, Min = 29, Max = 59), and for set size 7 it was 40.9 trials (SD = 7.0, Min = 24, Max = 57). Overall, the number of trials was lower for the older than the young

adults [$F(1, 42) = 4.58$, $p = .04$], due to the lower number of correct trials among the older adults (see Results).

Mean amplitude of the P3b ERP component was calculated in 100 ms bins for the interval 300 – 800 ms post stimulus onset. P3b peak latency was measured using the half area latency, which corresponds to the time point that divides the area under the P3b waveform (from 300 to 800 ms) into two equal regions. The half-area latency works well on large components, like the P3b, and is less sensitive to noise than peak latency (Luck, 2005).

The overall analysis approach was to first confirm that the P3b component was indeed modulated by task demands in both age groups, as we hypothesized. To do so, we tested for the presence of an effect of set size on P3b amplitudes in each 100 ms time window that encompassed the duration of the P3b (i.e., 300 – 800 ms) during the encoding phase (memory set presentation) and the probe phase in each age group. Next, only for those time bins that showed a significant set size effect in one or both age groups, we averaged across electrodes (where appropriate) and time bins to calculate the mean P3b amplitude for each set size. We then calculated the difference between mean P3b amplitude at set size 1 and 7 and used this as an index of neural processing that is sensitive to task demands. Likewise, for P3b latency, we first tested for an effect of set size and, if present, proceeded to calculate the difference in latency between set size 1 and 7 as an index of neural processing that is sensitive to task demands. The next step was to examine whether the amount of demand-related amplitude or latency modulation (i.e., difference between set size 1 and 7) correlated with CR composite score.

We also calculated neural inefficiency scores that directly relate the degree of demand-related P3b amplitude modulation to behavioral performance measures and tested if these scores were associated with composite CR. Neural inefficiency was defined as the amount of change in task-related neural processing as a function of behavioral performance. Neural inefficiency scores (the reciprocal of efficiency) were computed for each subject by dividing the change in task-related neural processing (i.e., slope of P3b mean amplitude with respect to set size) by behavioral performance values (where a higher value means better performance): d_L intercept, d_L slope, RT intercept^{-1}, and RT slope^{-1}. Neural inefficiency was used because it may be a more stable measure than efficiency (Zarahn et al., 2007). By this measure, less efficient individuals show greater changes in neural activation with increasing task demands to achieve the same or lower performance than more efficient individuals.

An alpha level of .05 was adopted for all statistical analyses. Greenhouse–Geisser corrections were applied where appropriate to correct for violations of the sphericity assumption. Significant main effects and interactions were followed by post hoc contrasts and Bonferroni-Holm corrected pairwise comparisons.

3. Results

3.1 Behavioral results

Sensitivity (d_L) was marginally lower for the older than the younger adults [$F(1, 42) = 3.08$, $p = .086$]. There was also a main effect of set size [$F(2, 84) = 127.62$, $p < .001$], and an age by set size interaction [$F(2, 84) = 7.24$, $p = .001$]. As set size increased, d_L decreased for both the younger [$F(2, 48) = 50.33$, $p < .001$] and older adults [$F(2, 36) = 84.42$, $p < .001$], but the amount of decrease in d_L was greater for the older than the younger adults, see Figure 2a. Pairwise comparisons showed a significant difference in d_L between set sizes 1 and 7 and between 4 and 7 and in both age groups (all $p < .0001$), while the difference between set sizes 1 and 4 was only significant in the young adults ($p < .005$). The slope in d_L was marginally greater in the older relative to the young adults (t(42) = 1.82, p = .076), but there was no difference in d_L intercept ($t < 1$).

For RT, there was a main effect of age group [$F(1,42) = 44.33$, $p < .0001$], indicating slower RTs in the old than young adults, a main effect of set size [$F(2, 84) = 291.47$, $p < .0001$] and an age by set size interaction [$F(2, 84) = 19.27$, $p < .0001$]. As set size increased, there was a significant increase in RT for younger [$F(2, 48) = 150.31$, $p < .0001$] and older adults [$F(2, 36) = 135.23$, $p < .0001$], with older adults showing a greater increase than the young adults, see Figure 2b. Pairwise comparisons showed reliable differences in RT between set sizes 1 and 4 and 4 and 7 in both age groups, all $p < .0005$. Both the RT-intercept ($t(42) = 3.20$, $p = .004$) and the slope in RT with respect to set size ($t(42) = 5.13$, $p < .0001$) were greater in the older than the younger adults.

Combining across age groups and partialing out the effects of age, the CR composite score was positively correlated with d_L at set size 4, d_L at set size 7, and change in d_L from set size 1 to 7 (d_L slope), all $r > .32$, all $p < .04$. The size of these correlations did not differ across age groups (as determined by the Fisher r - to – z transformation, all $p > .24$), except for the correlation between composite CR and d_L slope, which was significantly greater in the young than in the older adults ($z = 1.95$, $p = .05$). There were no significant correlations between composite CR and any of the RT measures (for age groups separately and when combining across age groups).

3.2 Electrophysiological results

P3b amplitude and latency were assessed at posterior parietal electrodes (PZ, P3 and P4), where the component was maximal (see Figure 3). Repeated measures ANOVA was used with factors for age group, set size, electrode, and time (for amplitudes only, 100 ms bins from 300 to 800 ms). Effects of time and electrode are not mentioned unless they involved interactions with set size and/or age group. The P3b latency data from one older participant was excluded from analysis because of excessive noise. Exclusion of this participant from all other analyses did not alter the results.

3.3 Encoding Phase

P3b Amplitude—P3b amplitudes to encoded items showed a significant interaction between age group and set size [$F(2, 84) = 3.83$, $p = .026$], between age group, set size, and

time [$F(8, 336) = 2.52$, $p = .011$], as well as between set size, time, and electrode [$F(16, 672) = 5.92$, $p < .001$], indicating set size differences based on age and time. Separate follow-up ANOVAs for each age group and time bin showed no significant effects involving set size for the older adults [all $p >= .08$], suggesting that set size did not reliably modulate P3b amplitudes for this age group during encoding. For the young adults, there were significant set size effects during the 500–800 ms time window (all $p < .05$), but no interaction between set size and electrode (all $p > .35$). Post-hoc t-test (averaging across electrodes and time bins) indicated that P3b amplitude increased from set size 1 to 7 in the young adults from 500–800 ms [$t(1, 24) = 2.45$, $p = .022$]. Set size 4 was intermediary and did not differ from set size 1, but was lower than set size 7 ($p = .007$).

P3b Latency—There was a significant main effect of set size [$F(2, 84) = 3.12$, $p = .05$] and a significant interaction between set size and electrode [$F(4, 168) = 4.87$, $p = .002$]. Although the interaction between age group and set size did not reach significance [$p = .10$], we analyzed the latency data separately for the two age groups because the amplitude data had revealed an effect of set size for the young but not older individuals. Consistent with the amplitude data, there was a main effect of set size on P3b latency for the young adults [$F(2, 48) = 5.54$, $p = .001$], but no effects involving set size for the older adults [all $p > .10$]. For the young adults, a post-hoc t-test (averaging across electrodes) revealed no difference in latency between set sizes 1 and 4 ($t < 1$), but significantly longer latencies at set size 7 than at set size 1 ($t(24) = 2.28$, $p = .03$) and 4 ($t(24) = 3.90$, $p = .0007$, see Figure 4.

Correlation with Cognitive Reserve—Since there was a significant set size effect on P3b amplitude from 500 to 800 ms in young adults, we averaged the amplitudes across this time window and across electrodes, separately for each set size, to calculate the mean change in P3b amplitude from set size 1 to 7 for each subject as an index of neural processing that is sensitive to task demands (i.e., mean amplitude at set size 7 – mean amplitude at set size 1). We then tested if this value correlated with the CR composite score. No significant correlation with composite CR was observed. Likewise, the correlation between the change in P3b latency from set size 1 to 7 (averaging across electrodes) and composite CR in the young subjects was not significant. This suggests that the load-related increase in P3b amplitude and latency in the young adults occurs independently of composite CR.

3.4 Probe Phase

P3b Amplitude—P3b amplitudes to probes were smaller for older than younger adults [$F(1, 42) = 6.69$ $p = .013$]. The effect of set size was significant [$F(2, 84) = 9.12$, $p = .0004$], as were the interactions between set size and time [$F(8, 336) = 4.38$, $p = .002$], and between set size, time, and electrode [$F(16, 672) = 2.26$, $p = .037$]. Separate follow-up ANOVAs for each time bin showed a significant set size effect for each time window (all $p < .03$), but no interactions between set size and electrode or set size and age (all $p > .15$). Post-hoc t-tests (averaging across electrodes and time bins) confirmed that P3b amplitude decreased from set size 1 to 7 in both the young [$t(1, 24) = 2.40$, $p = .025$] and older adults [$t(1, 18) = 3.52$, $p = .002$]. Set size 4 was intermediary and not significantly different from set size 7 ($p > .09$

for both age groups). For the older adults, the difference between set sizes 1 and 4 was significant (p = .005).

P3b latency—P3b latencies were longer for older than younger adults [$F(1, 41) = 8.22$, p = .007] and varied as a function of set size [$F(2,82) = 15.38$, $p < .001$]. In addition, there was a set size by electrode interaction [$F(4, 160) = 2.92$, p = .034], reflecting a smaller effect of set size at electrode P4 than at electrodes PZ and P3. Post-hoc t-tests, collapsing across electrodes, showed that latency was significantly shorter at set size 1 than at set size 7 in both younger [t(24) = 4.43, p < .001] and older adults [t(18) = 2.99, p = .009]. Set size 4 was intermediary and differed from set size 1 (p <= .056 in both age groups), but not from set size 7 (see Figure 5).

Correlation with Cognitive Reserve—Because there was a significant set size effect on P3b amplitude in each time bin from 300 to 800 ms in both age groups, we averaged the amplitudes across this time window and across electrodes, separately for each set size, to calculate the mean change in P3b amplitude from set size 1 to 7 for each subject (mean change in P3b amplitude = amplitude at set size 7 – amplitude at set size 1). We then tested if this value correlated with the CR composite score. Combining across age groups to increase power, but partialing out the effect of age to account for the age-related decrease in P3b amplitude, there was a negative correlation, $r(41) = -.40$ p = .009, such that individuals with higher composite CR showed less change in P3b amplitude with increasing task demands. See Figure 5 for a scatterplot of this correlation. This correlation was significant for the group of older adults (r(17) = −0.70, p = .001), but did not reach significance in the young adults $r(23) = -0.25$, p = .23. However, the size of the correlations was not significantly different across age groups (z = 1.07, p = .28). Additionally, the correlation between composite CR and change in P3b amplitude from set size 4 to 7 was significant for the young adults ($r(23) = -0.47$, p = .02), indicating that when task demands are sufficiently high, there is a similar relationship between demand-related change in P3b amplitude and composite CR in both young and older adults.

For P3b latency, we also averaged across electrodes and found that the CR composite score negatively correlated with the amount of change in P3b latency change from set size 1 to 7, combining across both age groups, partialing out the effects of age, $r(40) = -.55$, $p < .001$ (see Figure 5). Thus, higher composite CR was associated with a smaller change in the speed of neural processing as task demands increased. This correlation was significant for both age groups, $r(23) = -0.54$, p = .006 for young adults and $r(17) = -0.49$, p = .046 for older adults.

3.5 Relationship between neural inefficiency and cognitive reserve

There was a negative correlation between the CR composite score and neural inefficiency scores for load-related changes in P3b amplitude with respect to both accuracy (d_L slope: *partial r* (41) = −.33, p = .035) and reaction time (RT slope^{-1}: *partial* $r(41) = -.47$, p = .002; RT intercept^{-1}: *partial* $r(41) = -.42$, p = .005), partialing out the effects of age. This suggests that independent of age, higher levels of composite CR are associated with less neural inefficiency for P3b amplitude change with respect to d_L slope, RT slope, and RT

intercept (see Figure 6). Separate analyses for each age group confirmed that these correlations were significant in both the young and older adults (all $p <= .05$ one-tailed, except for RT intercept^{-1} for young adults, where p = .15) and the size of the correlations did not differ across age groups.

3.6. Does cognitive reserve modify age-related changes in P3b amplitude and latency?

We also tested if composite CR reduces the impact of aging on P3b amplitude (reduced with aging) and latency (increased with aging). ANOVAs with group (young, old) and composite CR (high, low) were performed for mean P3b amplitude and latency (averaging across set sizes) and for P3b amplitude and latency at set size 7. There were no significant interactions between age group and composite CR level, all $p >= .10$, indicating a similar age effect on P3b amplitude and latency across CR levels.

4. Discussion

We examined the relationship between individual differences in CR in young and older adults and individual differences in neural efficiency and capacity that have been hypothesized to underlie the beneficial effects of higher CR. We investigated this relationship by looking at the association between CR composite score and load-related changes in P3b amplitude and latency during the performance of a verbal working memory task that increased in difficulty from a set size of one to seven letters. As hypothesized, both young and older individuals with higher composite CR were more accurate in the task at higher set sizes than those with lower composite CR. Contrary to our predictions, there was no association between CR composite score and load-related changes in P3b amplitude or latency during the encoding phase of the task. For the probe (or retrieval) phase, we found that independent of subjects' age, higher levels of composite CR were associated with smaller changes in P3b amplitude and latency with increasing working memory load, as we had hypothesized. These findings support the view that young and older cognitively normal adults with higher CR have neural networks that operate more efficiently when task demands increase, consistent with prior fMRI studies (Bartres-Faz et al., 2009; Bosch et al., 2010; Habeck et al., 2003; Habeck et al., 2005; Steffener et al., 2011; Stern et al., 2008). Our results extend prior findings by showing that greater neural efficiency among high CR adults not only reflects the amount of neural activation (as indexed by ERP component amplitude or fMRI BOLD signal), but also the speed of neural processing, as indexed by ERP component latency.

4.1 Neural Efficiency

We further corroborated the association between CR and neural efficiency by testing the relationship between CR composite score and an index of neural inefficiency, which is the ratio of the amount of demand-related neural activity (i.e., P3b amplitude slope with increasing task load) per unit of behavioral performance (i.e., accuracy or RT slope with increasing task load). We found that, indeed, higher composite CR was associated with less neural inefficiency with respect to both accuracy (d_L-slope) and reaction time (RT-slope and RT-intercept). This suggests that individuals with lower composite CR showed greater

changes in activation as the task became more difficult although it benefited them less in terms of performance, reflecting less efficient processing.

The present results are compatible with those by Habeck et al. (2005), who used a verbal working memory task very similar to ours in an fMRI investigation of CR in young subjects. Habeck et al. (2005) identified spatial covariance patterns of brain regions for each phase of the task whose expression increased monotonically with increasing set size in the majority of subjects. The degree to which subjects expressed these load-related patterns during the delay and probe phases was inversely correlated with CR, indicating that smaller changes in load-related activation were associated with higher CR. The load-related pattern expressed during the encoding phase did not correlate with CR, consistent with the lack of a relationship between CR composite score and P3b amplitude and latency observed during the encoding phase of the present study.

Interestingly, while a few regions in the pattern identified by Habeck et al., (2005) for the probe phase showed an increase in activation with set size (cerebellum, inferior frontal gyrus), most regions showed a decrease with set size, including medial frontal and parietal regions, cingulate gyrus, middle temporal gyrus, and parahippocampal gyrus. Although our ERP results cannot be directly compared to these fMRI findings owing to the difference in methodologies and analyses, the spatial pattern identified by Habeck et al. (2005) likely overlaps with the network of regions that generated the P3b in the probe phase of the present study, the amplitude of which also decreased with increasing task demands. While the spatial localization of CR-related brain activity was not of primary interest in the present study, our results, in combination with these fMRI results suggests that the brain regions whose activity was modulated by composite CR in the present study consisted of a frontal-temporal-parietal network. This interpretation is bolstered by source localization studies that have consistently identified parietal, temporal-parietal, frontal, and cingulate cortex as generators of the posterior P3b (Frodl et al., 2000; Li et al., 2009; Moores et al., 2003).

More interestingly, the results from fMRI studies using other behavioral paradigms have also identified activity in frontal, temporal-parietal, and cingulate areas as being correlated with level of CR, suggesting that activity in these brain regions may be most sensitive to CR-related changes. As noted by Stern et al. (2008), there may be a general brain network that underlies the beneficial effects of CR across age groups and tasks and that may be broadly involved in executive and control processes. The present results would be consistent with this possibility, although future studies are needed to test if the P3b – CR relationships observed in this study generalize to other experimental tasks and stimulus types. If so, this would have potentially important clinical consequences, as the P3b is relatively easy to measure and could be used to track the effectiveness of interventions (both pharmacologic and behavioral) designed to increase CR and improve neural functioning among middle-aged and older adults. Many such cognitive training programs are currently available (e.g., Acevedo and Loewenstein, 2007; Olazaran et al., 2010), but consistent neural outcome measures that generalize across a variety of tasks are lacking. However, future work is needed to evaluate the reliability of the P3b for predicting CR level. Additionally, future research should examine the relationship between CR and other ERP components, particularly the P3a, which indexes frontal executive functions (Barcelo et al., 2006; Dien et

al., 2004). Given that this component appears to increase with aging (Alperin et al., 2014; Fabiani et al., 1998), it might also be associated with individual differences in CR.

Another noteworthy finding is that the correlations between composite CR and load-related changes in P3b amplitude and latency as well as between composite CR and several behavioral measures were observed in a sample that included both younger and older adults and were independent of age. This supports the view that CR develops across the lifespan. It is also consistent with the view that high levels of CR could provide functional resilience in the face of non age-related burden, such as traumatic brain injury that might occur at any age (Fay et al., 2010; Levi et al., 2013).

Our results also are in line with the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH; Reuter-Lorenz, 2008), which describes age-related changes in performance and brain activation in terms of neural efficiency and capacity, similarly to the concept of neural reserve. CRUNCH postulates that older adults have less efficient neural networks, requiring them to engage a network to a greater degree than young adults when task demands are low and leading them to reach the capacity of the network at lower levels of difficulty than young adults (e.g., Daffner et al., 2011; Schneider-Garces et al., 2010). Consistent with this model, we found that older adults had smaller P3b amplitudes and longer latencies during the probe phase, even at the lower set sizes, consistent with greater resource utilization and less efficient processing. Furthermore, the older adults showed greater performance decrements with increasing set size than the young adults, while the change in P3b amplitude and latency with increasing task difficulty during the probe phase was the same in both age groups, which also suggests less efficient processing.

It is also important to consider ERP studies that have tested the relationship between P3b amplitude or latency and intelligence. In line with our findings, Houlihan et al. (1998) utilized a similar Sternberg WM task and found that P3b amplitude during the probe phase decreased with set size. Furthermore, individuals with higher cognitive ability, as measured by the Multidimensional Aptitude Battery, had greater P3 amplitudes at the higher set sizes (and therefore smaller decrements with increasing set size), suggesting greater neural efficiency of processing.

Studies using other experimental paradigms are more difficult to compare with our results because they measured neural activity at a single level of task difficulty, rather than multiple levels. As such, they do not directly address how intelligence relates to individual differences in the way the brain copes with increasing task demands, but are more likely to measure the association between intelligence and task-specific neural processing. For instance, studies using oddball paradigms or cued Go-Nogo tasks have reported that individuals with higher cognitive ability elicited greater P3b amplitudes and shorter P3b latencies than individuals with lower cognitive ability (De Pascalis et al., 2008; Jausovec and Jausovec, 2000; Liu et al., 2011; O'Donnell et al., 1992; Wronka et al., 2013). Assuming that these tasks were at least moderately difficult, these results would be consistent with ours, in that we also found that individuals with higher composite CR had faster P3b latencies, as well as a trend toward larger P3b amplitudes, during the probe phase when task demands were high (i.e., set size of 7). The benefit of tasks that parametrically manipulate

difficulty, as was done in our study, is that they may be better able to assess how well individuals cope with increasing task demands irrespective of specific task features. This is important when studying CR, because it has been hypothesized that high CR promotes greater flexibility and adaptability to increasing task demands across a variety of tasks.

4.2 Neural Capacity

During the encoding phase of the task, only the young, but not the older adults, demonstrated an increase in P3b amplitude and latency with increasing task difficulty. This finding, along with better task performance among the young group, may provide some evidence of greater neural capacity in the young compared to the older adults. Specifically, the observed relationship suggests that young adults were able to boost activation when the task became more challenging and engage in more extensive stimulus processing, which may have supported their superior performance at the higher set sizes. Greater neural capacity (here defined as higher network expression at higher levels of task demand) in young compared to older adults has been described previously (e.g., Cappell et al., 2010; Holtzer et al., 2009; Stern et al., 2012). The biological basis of this age-related capacity difference is currently not known, but may be related to differences in neural connectivity and plasticity (Burke and Barnes, 2006), white matter integrity (e.g., Bennett and Rypma, 2013), or brain oxygen metabolism (Hutchison et al., 2012) that manifest with aging.

It is important to note that this age-related capacity difference was unrelated to individual differences in CR. Theoretical models of CR have postulated that higher CR is associated with both greater neural efficiency and greater neural capacity, the two components of neural reserve (Stern, 2009). While there is increasing evidence for a relationship between CR and neural efficiency, few studies have reported associations between CR and neural capacity (e.g., Scarmeas et al., 2003). Although null findings need to be interpreted cautiously, this might indicate that CR is more closely linked to neural efficiency than to neural capacity. Another possibility is that the load-related processes indexed by the P3b during the encoding phase (such as sustained attentional allocation) are less amenable to CR-related influences than the load-related processes indexed by the P3b during the test phase (such as categorization, or working memory updating).

4.3 Cognitive reserve and age-related changes in neural activity

Consistent with prior studies, we found lower P3b amplitudes and longer latencies for the older adults compared to the young individuals (McEvoy et al., 2001; Strayer et al., 1987). This age difference did not vary as a function of CR composite score, suggesting that CR does not directly alter the effects of aging on the P3b component. This finding is consistent with the theoretical model of CR (e.g., Barulli and Stern, 2013; Stern, 2009), which proposes that CR does not directly alter age or pathology-related neural changes, but rather serves to modify the behavioral and clinical expression of those changes. In line with this interpretation, both high and low composite CR older adults had smaller P3b amplitudes and longer latencies than young adults even when task demands were low, but the high composite CR individuals tended to perform better (as measured by d_L) than the low composite CR individuals. At the same time, these findings do not preclude the possibility

that CR modulates other age-related neural changes not examined in the current study, as has been proposed by other investigators (Nyberg et al., 2012).

4.4 Conclusions

In sum, this study provided further support for the concept of neural reserve by demonstrating that higher composite CR is associated with greater neural efficiency in terms of less neural activity and faster processing speed with increasing task demands. While our study examined verbal intelligence and educational background as components of CR, we acknowledge that factors related to an enriched environment – such as occupational complexity and participation in leisure and social activities – are also important components of CR. Therefore, future studies are needed to address the generalizability of our findings to other proxy measures of CR. We note, however, that education, vocabulary knowledge, and reading ability tend to have similar clinical effects on dementia risk and cognitive aging as these other components of CR (Richards and Sacker, 2003; Scarmeas et al., 2001), suggesting that our findings are applicable to the broader concept of CR. Additionally, this study underscores the utility of ERPs and other electrophysiological measures for testing neural mechanisms of CR.

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Highlights

- Healthy young and older adults performed a verbal working memory task.
- High cognitive reserve (CR) was associated with smaller changes in P3b amplitude and latency with increasing task difficulty, regardless of age.
- Our findings underscore the utility of ERPs for testing neural mechanisms of CR.

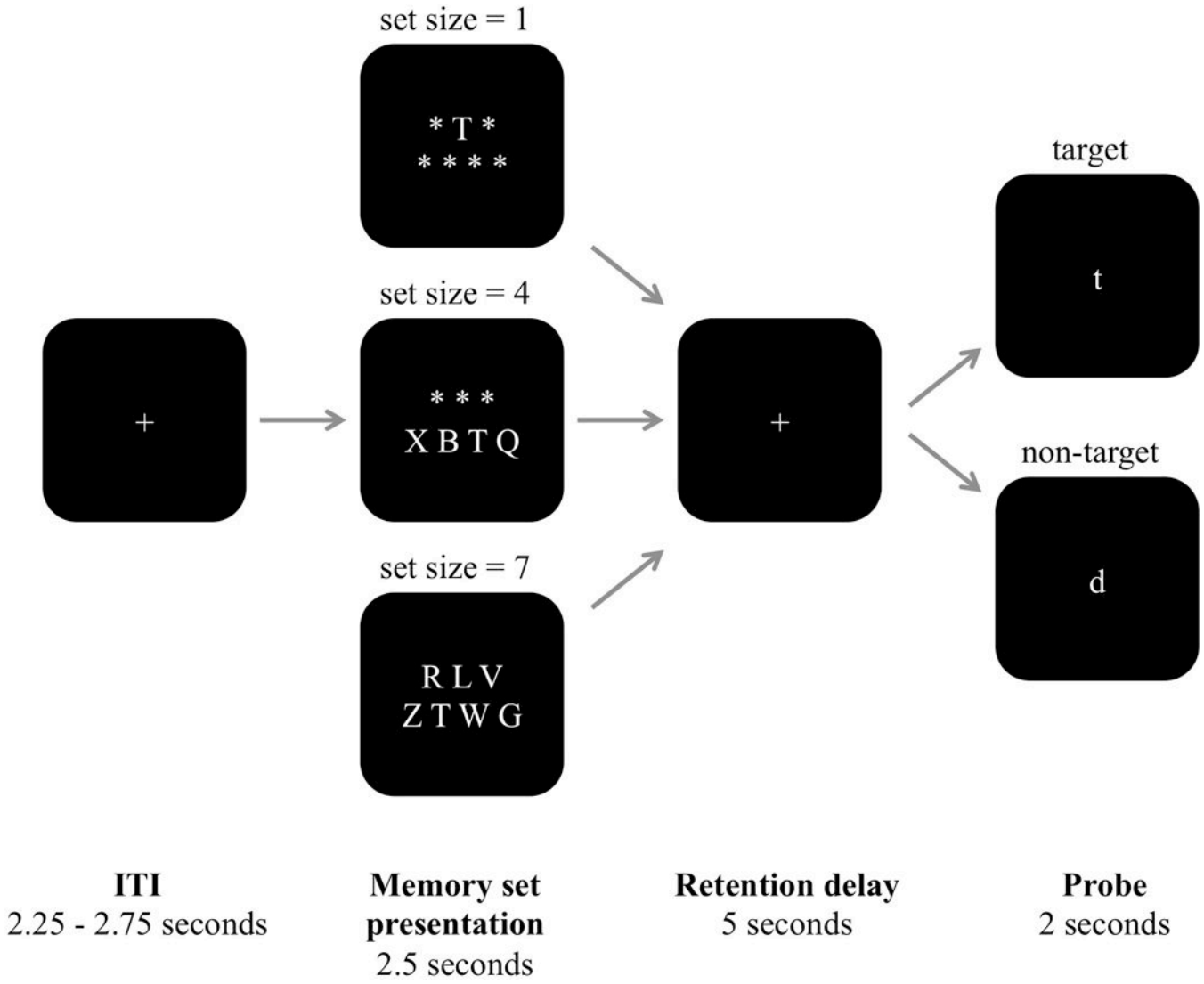

Figure 1.
A schematic diagram of the Sternberg verbal working memory task illustrating the time course of a single trial.

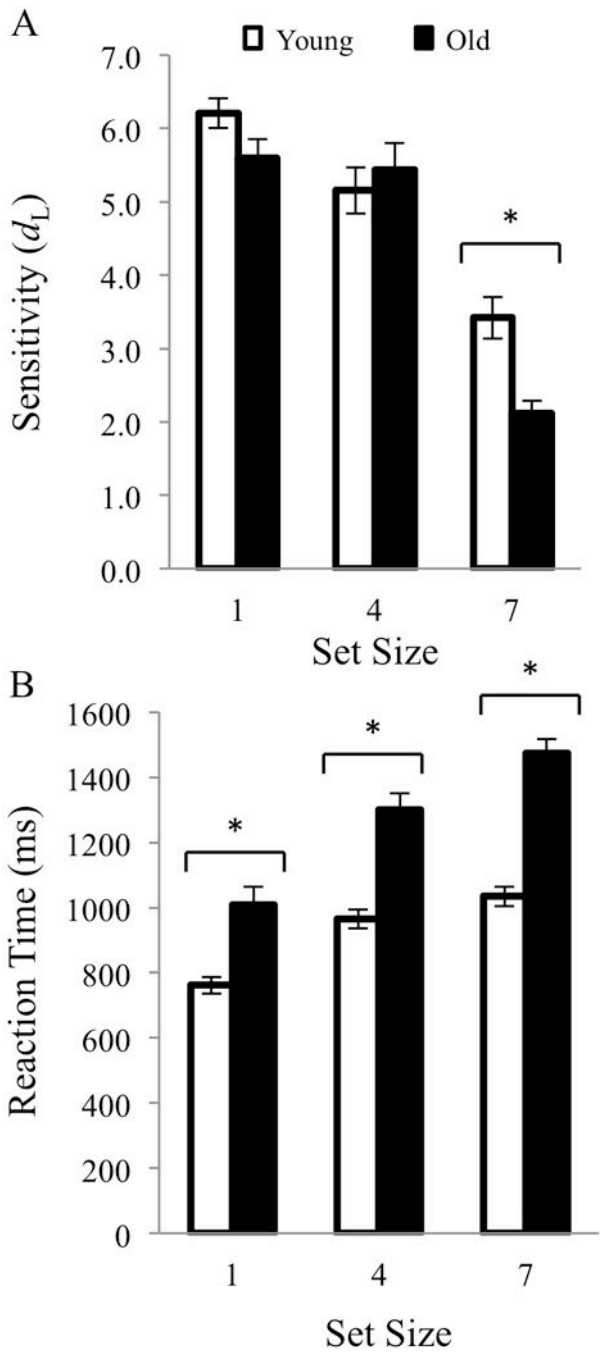

Figure 2.

Behavioral performance on the verbal working memory task. These graphs depict the parametric modulation of (A) mean sensitivity (d_L) and (B) mean reaction time as a function of increasing set size for younger and older adults. * Significant difference between groups, $p < .05$.

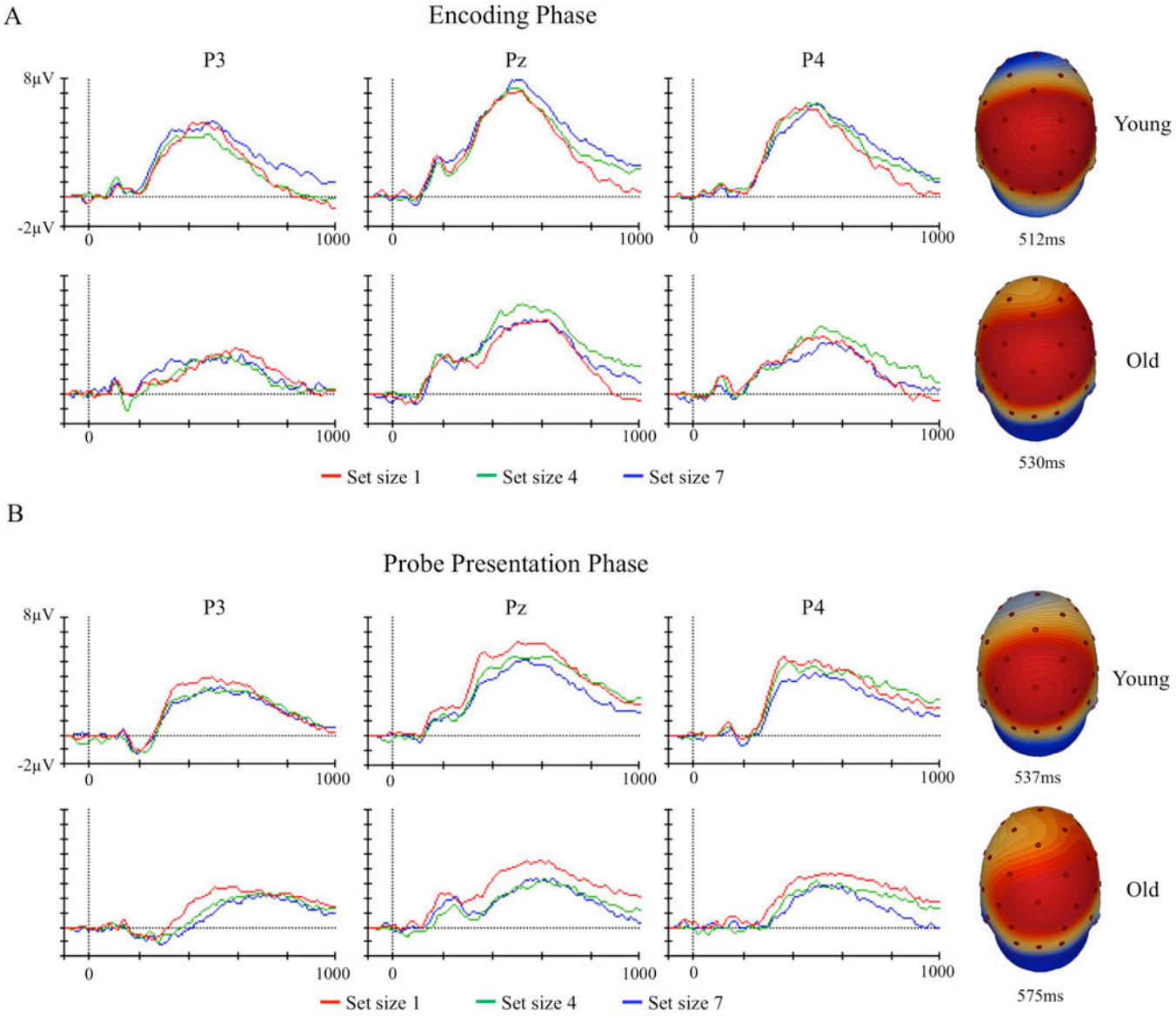

Figure 3.

Stimulus-locked, grand-averaged waveforms showing the P3b component during (A) the encoding phase and (B) the probe presentation phase. For the encoding phase, there was no reliable effect of set size on P3b amplitude and latency in the older adults, whereas young adults showed an increase in amplitude with increasing set size from 500 – 800 ms. For the probe phase, as set size increased, the amplitude of the P3b component decreased monotonically from 300–800 ms and the half-area latency increased in both young and older adults. The voltage maps on the right show the scalp distribution of activity at the time the P3b component peaked (averaging across set-sizes).

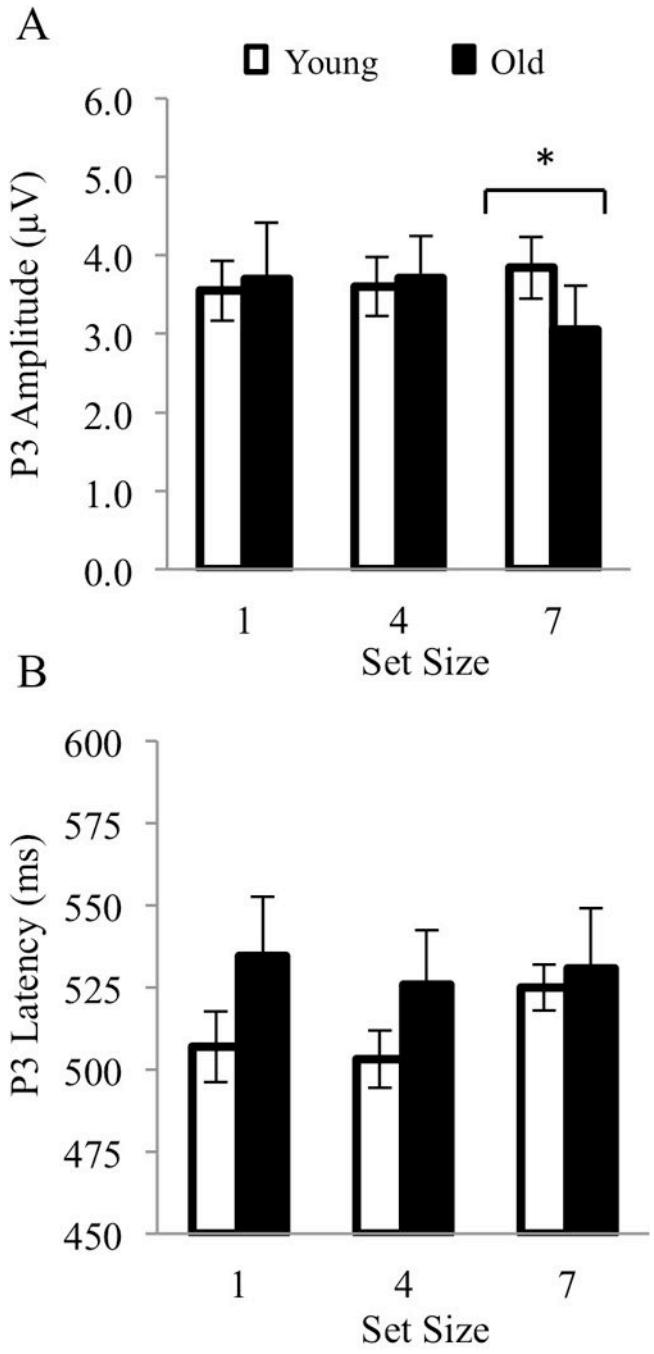

Figure 4.

Encoding phase. (A) Mean P3b Amplitudes by set size from 500 – 800 ms and (B) Mean P3b latencies by set size. P3b amplitude from 500 – 800 ms increased from set size 1 to 7 in the younger adults, but not older adults. Likewise mean P3b latency increased from set-size 1 to 7 in the young but not the older adults. However, these changes were not associated with CR (amplitude: $p = .32$; latency: $p = .76$). * Significant difference between groups, $p < .05$.

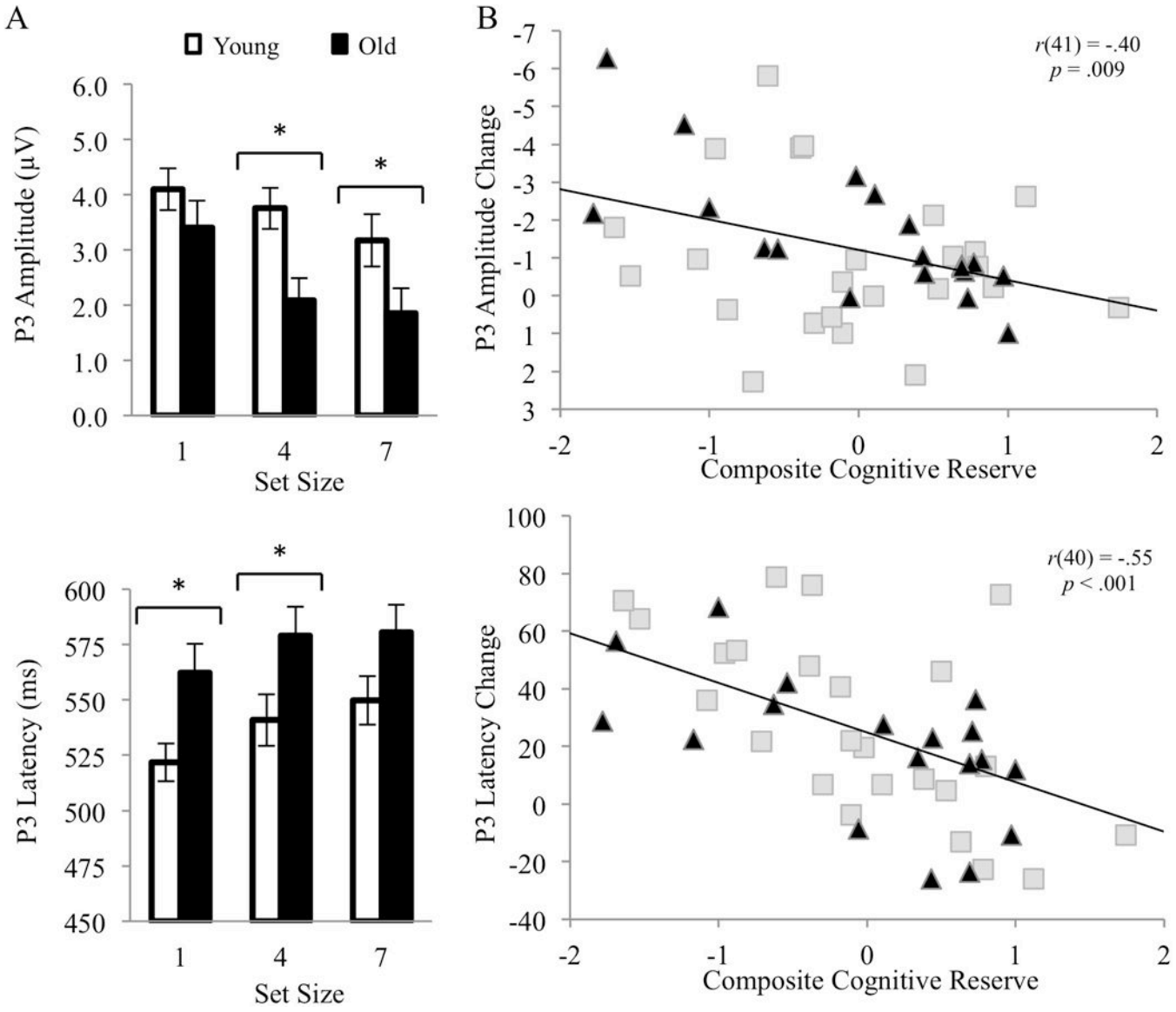

Figure 5.

Probe presentation phase. (A) P3b Amplitudes (from 300 – 800 ms) and latencies by set size for the probe presentation phase. (B) Scatterplots illustrating the correlation between composite cognitive reserve score and the change in P3b peak amplitude from 300 – 800 ms (top), and the correlation between composite cognitive reserve and P3b peak latency (bottom) during the probe presentation phase for younger and older adults. Correlation coefficients are for the entire group, partialing out the effects of age. * Significant difference between groups, $p < .05$.

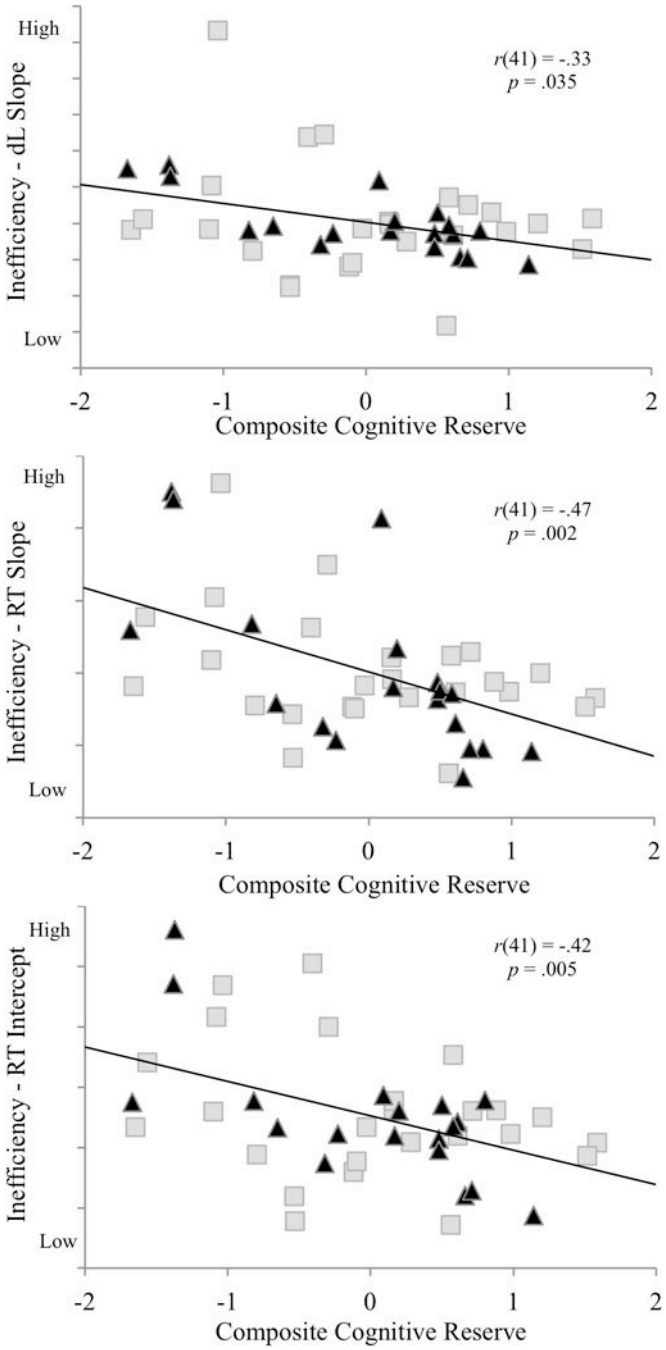

Figure 6.

Scatterplots illustrating the correlation between composite cognitive reserve scores and neural inefficiency with respect to d_L slope (top panel), RT slope (middle panel), and the RT intercept (bottom panel) during the probe presentation phase for younger adults (□) and older adults (▲), partialing out the effects of age.

Table 1

Participant Characteristics

	Young (n = 25)	Old (n = 19)
Female/Male	10/15	17/2
Age **	20.1 (2.3)	70.2 (5.1)
Education (yr) *	14.0 (1.41)	16.2 (3.3)
DRS	N/A	142.6 (2.0)
NART-IQ **	112.4 (6.1)	120.8 (6.5)
WAIS-R vocabulary	11.7 (2.8)	12.7 (2.2)

† Note: means and standard deviations (in parentheses) for demographic variables and neuropsychological test scores. DRS, Dementia Rating Scale; NART-IQ, North American Adult Reading Test estimated IQ; WAIS-R vocabulary, Wechsler Adult Intelligence Scale, Revised, vocabulary subtest, age-scaled score.

* Significant difference between groups, $p < .05$.

** Significant difference between groups, $p < .0001$.