in Aging Neur

ORIGINAL RESEARCH
published: 01 December 2017
doi: 10.3389/fnagi.2017.00392

The Impact of Age and Cognitive Reserve on Resting-State Brain Connectivity

Jessica I. Fleck[1], Julia Kuti[1], Jeffrey Mercurio[2], Spencer Mullen[1], Katherine Austin[3] and Olivia Pereira[4]*

[1] School of Social and Behavioral Sciences, Stockton University, Galloway Township, NJ, United States, [2] Department of Cell Biology and Molecular Biology, National Institute of Child Health and Human Development, Bethesda, MD, United States, [3] School of Graduate Studies, Stockton University, Galloway Township, NJ, United States, [4] Department of Biomedical Research, Nemours Hospital for Children, Wilmington, DE, United States

Cognitive reserve (CR) is a protective mechanism that supports sustained cognitive function following damage to the physical brain associated with age, injury, or disease. The goal of the research was to identify relationships between age, CR, and brain connectivity. A sample of 90 cognitively normal adults, ages 45–64 years, had their resting-state brain activity recorded with electroencephalography (EEG) and completed

OPEN AC

Edited by:
Aurel Popa-Wagner,
University of Rostock, Germany

Reviewed by:
Raluca Sandu Vintilescu,
University of Medicine and Pharmacy of Craiova, Romania
Vinay V. Parikh,
Temple University, United States

****Correspondence:***
Jessica I. Fleck
jessica.fleck@stockton.edu

Received: *01 August 2017*
Accepted: *13 November 2017*
Published: *01 December 2017*

Citation:
Fleck JI, Kuti J, Mercurio J, Mullen S, Austin K and Pereira O (2017) The Impact of Age and Cognitive Reserve on Resting-State Brain Connectivity. Front. Aging Neurosci. 9:392. doi: 10.3389/fnagi.2017.00392

consideration in research exploring the influence of CR on resting-state activity. Healthy older adults demonstrate lower task-related activity than younger adults (e.g., Cabeza et al., 2004; Grady et al., 2006). In addition, research exploring age-related changes in resting-state activity has determined that connectivity within resting-state networks (e.g., DMN and attention networks) decreases during aging (see Ferreira and Busatto, 2013; Sala-Llonch et al., 2015

Clock Drawing Test (Strauss et al., 2006), a measure of verbal intelligence, and several measures of memory and executive function. The National Adult Reading Test – Revised (NART-R; Blair and Spreen, 1989) was used in the present research to estimate verbal IQ. The NART-R contains 61 words with non-phonetic spellings. Participants are asked to read the words aloud. The number of incorrectly pronounced words is used to estimate the participant's verbal IQ.

To assess memory function, the Digit Span subtest of the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS – IV; Wechsler, 2008) and the California Verbal Learning Test – Second Edition (CVLT-II; Delis et al., 2000) were administered. For the Digit Span, a measure of working memory, individuals were read a series of numbers and were asked to repeat those numbers in the same order (forward), in reverse order (backward) or in ascending order (sequencing), for the respective sections of the assessment. In contrast, the CVLT-II (Delis et al., 2000) was administered as an assessment of long-term memory. Individuals were asked to learn a list of 16 words from four categories in five trials, with each trial including list presentation and list recall, and to subsequently recall those words after a brief distractor task (short-term recall) and again after a 20-min delay (long-term recall). For the current research, the number of items recalled during the encoding phase for trials 1 – 5 were summed to generate a CVLT-II Trials I-V score. In addition, the total number of list items recalled after the 20-min delay (CVLT-II Delayed Recall) was included as a measure of long-term memory.

To determine participants' abilities in flexible thinking, strategy use, and related processes, participants completed the Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency Test (Delis et al., 2001), as well as The Trail Making Test (Reitan and Wolfson, 1993). For Verbal Fluency, participants were asked to generate as many words as possible that began with a specific letter (i.e., Letter Fluency), and were asked to generate as many category members as possible (i.e., Category Fluency), with 60 s per trial. The total number of unique, correct responses were summed to generate total scores for Letter Fluency and Category Fluency. In the Trail Making Test (Reitan and Wolfson, 1993) individuals are asked to connect, in numerical order, encircled numbers that are randomly presented on a page (i.e., Trails A) and then, to connect encircled numbers and letters in alternating order (e.g., 1 to A, A to 2, 2 to B; Trails B). Trails A and Trails B completion times were used as performance indicators.

Procedure

The research procedure for the project was approved by Stockton University's Institutional Review Board. Participants completed two research sessions each lasting 1 – 1.5 h in duration, scheduled 1–2 weeks apart. All participants provided written informed consent and then completed the EEG recording and self-report measures as part of Session 1. During the EEG recording, participants had their eyes-open and eyes-closed, resting-state EEG activity recorded for 3 min each. Prior to the recording, participants were asked to sit in a relaxed position and to keep their minds free from other thoughts. Participants were visually monitored for adherence to the instructions, as well as drowsiness during the recording session.

The battery of neuropsychological measures was administered during Session 2. All participants completed the neuropsychological measures in the same order: (a) MMSE-II, (b) Digit Span, (c) CVLT-II, (d) Trails A and B, (e) NART-R, (f) The Clock Drawing Test, (g) CVLT-II – 20-min delayed recall and recognition, and (h) Verbal Fluency. After completing the assessments, participants were debriefed, thanked for their participation, and the session concluded. We note that participants who scored 2.0 or more standard deviations below their age-appropriate mean on any one assessment, or 1.5 standard deviations below their age-appropriate mean on two or more assessments, were sent a letter recommending a follow-up assessment in the community.

RESULTS

Cognitive reserve was calculated for each participant by creating a composite variable using estimated verbal IQ score (NART-R) and years of education. Participants' scores on IQ and education were Z-transformed and averaged to form the composite score. We observed no violations of normality nor the presence of outliers when we examined the composite scores for normality. Participants were divided into CR groups (low-CR; *n* D 43,

TABLE 1 | Descriptive statistics (means and standard deviations) for neuropsychological measures by CR group.

	Low CR	High CR
n	43	47
Age	58.72 (4.11)	58.32 (4.62)
Education	13.56 (1.91)	17.38 (1.62)
Verbal IQ	109.62 (5.11)	118.24 (4.82)
MMSE	28.21 (1.54)	29.00 (1.10)
Digit span total	26.26 (5.15)	29.36 (4.28)
CVLT total recall	46.72 (7.88)	50.83 (9.90)
CVLT delayed recall	10.16 (2.95)	11.62 (3.00)
Trails A	26.82 (7.34)	26.60 (7.91)
Trails B	62.96 (29.82)	59.68 (17.51)
Letter fluency	40.60 (10.84)	48.91 (9.61)
Category fluency	42.23 (7.94)	45.60 (6.17)

TABLE 2 | Univariate ANOVA results comparing low-CR and high-CR groups on neuropsychological measures.

Measure	*F*	*P*	R^2
MMSE	8.749	0.004	0.094
Digit span total	9.098	0.003	0.098
CVLT total recall trials I-V	5.025	0.028	0.056
CVLT 20-min delayed recall	6.091	0.016	0.068
Trails A	0.077	0.782	0.001
Trails B	0.395	0.531	0.005
Letter Fluency	13.731	$<$0.001	0.140
Category fluency	5.139	0.026	0.058

Significant at the corrected alpha level of 0.00625.

high-CR; n D 47) using a median split. The unequal split between conditions arose because three participants had z scores of 0.08 and were all placed in the high-CR group. Descriptive statistics for key demographic and neuropsychological variables are presented separately by CR group in **Table 1**. Prior to analysis, we screened all neuropsychological variables for violations of normality and linearity, as well as for the presence of univariate and multivariate outliers. One univariate outlier on the Trails B assessment (Delis et al., 2001) was addressed using pairwise deletion. No multivariate outliers were identified using Mahalanobis distance ($p < 0.001$). No other violations were detected.

We separately calculated mean intrahemispheric coherence for electrode pairs in the left hemisphere and the right hemisphere, allowing us to focus on differences in coherence between hemispheres for high-CR and low-CR groups. Mean coherence was separately calculated for each frequency band (delta, theta, low alpha, high alpha, beta, and gamma) under eye-closed and eyes-open recording conditions.

To explore potential differences in cognitive performance between CR groups (low-CR, high-CR), a between-subjects multivariate analysis of variance was performed using the eight neuropsychological assessment scores listed in **Table 2** as dependent variables. Using Wilks' Lambda, the combined dependent variables were significantly affected by CR, $F(8, 77)$ D 3.635, p D 0.001, $!^2_p$ D 0.274. To explore differences between CR groups for individual dependent variables, univariate ANOVAs were conducted separately for each neuropsychological assessment (see **Table 2**). Using a corrected alpha level of 0.00625 (0.05/8 neuropsychological tests), a significant difference in performance was observed between CR conditions for MMSE, Digit Span Total, and Fluency. In all instances, high-CR participants exhibited stronger cognitive performance than low-CR participants. There was no significant difference between CR conditions for age, $F(1,88)$ D 0.188, p D 0.665, $!^2_p$ D 0.002.

Using Pearson correlations, we examined the relationship between age and coherence separately for high-CR and low-CR groups under eyes-closed and eyes-open recording conditions (see **Table 3**). Correlations were calculated for each frequency band and all analyses were conducted as two-tailed tests, using a corrected alpha of 0.0083 (0.05/6 frequency bands). Relationships marked as significant at the 0.01 level in **Table 3** also met the 0.0083 corrected alpha level for significance. For low-CR participants, we observed significant inverse relationships between age and brain coherence over the left hemisphere, with most significant correlations present under eyes-open recording conditions. In contrast, for high-CR participants we detected significant positive relationships between age and coherence over the right hemisphere; these correlations were only statistically significant for the theta and high alpha frequency bands under eyes-closed recording conditions. As reflected in **Table 3**, most correlation coefficients between age and brain coherence were negative for low-CR participants, whereas most correlation coefficients between age and brain coherence were positive for high-CR participants. The relationships between age and coherence are plotted together for the two CR groups in **Figures 1A,B**.

In order to more fully examine the complex relationships between age, CR, and brain connectivity presented in **Table 3** and **Figures 1A,B**, we divided participants into high and low age groups using a mean split. Participants below the mean age of 58.51 years were placed in the younger group. We then conducted six mixed model ANOVAs, one for each frequency band, exploring differences between Age and CR groups in global brain connectivity. Age and CR were between-subjects variables in the design and hemisphere (left, right), and recording condition (eyes-closed, eyes-open) were within-subjects variables. Descriptive statistics for coherence are reported by condition for the left and right hemispheres, under eyes-closed and eyes-open recording conditions in **Table 4**. Because of our interest in understanding the impact of age and CR on coherence, we focused on significant interactions that included age, CR, or both age and CR as variables. Significant main-effects or interactions involving only within-subjects variables are not reported. For all mixed model ANOVAs we used a corrected alpha of 0.0083 (0.05/6 frequency bands); significant interaction results are summarized in **Table 5**.

Several interaction patterns emerged as a result of our analyses. First, significant age by hemisphere interactions were observed for all frequency bands, from delta through high alpha, but failed to reach significance for beta or gamma frequencies. Least significant difference (LSD) *post*

TABLE 3 | Correlations between age and resting-state EEG coherence.

	Low CR				High CR			
	Eyes closed		Eyes open		Eyes closed		Eyes open	
	LH	RH	LH	RH	LH	RH	LH	RH
Delta	0.245	0.171	0.388	0.192	0.082	0.341	0.052	0.172
Theta	0.332	0.107	**0.526**	0.167	0.234	**0.385**	0.231	0.289
Low alpha	0.184	0.184	**0.413**	0.038	0.104	0.194	0.130	0.288
High alpha	0.254	0.200	0.319	0.089	0.103	**0.403**	0.033	0.253
Beta	0.330	0.141	**0.429**	0.194	0.114	0.302	0.025	0.183
Gamma	**0.402**	0.255	**0.493**	0.313	0.212	0.234	0.069	0.150

$p < 0.05$, $p < 0.01$, $p < 0.001$. *Correlations in bold are significant following alpha correction.*

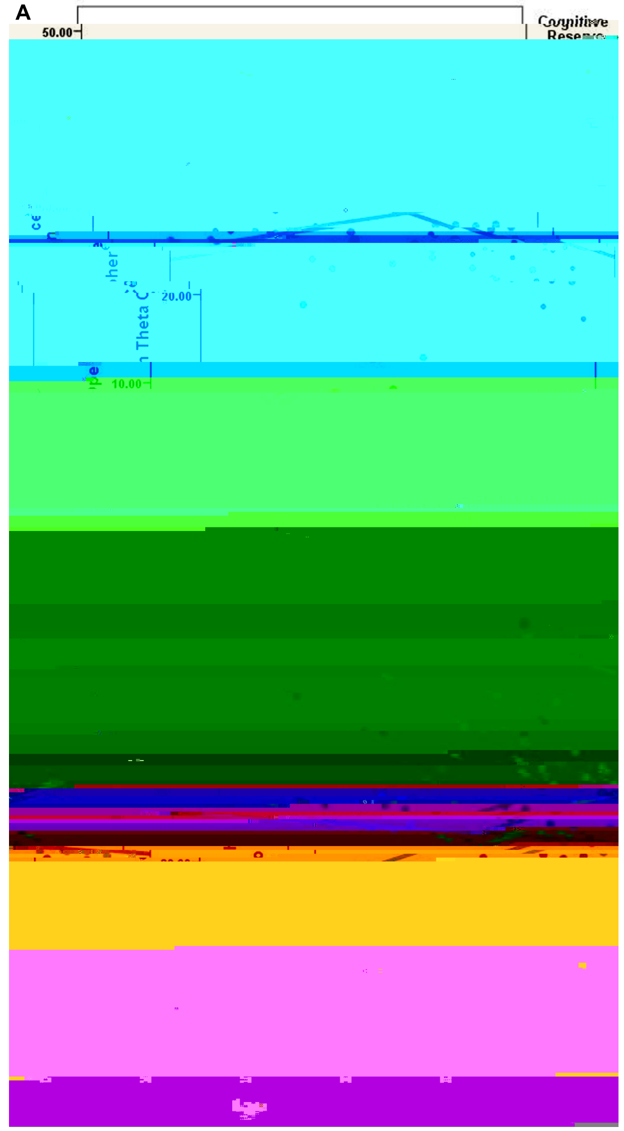

FIGURE 1 | (A) The relationship between age and eyes open theta coherence — left hemisphere; low CR: *r* D 0.526, high CR: *r* D 0.231. **(B)** The relationship between age and eyes closed theta coherence – right hemisphere; low CR: *r* D 0.107, high CR: *r* D 0.385.

TABLE 4 | Coherence descriptive statistics, means (standard deviations).

	Younger		**Older**	
	Low CR	**High CR**	**Low CR**	**High CR**
Delta				
Closed				
Left	28.34 (5.88)	28.76 (10.80)	25.32 (5.85)	28.81 (6.06)
Right	28.08 (7.66)	24.25 (8.07)	26.71 (7.94)	31.67 (6.91)
Open				
Left	28.89 (6.14)	26.86 (10.62)	24.50 (5.28)	26.75 (6.12)
Right	27.50 (6.79)	24.10 (9.02)	26.07 (6.66)	29.26 (7.60)
Theta				
Closed				
Left	33.94 (5.50)	31.48 (7.95)	29.47 (7.03)	33.58 (7.29)
Right	32.09 (7.46)	29.32 (9.82)	32.99 (7.52)	37.60 (6.00)
Open				
Left	33.68 (5.76)	27.57 (8.42)	27.36 (5.06)	29.98 (4.97)
Right	32.50 (9.25)	27.56 (9.30)	31.88 (6.93)	34.23 (6.41)
Low alpha				
Closed				
Left	40.94 (7.23)	40.80 (7.66)	36.22 (8.01)	40.87 (8.79)
Right	33.01 (7.66)	37.78 (9.51)	38.22 (8.66)	42.28 (8.19)
Open				
Left	37.55 (7.97)	32.01 (7.87)	30.69 (5.33)	33.24 (6.04)
Right	32.19 (7.42)	30.32 (8.75)	34.65 (8.32)	36.24 (6.37)
High alpha				
Closed				
Left	37.11 (4.00)	37.77 (7.94)	33.02 (7.80)	38.79 (7.00)
Right	34.21 (7.58)	33.73 (8.24)	33.97 (6.04)	39.86 (5.64)
Open				
Left	35.02 (5.76)	31.08 (8.82)	29.85 (6.12)	32.01 (5.48)
Right	31.88 (7.69)	28.93 (7.10)	32.64 (7.12)	35.05 (6.47)
Beta				
Closed				
Left	30.59 (5.79)	29.91 (7.11)	27.04 (5.17)	32.57 (6.77)
Right	29.67 (9.03)	27.21 (6.00)	29.60 (6.41)	33.72 (5.92)
Open				
Left	29.46 (8.37)	25.06 (8.01)	24.10 (5.32)	26.11 (6.07)
Right	29.17 (10.88)	22.64 (6.42)	26.98 (7.34)	28.41 (8.92)
Gamma				
Closed				
Left	29.37 (11.98)	25.22 (8.91)	22.26 (5.38)	31.52 (13.95)
Right	30.28 (16.78)	22.05 (5.74)	25.20 (8.99)	30.84 (11.87)
Open				
Left	28.56 (11.37)	22.10 (9.38)	20.49 (6.10)	24.19 (10.63)
Right	30.41 (15.58)	17.32 (4.55)	23.37 (10.87)	23.03 (12.30)

hoc analyses were conducted within each frequency band to clarify the nature of the interactions (see **Figure 2**). For younger participants left-hemisphere coherence was greater than right-hemisphere coherence for delta, low alpha, and high alpha frequencies. In contrast, for older participants right-hemisphere coherence was greater than left-hemisphere coherence for all frequency bands, for delta through high alpha. In addition, comparisons between age groups conducted separately by hemisphere revealed greater right-hemisphere coherence for older participants than for younger participants in theta, low alpha, and high alpha frequency bands. No significant differences were observed between age groups for left-hemisphere coherence. The three-way interaction for age, CR, and hemisphere failed to reach significance for any of the frequency bands, suggesting no significance difference in the above patterns between CR groups.

A second pattern within the interaction results included significant CR by recording condition interactions for all frequency bands except delta. LSD *post hoc* analyses were conducted for each frequency band and the results are presented

TABLE 5 | Significant ANOVA interactions showing differences in EEG coherence between age and CR conditions.

	F	*p*	R^2
Delta			
Age Hemisphere	8.771	0.004	0.093
Theta			
CR Recording condition	10.514	0.002	0.109
Age Hemisphere	10.486	0.002	0.109
Age CR	9.336	0.003	0.098
Low alpha			
CR Recording condition	10.313	0.002	0.107
Age Hemisphere	17.341	<0.001	0.168
High alpha			
CR Recording condition	7.626	0.007	0.081
Age Hemisphere	11.63	0.001	0.119
Age CR	7.608	0.007	0.081
Beta			
CR Recording condition	24.685	<0.001	0.223
Age CR	7.295	0.008	0.078
Gamma			
CR Recording condition	18.229	<0.001	0.175
Age CR	10.237	0.002	0.106

in **Figure 3**. In low-CR participants, greater coherence was exhibited for eyes-closed than eyes-open recording conditions, for low alpha, high alpha, and beta frequencies. The same pattern was exhibited for high-CR participants; however, the increase in coherence from eyes-open to eyes-closed recordings for high-CR participants were more substantial than that exhibited by 46(0.002)-5646(080ern)]TJ 0 -11.4577n
.i

FIGURE 3 | Mean coherence in low CR and high CR participants for eyes-closed (dark gray bars) and eyes-open (light gray bars) recording conditions. Error bars reflect the standard error for each condition. Lines connect conditions that differ significantly from each other, with the endpoints of each line over the middle of the bars for conditions that differ significantly from each other during pairwise comparisons. $p < 0.05$, $p < 0.01$, $p < 0.001$.

coherence under eyes-closed versus eyes-open recording conditions between low-CR and high-CR groups. We observed greater connectivity under eyes-closed than eyes-open recording conditions for both low-CR and high-CR participants, with a more substantial difference in coherence between recording conditions for high-CR participants. These findings coincide with prior research by Knyazev et al. (2015) who reported decreased connectivity during eyes-open versus eyes-closed recording conditions for both younger and older participant groups. Prior research reporting greater alpha power under eyes-closed than eyes-open recording conditions observed a relationship between the degree of power change between recording conditions and measures of arousal, such as skin conductance level (Barry et al., 2007). We observed a more substantial decrease in alpha coherence from eyes-closed to eyes-open conditions in high-CR than in low-CR participants, which may reflect greater arousal in response to visual stimulation in conjunction with high CR. Therefore, although speculative, the differences between recording conditions in the present research may reflect the influence of CR on arousal level.

The most significant finding in our research is the interaction effect for age and CR on brain coherence. Theories of CR suggest that high levels of CR can benefit the individual through increased neural efficiency, as well as neural compensation (Stern, 2002, 2009). As an example, Speer and Soldan (2015) demonstrated that participants with high levels of CR

k,ortge ts whicxrt661(veiv343)we26(moat)-491(pre)2ased

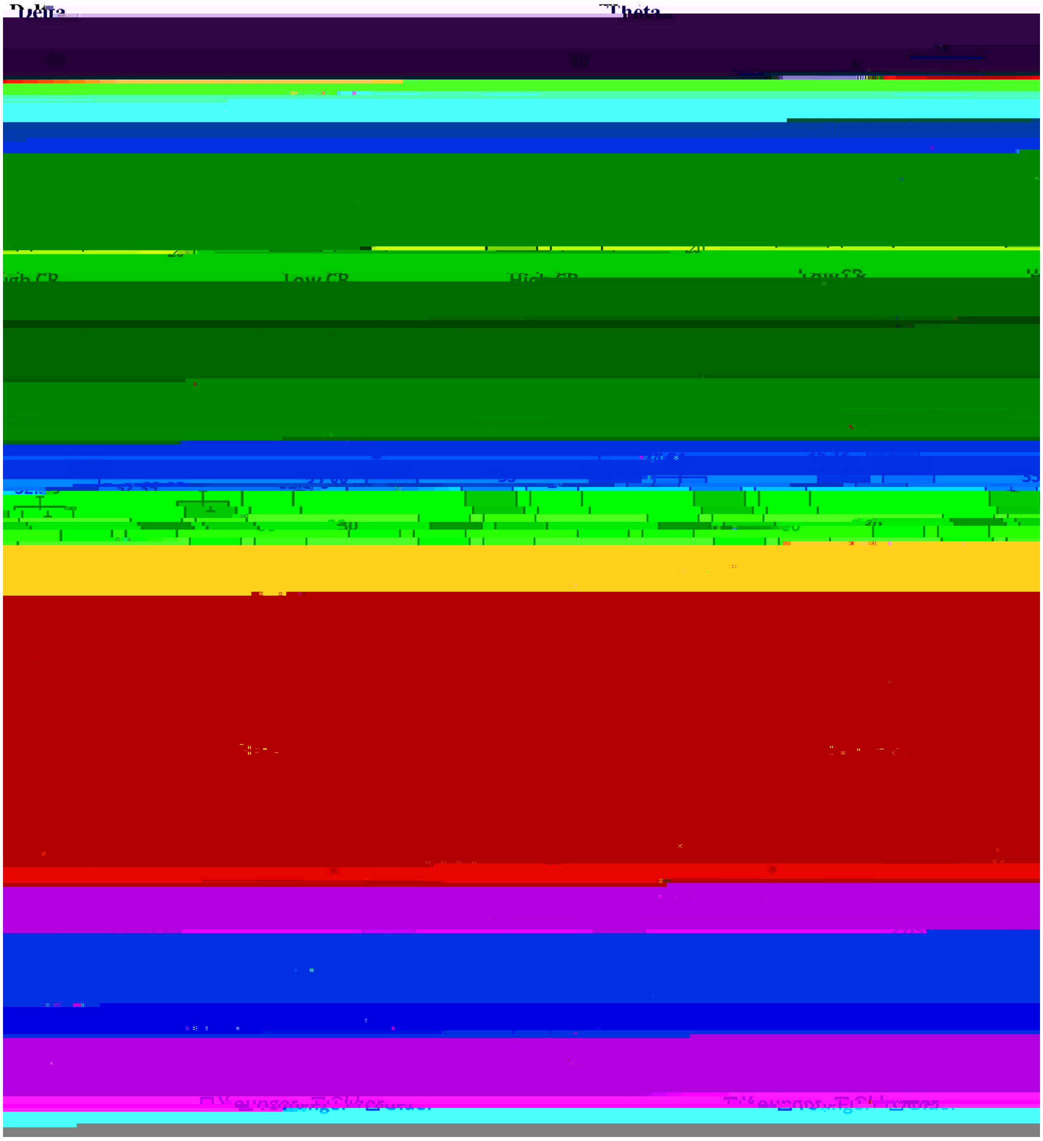

FIGURE 4 | Mean coherence for younger (dark gray bars) and older (light gray bars) participants in low CR versus high CR conditions. Error bars reflect the standard error for each condition. Lines connect conditions that differ significantly from each other, with the endpoints of each line over the middle of the bars for conditions that differ significantly from each other during pairwise comparisons. $p < 0.05$, $p < 0.01$, $p < 0.001$.

a brief delay. Participants who were high in CR showed a reduction in the electrical changes in the brain that typically occur during longer, more difficult trials in response to stimuli presented during the recognition phase (i.e., a reduction in amplitude decrease and less of an increase in latency of the Pb3 component). As noted by the researchers, higher levels of CR mitigated the neural changes associated with more difficult trials, demonstrating that high CR results in an increase in neural efficiency. Thus, Speer and Soldan's findings offer support for the influence of CR on brain activity during task-directed cognition.

In the present research, differences in coherence between high-CR and low-CR groups varied for younger and older

Babiloni, C., Frisoni, G., Vecchio, F., Lizio, R., Pievani, M., Geroldi, C., et al. (2009). Global functional coupling of resting EEG rhythms is abnormal in mild cognitive impairment and Alzheimer's disease: a multicenter EEG study. *J. Psychophysiol.* 23, 224–234. doi: 10.1027/0269-8803.23.4.224

Barry, R. J., Clarke, A. R., Johnstone, S. J., Magee, C. A., and Rushby, J. A. (2007). EEG differences between eyes-closed and eyes-open resting conditions. *Clin. Neurophysiol.* 118, 2765–2773. doi: 10.1016/j.clinph.2007.07.028

Bartrés-Faz, D., Solé-Padullés, C., Junqué, C., Rami, L., Bosch, B., Bargalló, N., et al. (2009). Interactions of cognitive reserve with regional brain anatomy and brain function during a working memory task in healthy elders. *Biol. Psychol.* 80, 256–259. doi: 10.1016/j.biopsycho.2008.10.005

Barulli, D., and Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends Cogn. Sci.* 17, 502–509. doi: 10.1016/j.tics.2013.08.012

Bastin, C., Yakushev, I., Bahri, M. A., Fellgiebel, A., Eustache, F., Landeau, B., et al. (2012). Cognitive reserve impacts on inter-individual variability in resting-state cerebral metabolism in normal aging. *Neuroimage* 63, 713–722. doi: 10.1016/j.neuroimage.2012.06.074

Blair, J. R., and Spreen, O. (1989). Predicting premorbid IQ: a revision of the National Adult Reading Test. *Clin. Neuropsychol.* 3, 129–136. doi: 10.1080/13854048908403285

Bosch, B., Bartrés-Faz, D., Rami, L., Arenaza-Urquijo, E. M., Fernández-Espejo, D., Junqué, C., et al. (2010). Cognitive reserve modulates task-induced activations and deactivations in healthy elders, amnestic mild cognitive impairment and mild Alzheimer's disease. *Cortex* 46, 451–461. doi: 10.1016/j.cortex.2009.05.006

Brosnan, M. B., Demaria, G., Petersen, A., Dockree, P. M., Robertson, I. H., and Wiegand, I. (2017). Plasticity of the right-lateralized cognitive reserve network in ageing. *Cereb. Cortex*. doi: 10.1093/cercor/bhx085 [Epub ahead of print].

Cabeza, R., Daselaar, S. M., Dolcos, F., Prince, S. E., Budde, M., and Nyberg, L. (2004). Task- independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cereb. Cortex* 14, 364–375. doi: 10.1093/cercor/bhg133

Celone, K. A., Calhoun, V. D., Dickerson, B. C., Atri, A., Chua, E. F., Miller, S. L., et al. (2006). Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: an independent component analysis. *J. Neurosci.* 26, 10222–10231. doi: 10.1523/JNEUROSCI.2250-06.2006

Cheung, M. C., Chan, A. S., Han, Y. M., and Sze, S. L. (2014). Brain activity during resting state in relation to academic performance. *J. Psychophysiol.* 28, 47–53. doi: 10.1027/0269-8803/a000107

Cole, M. W., Yarkoni, T., Repovš, G., Anticevic, A., and Braver, T. S. (2012). Global connectivity of prefrontal cortex predicts cognitive control and intelligence. *J. Neurosci.* 32, 8988–8999. doi: 10.1523/JNEUROSCI.0536-12.2012

1d0oi1036/j.ti07/si0702-39.815 -8Td64 Td [(doi:)-200 803/a011542.207(2T 0 1 k 0 0 0 1 K 0 0 0 1 k 0 0 0 1 K 0 0 0 1 k 0 0 0 1 K -9

Damoiseaux, J. S. (2012). Resting-state fMRI as a biomarker for Alzheimer's disease? *Alzheimers Res. Ther.* 4:8. doi: 10.1186/alzrt106

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., and Cabeza, R. (2008). Que PASA? The posterior–anterior shift in aging. *Cereb. Cortex* 18, 1201–1209. doi: 10.1093/cercor/bhm155

Delis, D. C., Kaplan, E., and Kramer, J. H. (2001). *Delis-Kaplan Executive Function System*. San Antonio, TX: The Psychological Corporation.

Delis, D. C., Kramer, J. H., Kaplan, E., and Ober, B. A. (2000). *California Verbal Learning Test: Adult Version Manual*. San Antonio,