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A neural implementation of cognitive reserve: Insights from a longitudinal fMRI study of set-switching in aging

Fatemeh Hasanzadeh [a,b], Christian Habeck [a,b,c], Yunglin Gazes [a,b,c,d], Yaakov Stern [a,b,c,*]

[a] Cognitive Neuroscience Division, Department of Neurology, Columbia University, New York, NY, United States
[b] Gertrude H. Sergievsky Center, Columbia University, New York, NY, United States
[c] Taub Institute for Research in Alzheimer's Disease and the Aging Brain, Columbia University, New York, NY, United States
[d] Montclair State University, Department of Psychology, Montclair, NJ, United States

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ABSTRACT

Aging is often accompanied by changes in brain structure and executive functions, particularly in tasks involving cognitive flexibility, such as task-switching. However, substantial individual differences in the degree of cognitive impairment indicate that some individuals can cope with brain changes more effectively than others, suggesting higher cognitive reserve (CR). This study identified a neural basis for CR by examining the longitudinal relationship between task-related brain activation, structural brain changes, and changes in cognitive performance during an executive task-switching paradigm including single and dual conditions. Fifty-two older individuals were assessed at baseline and followed up after five years. Structural brain changes related to task-switching performance were analyzed using elastic net regression. Task-related functional brain activation was measured using ordinal trends canonical variate analysis (OrT CVA), capturing patterns of activation increasing from single to dual conditions. A differential task-related expression score (dOrT) was calculated as the difference in pattern expression scores between single and dual conditions at baseline. A linear regression model tested whether dOrT moderated the impact of brain changes on changes in switch cost over five years. Results showed a significant interaction between changes in brain structure and dOrT activation on switch cost change, indicating a moderation effect of task-related activation. Higher dOrT buffered the impact of brain structural decline on switch costs, enabling older adults to better cope with age-related brain structural changes and preserve cognitive flexibility. These findings suggest that these task-related activation patterns represent a neural basis for CR.

1. Introduction

Aging is accompanied by various alterations in brain structure and functions, including decline in executive functions (Buckner, 2004). One of the main components of executive functions is task-switching, an ability that fundamentally influences flexibility in cognition and behavior (Monsell, 2003; Vandierendonck et al., 2010). Switching or shifting between tasks impacts our performance, typically manifesting as an increase in response time and/or error rate compared to performing each task separately. This performance cost incurred by switching is referred to as "switch cost" (Monsell, 2003). Prior research has demonstrated behavioral performance decline (Meiran et al., 2001; Wasylyshyn et al., 2011), associated alteration in underlying neural activation (Aron et al., 2004; Badre and Wagner, 2006; Brass and Von Cramon, 2002; Dove et al., 2000; Gazes et al., 2015, 2012; Uddin, 2021), as well as structural deterioration (Gold et al., 2010; Nguyen et al., 2019; Oh et al., 2018) within brain regions that mediate executive task control during task-switching in older adults. Older adults typically show larger switch costs when switching between tasks (Wasylyshyn et al., 2011), which has been linked to reduced flexibility in cognitive control (Oh et al., 2018). However, there are substantial individual differences in the degree of task-switching impairment (Kray and Lindenberger, 2000). While some older adults maintain high cognitive functioning despite age-related brain changes, others experience more decline. This

* Correspondence to: Cognitive Neuroscience Division, Department of Neurology, Columbia University, 630 W 168th St, P&S Box 16, New York, NY 10032, United States.
E-mail address: ys11@cumc.columbia.edu (Y. Stern).

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variability suggests that differences in underlying neural activations likely enable some older individuals to cope more effectively with structural brain changes than others (Stern, 2009). A key concept that elucidates this phenomenon is cognitive reserve (CR). CR is a property of the brain that enables higher cognitive performance compared to what would be expected, considering the extent of brain changes associated with life-course events, as well as brain injury or disease (Stern et al., 2023). Studying CR requires assessing relationships between brain changes and cognitive performance, along with variables that influence or moderate this relationship. This moderating variable can be IQ, exposure like education and occupation, or the specific neural mechanisms that influence the impact of brain changes on cognition. CR is demonstrated when a hypothesized moderating factor like sociocultural or brain functional measure impacts the relationship between brain changes and cognitive performance.

In the current longitudinal study with two measurement time points (baseline and 5-year follow-up), we aimed to investigate differential task-related neural activation during the performance of an experimental task-switching paradigm as a potential neural implementation of CR. Specifically, we explored whether greater engagement of task-related functional brain networks during the performance of an executive control function (ECF) task is associated with more preserved cognitive performance in the presence of age-related structural brain changes that would typically impair cognition. To obtain task-related brain networks, we applied ordinal trend canonical variates analysis (OrT CVA) to functional MRI (fMRI) data recorded from the single and dual task conditions in a set-shifting paradigm. OrT CVA is a multivariate technique that detects a consistent set of brain regions displaying correlated changes in activation as task difficulty increases among participants (Habeck, Krakauer, et al., 2005). So, this technique allows the characterization of individual differences in functional brain responses to increasing task-switching demands, here the difference between single to dual conditions. A multivariate structural brain measure was constructed by applying an elastic net linear regression model to extract a summary metric of volume and thickness changes in several cortical and subcortical regions that impact task performance. We then examined changes in task-switching performance (as measured by switch cost) over 5 years and how these changes were impacted by changes in brain structure and brain function. We hypothesized that the impact of structural brain changes on task-switching performance would be moderated by the level of differential task-related activation between single to dual conditions. This hypothesis is grounded in cognitive reserve theory, particularly the concept of capacity which posits that individuals with higher cognitive reserve have greater capacity to engage neural resources as task demands increase (Stern et al., 2020). This greater capacity may allow them to maintain performance in the face of age-related brain changes or increasing task complexity.

Key features of this study include a longitudinal design over 5 years to examine the changes in brain structure and cognition. Moreover, we used advanced data analysis methods, including OrT CVA to characterize task-related fMRI patterns. Most importantly, in this study we moved beyond traditional CR proxies like IQ and education and identified neural representation of cognitive reserve. This is the first study to directly investigate directly investigate differential functional activation as a neural marker of cognitive reserve in ECF tasks, testing whether greater engagement of specific functional networks mitigates the impact of structural decline on switch cost. The longitudinal approach assessing whether brain activation moderates trajectories of cognitive function and brain structure unveils new insights into the neural implementation of CR.

2. Materials and methods

2.1. Participants

In the present study, a total of 52 individuals in later adulthood with the baseline age range of 60–71 years (average age of 64.79 ± 3 years) were assessed over two time points: baseline and a 5-year follow-up. Detailed participants' information can be found in Table 1. Inclusion criteria included being right-handed, having a normal or corrected-to-normal vision, proficient in English, and having no history of psychiatric or neurological disorders. Additionally, participants underwent screening for dementia and mild cognitive impairment using the Dementia Rating Scale (Mattis, 1988) at both baseline and follow-up assessments. All participants provided written informed consent. The Institutional Review Board of the College of Physicians and Surgeons of Columbia University reviewed and approved all protocols based on the guidelines and regulations.

2.2. Task design and stimulus presentation

The task was based on the design of Koechlin et al.'s (Koechlin et al., 2003) Experiment 2, using a color-cued task-switching paradigm with a no-go component to probe cognitive processes related to task-switching (Fig. 1). The task consisted of two single blocks and two dual blocks. Each block lasted 33.6 s and contained 12 letter stimuli to which participants responded with timed button presses. Before each block, a 4.8-second instruction cue was indicated to inform about the required action. Responses involved right or left button presses, or no action, based on color-coded cues: green for vowel/consonant judgments, red for lower/upper case judgments, and white for no-go trials. The experiment also included two 33.6 s rest blocks with no stimulus presentation and responses. The fMRI acquisition session consisted of six functional runs, each containing the four active and two rest blocks in a Latin Square order to minimize any potential sequencing biases (Gazes et al., 2012).To promote stable cognitive/behavioral performance during the scanning session, participants completed a pre-training session outside the scanner, including task instructions review, practice blocks, and auditory error feedback.

The stimulus presentation was executed using an LCD projector, projected onto a screen situated at the foot of the MRI bed. Participants viewed stimuli through mirrors within the head coil. Responses were collected using a LUMItouch response system and task administration, synchronization, and data collection were managed using E-Prime software running on a computer.

2.3. Behavioral analysis

Behavioral performance was assessed by collecting the median reaction time for correct trials in single and dual conditions at baseline and follow-up. The difference in median reaction time between the two task conditions was referred to as the switch cost, which was calculated for both baseline and follow-up.

2.4. MRI acquisition

Structural and functional MRI data were acquired at baseline and follow-up. For the baseline session, all participants underwent MRI scanning on a 3.0 T Philips Achieva scanner equipped with a standard quadrature head coil. In the follow-up session, data from 39 participants were acquired using the same Philips scanner, while data from the

Table 1
Participants information.

Characteristics	
N	52
Sex (Male/Female)	25/27
Baseline Age (Mean ± SD)	64.82±3
Years of Education (Mean ± SD)	16.13± 2.09
NART-IQ (Mean ± SD)	119±7.97
Baseline DRS (Mean ± SD)	140.5±2.8
Follow-up DRS (Mean ± SD)	139.7±2.76

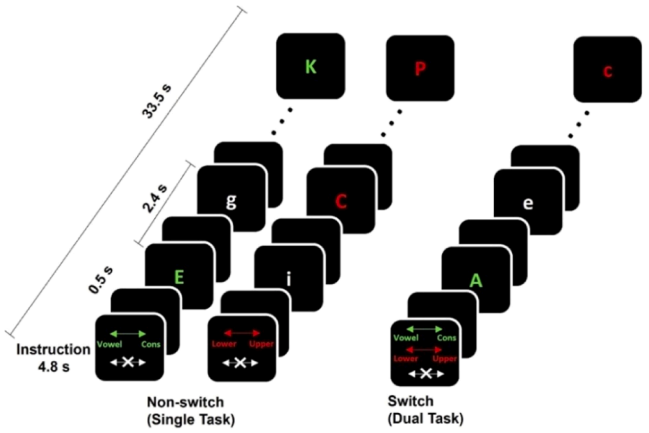

Fig. 1. Block examples of single and dual block conditions. In the single condition, participants were assigned either a vowel/consonant task or a lower-case/upper-case task. While in the dual condition, participants were required to switch between these two tasks. The colors represent task cues: white for no-go trials, red for the upper/lower-case task, and green for the vowel/consonant task. Arrows indicate the assigned response hands: left for lower-case/right for upper-case and left for vowel/right for consonant. At the start of each block, instructions were shown for 4.8 s. The time interval between the onsets of each letter trial was 2.4 s, including the interstimulus interval blank screen (0.5 s).

remaining 13 participants were acquired on a 3.0 T Siemens PRISMA scanner.

High-resolution T1-weighted images on the Philips scanner were obtained via a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence with parameters including TR of 6.5874 ms, TE of 2.98 ms, flip angle of 8°, voxel size of 1 mm isotropic, and acquisition matrix size of 256 x 256 x 165. Functional images were acquired with the parameters including TR of 2000 ms, TE of 20 ms, flip angle of 72°, voxel size of 2 mm x 2 mm x 3 mm, and acquisition matrix size of 112 x 112 x 41 x 111. On the Siemens scanner, the T1 MPRAGE parameters were TR of 2400 ms, TE of 2960 ms, flip angle of 9°, voxel size of 0.5 mm isotropic, and acquisition matrix size of 416 x 512 x 512 and the functional image parameters were TR of 1008 ms, TE of 37 ms, flip angle of 52°, voxel size of 2 mm isotropic, and acquisition matrix of 104 x 104 x 72 x 217.

2.5. Brain structural analysis

For the structural brain analysis, we utilized the Desikan-Killiany atlas (Desikan et al., 2006) to segment the brain into cortical and subcortical regions. These regions included key areas such as the hippocampus, amygdala, insula, fusiform gyrus, and precentral gyrus.

T1-weighted structural scans for each participant were processed using FreeSurfer v5.1.3. FreeSurfer's longitudinal pipeline, which automatically corrected for intra-subject variability across time points were used ensuring accurate measurements of cortical thickness and volume. For quality control of processing, the boundaries between white and gray matter, as well as gray matter and cerebrospinal fluid, were carefully examined slice by slice. If discrepancies were identified, manual control points were added, and the reconstruction process was repeated until acceptable results were achieved for all participants. Subcortical structure borders were visualized using TkMedit and cross-checked against actual brain regions, with manual corrections made as necessary.

Using the segmented brain regions, we extracted a multivariate structural brain change index associated with switch cost change over time. This index was derived through an Elastic Net regression model, applied to the changes in volume and thickness of the selected brain regions among 149 candidates, between baseline and follow-up. The dependent variable in the model was the change in switch cost from baseline to follow-up. The data were partitioned into training and testing sets, with 80 % used for training and 20 % for testing. The Elastic Net model, trained using 3-fold cross-validation, identified the brain measures most predictive of switch cost change. The brain change index was then calculated as a linear combination of these selected measures. To ensure the robustness of our findings, model performance was evaluated on both the training and testing datasets, minimizing the risk of overfitting. Finally, this brain structure change index was used in further analyses to explore the relationship between changes in age-related brain measures and cognitive performance over time.

2.6. fMRI analysis

2.6.1. Preprocessing

Preprocessing and analyses of fMRI data were performed using FMRIB Software Library (FSL) v5.0 and custom-written Python code. Functional images were initially realigned to the first volume and then corrected for slice acquisition order. Subsequently, they were smoothed using a 5 mm^3 nonlinear kernel and normalized for intensity. A high pass filter was applied using a Gaussian kernel with a cutoff frequency of 0.008 Hz. The first functional volume was then co-registered to the template-aligned T1-weighted image using FMRIB's Linear Image Registration Tool (FLIRT) with the normalized mutual information cost function. The transformation parameters obtained were then used to map the statistical parametric maps from the subject-level analysis to standard space.

To address potential confounds from using different MRI scanners, we employed the Combining Batch (COMBAT) harmonization method for our fMRI data (Fortin et al., 2018, 2017; Johnson et al., 2007). This approach minimizes scanner-related confounds while preserving biological variability. To enhance the power of scanner effect estimate, our harmonization process included data from 82 participants (including a group of young individuals who were removed from the main analysis because the current study only focused on individuals in later adulthood). We used task and timepoint information in the covariate array for COMBAT. An aging covariate array and a subject-task intercept array were included to capture aging effects and time-invariant subject and task effects. This ensures that COMBAT does not remove variability due to aging or other relevant demographic factors, while effectively mitigating potential confounds introduced by scanner differences.

The fMRI Expert Analysis Tool (FEAT) module within FSL was used for subject-level analysis. The fMRI time-series data underwent pre-whitening to correct for intrinsic autocorrelations. For each participant, a block-based analysis was conducted. The predictor variables in the first-level design matrix comprised epochs representing each unique experimental task block. Within each of the six runs, one predictor for each of the four task blocks and one predictor for instructions were separately modeled. Each epoch was convolved with a model of the hemodynamic response function. Contrasts for single-task and dual conditions were then entered into the task-related activation analysis.

2.6.2. Task-related activation patterns

To identify functionally activated brain regions, OrT CVA was employed on both baseline and follow-up data. OrT CVA is a multivariate data-driven technique that identifies patterns of regional functional activation that show a monotonic change across multiple experimental conditions (in the current study single and dual conditions). The extracted functional activation patterns, called ordinal trends (OrT), indicate sustained activity across graduated increase in task demand (Habeck, Krakauer, et al., 2005; Habeck, Rakitin, et al., 2005). The technique utilizes a specialized design matrix to enhance variance contributions from patterns that exhibit within-subject increases in pattern scores from single to dual conditions. The test statistic that is used to assess the significance of the task condition relationship of the derived activation pattern is the number of exceptions i.e. the number of individuals showing decreased pattern expression from single to dual

condition and thus violate the majority rule of an increase. A null distribution is generated using a permutation test with 1000 iterations, where condition assignments are randomized within participants. The p-value is determined by the fraction of times the permutation test yields a number of exceptions as low or lower than the point estimate. To ensure the robustness of voxel loadings in the derived pattern, a simple bootstrap technique is employed. The data are resampled with replacement (without randomizing subject and condition assignments), and the analytic point-estimate process is repeated 500 times. Z-values for the voxel loadings are computed as the ratio of the point estimate of the loading divided by the bootstrap standard deviation around this point estimate. The identified pattern is projected to baseline data and for each subject, the OrT score is computed for both single and dual conditions at baseline. Then differential task-related expression score (dOrT) is calculated as the difference between OrT scores of derived patterns in single and dual conditions at baseline.

2.7. Statistical analysis

To investigate changes in reaction time over time, a repeated measures analysis of variance (ANOVA) was conducted on the reaction time data with task condition (dual vs. single) and time point (baseline vs. 5-year follow-up) as within-subjects factors. The key analysis in the current study centers on examining how individual differences in task-related brain activation patterns, considered as a neural implementation of CR, may moderate the effects of age-related structural brain changes on changes in switch cost over time. To test this, a multivariate linear model was utilized. The dependent variable in this model was the change in switch cost, while independent variables included the structural brain change index, dOrT score, and their interaction term. Baseline age, switch cost at baseline, sex, and scanner ID variable were included as covariates. Scanner ID was included in the model to account for potential differences in data acquired from the two MRI scanners.

3. Results

3.1. Behavioral analysis

Reaction time for the single and dual conditions along with switch cost at baseline and follow-up are reported in Table 2. To evaluate the effect of task condition (single and dual), and time point (baseline and follow-up) on behavioral performance, a two-way repeated measures ANOVA was conducted on reaction time. The analysis revealed significant main effects for both task conditions ($F(1, 51) = 10.19$, $p = 0.002419$) and time point ($F(1, 51) = 314.06$, $p < 0.001$). However, the interaction effect between task condition and time point was not statistically significant ($F(1, 51) = 1.4907$, $p = 0.22772$). These findings indicate that both task condition and time point independently influenced the reaction time. The task condition effect suggests that there is a significant difference in reaction times between single and dual conditions, irrespective of time. Similarly, the significant main effect of timepoints shows that reaction time changed from baseline to follow-up, regardless of the condition. The non-significant interaction implies that the effect of timepoint was consistent across both conditions, and vice versa. As Table 2 indicates, there is an increase in switch costs from baseline to follow-up, although it is not statistically significant. Fig. 2 shows individual (grey) and population (bold black) trajectories of changes in switch cost with age. It is important to note that higher switch costs are associated with poorer performance.

Table 2
Mean reaction time (RT) for the single and dual conditions and switch cost (RT dual- RT single) at baseline and follow-up.

	Baseline (Mean ± SD)	Follow-up (Mean ± SD)
RT single	0.87±0.13	0.93±0.15
RT dual	1.15±0.22	1.24±0.22
Switch cost	0.28±0.13	0.31±0.17

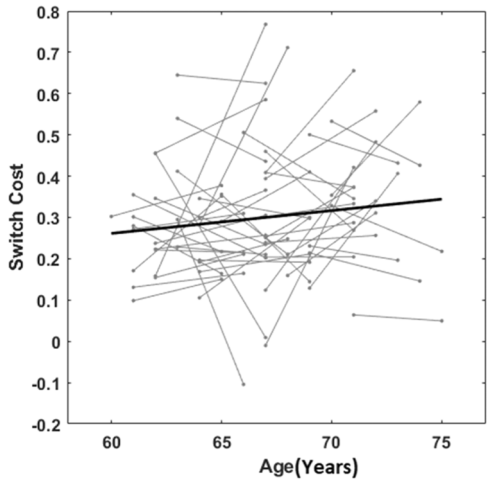

Fig. 2. Individual (grey) and population (bold black) trajectories of switch cost (difference in median reaction time between single and dual conditions) across age.

3.2. Brain structure index

Elastic Net regression was used to extract a brain change index from the volume and thickness change of 149 cortical and subcortical brain regions to best predict the switch-cost change from baseline to follow-up. The model was applied using leave-one-out cross validation. Multiple models were trained with different alpha values and based on cross-validation analysis an alpha value of 0.55 was selected for the Elastic Net model which balanced the L1 (lasso) and L2 (ridge) regularization and minimized the error. The lambda value that minimized the mean squared error was selected, and the corresponding coefficients were obtained while 11 brain measures were selected (Table 3).

3.3. fMRI OrT patterns

The OrT analysis identifies task-related patterns that show a significant change in expression from the single to the dual condition ($p < 0.001$ of permutation test for N=1000 iterations). The patterns with z values above threshold ($|z|>2$) and with cluster size >100 voxels were used for analysis. The positive weights within the pattern correspond to regions exhibiting greater activation from the single to the dual condition, while regions with negative weights demonstrate a decrease in activation during the shift from the single to the dual condition.

The task-positive and -negative networks are identified using FDR-

Table 3
Selected brain measure by elastic net regularization to obtain brain structure change index.

Brain Measure	Hemisphere
Subcortical Gray Matter Volume	-
Cuneus Volume	Left
Lingual Volume	Left
Medial Orbitofrontal Volume	Left
Medial Orbitofrontal Thickness	Left
Pars Orbitalis Volume	Left
Posterior Cingulate Volume	Left
Lateral Occipital Volume	Right
Pars Opercularis Volume	Right
Temporal Pole Thickness	Left
Entorhinal Thickness	Right
Lateral Occipital Thickness	Right
Middle Temporal Thickness	Left

corrected thresholds for both single and dual task conditions, as illustrated in Fig. 3 and reported with details in Table A.1 (Appendix A). The identified pattern is extracted based on stacked baseline and follow-up data, then we used the OrT score of the identified pattern which is projected to baseline data for the analysis.

3.4. Task-related activation moderates the association between brain structure change and changes in switch cost from baseline to follow-up

A subsequent linear regression model was applied to check the relation between change in brain structural index and change in switch cost from baseline to follow-up, and to explore the moderation effect of baseline OrT pattern expression score on this relationship. The model included structural brain change index, dOrT score, and their interaction term as the independent variable and change in switch cost as the dependent variable. Baseline age, switch cost at baseline, sex, baseline intracranial volume and scanner ID variable included as covariates.

The linear regression model revealed significant findings (Table 4). Structural brain change index ($\beta = 0.5763$, $p = 0.0001$) were positively associated with change in switch cost, suggesting that higher structural brain change index were linked to an elevated change in switch costs. Notably, the interaction term of dOrT and structural brain change index presented a significant negative association with switch cost change ($\beta = -0.035$, $p = 0.005$). This significant interaction indicates that the dOrT moderated the effect of brain change on change in switch cost. In other words, dOrT decreased the effect of brain change on change in switch cost. Meanwhile, baseline age, sex, Intracranial Volume, scanner ID and dOrT did not have statistically significant effects in the model. The scanner ID is a variable that is used to account for the effect of two applied MRI scanners (Philips Achieva and Siemens PRISMA) and its corresponding p value approaches significance ($p = 0.0637$), although it doesn't reach the statistical significance level of 0.05.

To examine the specificity of our findings, we conducted additional analyses on general slowing observed over the 5-year period. For changes in single-task RT, structural brain changes were significantly associated with increased RT ($\beta = 0.2$, $p < 0.01$), and dOrT significantly moderated this relationship (interaction $\beta = -0.004$, $p = 0.04$). For changes in dual-task RT, structural brain changes were significantly associated with increased RT ($\beta = 0.33$, $p < 0.01$), but the interaction effect was not significant (interaction $\beta = -0.005$, $p = 0.2$). These results indicate that the moderating effect of dOrT is present for both the simpler single-task condition and the more complex switch cost measure, but not for the dual-task condition

To illustrate the moderation effect of dOrT on the relation of brain change and switch cost change, simple slope analyses (Preacher et al., 2006) were applied. As shown in the interaction plot (Fig. 4), the positive relationship between brain changes and increased switch costs is more pronounced in the low dOrT group compared to the high dOrT group. Specifically, for participants with low dOrT, greater brain change is associated with larger increases in switch costs. In contrast, the relationship is considerably weaker for those who have high OrT. These findings suggest that the degree to which brain changes affect the switch costs depends significantly on the dOrT score. When the differential activation in identified patterns is low, individual differences in brain changes were more tightly coupled with switch costs. However, this structural brain-behavior relationship is attenuated under conditions of higher differential activation in the OrT patterns.

Additionally, the Johnson-Neyman plots are used to probe the region of significance of the interaction between brain change and dOrT on switch cost change. This analysis uses 95 % confidence intervals to determine the range of values of the moderator (dOrT) for which the effect of the predictor (brain change index) on the outcome (switch cost change) is statistically significant. The resulting Johnson-Neyman plot (Fig. 5) depicts a line with a negative slope, indicating that the effect of

Table 4
Fixed effect coefficients of Linear Mixed Effects Model.

	β	t stat	p value
Intercept	−0.0782	−0.1869	0.8527
Baseline Switch Cost	0.2523	1.5341	0.1329
Baseline Age	0.0000	−0.0055	0.9956
Sex-Female	0.0297	0.5644	0.5756
Scanner ID-PRISMA	−0.0960	−1.9070	0.0637
Baseline Intracranial Volume	0.0142	0.5325	0.5973
dOrT	−0.0018	−0.5232	0.6037
Brain Change Index	0.5763	4.4466	0.0001
dOrT x Brain Change	−0.0351	−2.9501	0.0053

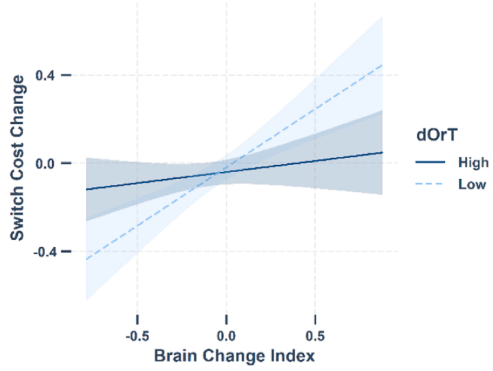

Fig. 4. The interaction effect between brain changes and dOrT on switch cost (difference in median reaction time between single and dual conditions) changes. Low dOrT which is differential task-related expression score of patterns obtained by ordinal trends canonical variate analysis (1 SD below the mean) is depicted by the dashed line, and high dOrT (1 SD above the mean) by the solid line.

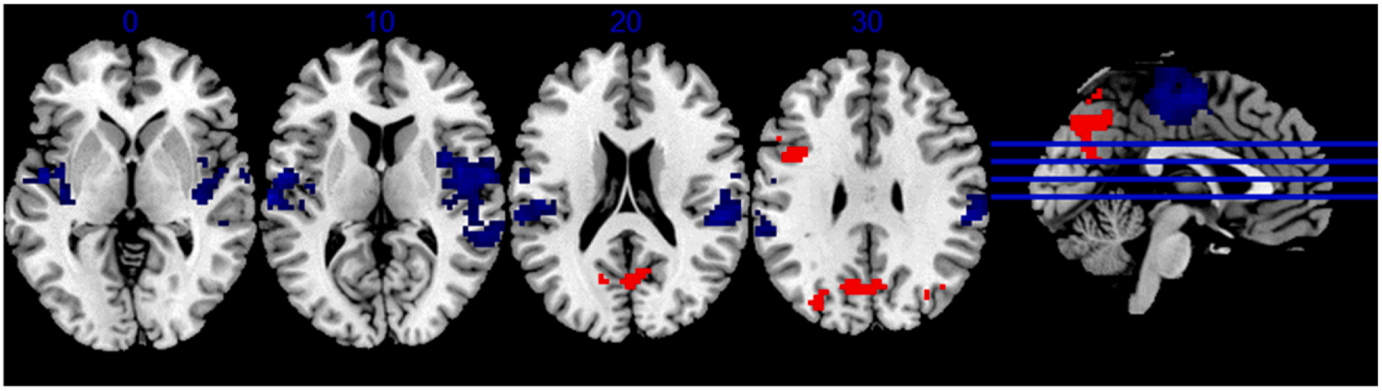

Fig. 3. Brain regions with positive (red) and negative (blue) loadings in the OrT patterns (obtained by ordinal trends canonical variate analysis or OrT CVA).

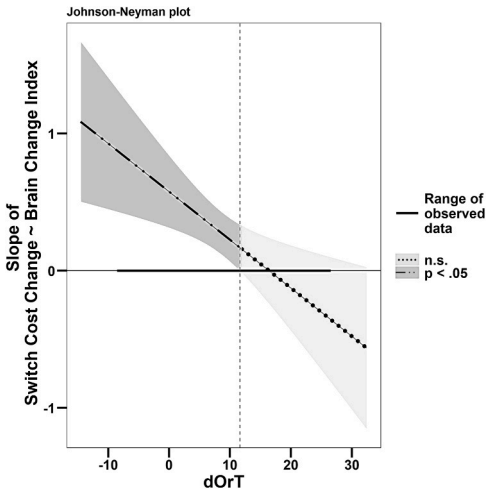

Fig. 5. Johnson-Neyman plot depicting the conditional relationship between brain change index and switch cost change across levels of dOrT (differential task-related expression score of patterns obtained by ordinal trends canonical variate analysis). The dashdotted line indicates a statistically significant relationship ($p<0.05$) between brain change index and switch cost (difference in median reaction time between single and dual conditions) change. The dotted line indicates a non-significant relationship.

brain change on switch cost change diminishes as dOrT increases. When dOrT is lower than 11.63, the effect of brain change on switch cost change is statistically significant ($p<0.05$) while for dOrT higher than 11.63, the relation is no longer significant. The value of 11.63 corresponds closely to the 75th percentile of our sample (11.56), indicating that for approximately 25 % of participants with the highest dOrT scores, there was no significant relationship between brain structural changes and switch cost changes. The dOrT scores in our sample ranged from −8.37–26.31 (specified by bold black horizontal line in Fig. 5), with a mean of 7.86 (SD = 6.00) and a median of 7.29.

4. Discussion

This longitudinal study provides evidence that greater expression of a specific pattern of task-related brain activation can moderate the impact of brain-structural change on change in switch cost over time. This suggests that enhanced engagement of the identified networks during an executive task enables the preservation of task-switching abilities despite the accumulation of age-related structural brain changes. The Framework for Terms Use in the Research of Reserve and Resilience defines cognitive reserve as a property of the brain that allows for cognitive performance that is better than accepted given the degree of life course related brain changes and brain injury of disease. The observed moderating effect of the dOrT score demonstrates that the differential expression of the identified task-related pattern is a neural implementation of cognitive reserve (Stern et al., 2023).

The reported analyses focus on participants in later adulthood, aged 60 and above. This choice is motivated by the CR hypothesis, which explores functional cognitive processes in the presence of significant age or disease-related structural brain changes (Stern et al., 2023). The results suggest that greater capacity to upregulate functional brain networks enables the preservation of task-switching capabilities in the presence of structural brain changes, specifically in old age. This finding aligns with the concept of capacity, one of the potential mechanisms underlying CR suggested by Stern (Stern, 2009). Capacity is defined as "the maximum degree to which a task-related brain network can be activated to keep performing a task in the face of increasing demands" (Stern et al., 2020). Our findings provide direct evidence for this mechanism, showing that individuals with higher dOrT scores exhibited greater increases in activation from single to dual task conditions. This higher functional capacity at baseline may allow individuals to maintain cognitive performance over time despite accumulating structural brain changes. Prior cross-sectional studies also found that older individuals who sustain task-switching abilities exhibit greater prefrontal and parietal activation than those with switching deficits (Gazes et al., 2012; Gold et al., 2010). Our longitudinal findings extend these observations, demonstrating that this increased activation moderates the impact of structural brain changes on cognitive decline over time.

Our additional analyses revealed that dOrT moderates general slowing in the single-task condition and longitudinal changes in switch cost, but not general slowing in the dual-task condition. This pattern suggests that the neural implementation of reserve we identified may be most effective at certain levels of cognitive demand, aligning with Stern's conceptualization of reserve (Stern, 2009) as a feature of brain function with varying effects across different task difficulties. The absence of a moderating effect in the dual-task condition might indicate a complexity threshold beyond which this specific neural implementation of reserve is less effective.

The OrT analysis we employed identifies patterns of coordinated brain activity across the entire brain, rather than focusing on isolated regional activations. This multivariate approach captures the complex interplay of neural systems involved in task performance. While it provides valuable insights into network-wide activation patterns, it is important to recognize that the OrT method emphasizes the collective behavior of brain regions rather than pinpointing specific localized functions. In this context, we observed that certain brain regions showed increased activation from single to dual task conditions, included areas associated with executive function, attention, and cognitive control, such as the precuneus, inferior parietal Lobule, and precentral gyrus (Barber and Carter, 2005; Cavanna and Trimble, 2006). The precuneus, which showed the highest positive loading in our OrT pattern, has been implicated in a wide range of cognitive functions, including visuo-spatial imagery, episodic memory retrieval, and self-processing operations (Cavanna and Trimble, 2006). Precuneus also has been associated with task switching (Kim et al., 2012) and its activation is related to maintaining task-relevant information (Loose et al., 2017) and showed greater activity in preparation to switch between tasks (Barber and Carter, 2005). The increased engagement of this region in individuals with higher dOrT scores may reflect a greater capacity to efficiently prepare for switching between tasks. It is reported that the precuneus may support the anticipatory aspect of task switching by preparing the cognitive system for task performance under heightened attentional demands. In contrast, the inferior parietal activation which is also found to be involved during task switching, may associated with the reconfiguration of task set (Barber and Carter, 2005). The other region in our identified pattern is precentral gyrus which is primarily associated with motor function and its inclusion in our CR pattern may reflect the motor processes required for efficient task-switching. A meta-analyses on brain regions associated with different types of task switching found that precentral gyrus is preferentially activated for different task switching (Kim et al., 2012). The negative loadings in our OrT pattern, primarily in temporal and insular regions, suggest that effective CR involves both enhancement and suppression neural activity. This could be related to the idea that cognitive efficiency involves both the upregulation of task-relevant networks and the downregulation of task-irrelevant activity (Gazzaley et al., 2005).

The observed variability in the degree of activation of identified patterns during single and dual task conditions among our participants, all of whom are in later adulthood, highlights the heterogeneous nature of cognitive aging. Although our study did not compare young and older adults, this variability may be related to the concept of neural dedifferentiation, where brain regions that once showed specialized responses for specific cognitive processes in young adults become less specialized in older adults, responding more similarly across different cognitive tasks (Goh, 2011). This reduced neural selectivity is thought to contribute to cognitive decline, particularly in fluid cognitive abilities

(Koen & Rugg, 2019). Neural dedifferentiation is characterized by less distinctive cognitive representations, reduced selectivity in posterior brain regions, increased and less selective frontal recruitment, and alterations in functional connectivity, all of which contribute to age-related cognitive changes across various domains including perception, memory, and executive function (Goh, 2011). In another study, Goh et al demonstrated that cognitive aging is not a uniform process, but rather a heterogeneous one with different components of executive and memory processes showing distinct longitudinal changes. They found declines in inhibition, manipulation, semantic retrieval, phonological retrieval, switching, and long-term memory, while abilities such as abstraction, capacity, chunking, discrimination, and short-term memory were maintained or even improved with age (Goh et al., 2012). The individual differences we observed in task-related activation patterns suggest that the degree of dedifferentiation may vary among older adults. Despite calculating the same neural pattern across participants, we found individual differences in the degree of change in activation between single and dual conditions. This variability, quantified by the differential expression of the dOrT, led to differences in the impact of brain structural change on switch costs in aging. It has been posited that aging decreases the extent to which behavior is specialized or differentiated for individual tasks (Park et al., 2004). In current results, higher dOrT scores, indicating greater differentiation between single and dual task conditions, were associated with a lower impact of structural brain changes on switch costs (i.e. better performance). These findings suggest that the ability to maintain more differentiated neural responses to varying task demands may be a key factor in cognitive resilience among older adults. Individuals who show less dedifferentiation (as indicated by higher dOrT scores) appear to be better able to cope with structural brain changes, maintaining better task-switching performance. This underscores the importance of considering individual differences in neural activation patterns when studying cognitive resilience in aging, even within a group of older adults.

In the brain structural analysis, the elastic net model identified a set of cortical and subcortical regions whose structural changes were associated with changes in task-switching performance over time. Instead of focusing on a predetermined set of brain areas, this data-driven approach revealed a widespread pattern of age-related changes in grey matter volume and cortical thickness. Some regions identified by the model, including the posterior cingulate cortex, have been reported in earlier studies to have related activation with cognitive flexibility (Razzaq et al., 2022) and task-switching (Hayden et al., 2010; Leech and Sharp, 2014). Moreover pars opercularis and pars orbitalis are parts of the inferior frontal gyrus, which is reported as the second most significant region in switching paradigms in a meta-analysis (Derrfuss et al., 2005). The inclusion of medial orbitofrontal and entorhinal regions in our structural change index is noteworthy, as these areas are among the earliest to show age-related atrophy and are particularly vulnerable in neurodegenerative conditions like Alzheimer's disease (Fjell et al., 2014). Their association with changes in task-switching performance may underscore the close link between structural brain health and cognitive function in aging.

The current study applied OrT CVA to characterize differential brain activation patterns underlying executive control processes. OrT CVA identifies ordinal trends in brain activity on a subject-by-subject basis rather than just looking at group averages; hence, it is an excellent candidate for studying individual differences. Moreover, it analyzes the entire brain unbiasedly and does not require a priori specification of brain regions of interest. (Habeck, Krakauer, et al., 2005; Habeck, Rakitin, et al., 2005).

This study has its limitations. The number of participants is relatively low. Longitudinal studies with larger sample sizes would provide a more complete and accurate understanding of the changes in brain structure, function, and cognitive performance over time. Moreover, the study could be extended to young individuals in order to explore similarities or differences in the neural substrates of cognitive performance between older adults and younger individuals, and address whether more youthful appearing activation patterns are associated with cognitive reserve as well. Furthermore, while the task-switching paradigm effectively measured executive function, future studies can include a broader range of cognitive tasks to better assess the neural implementation of cognitive reserve across various cognitive domains.

5. Conclusion

This longitudinal study provides novel evidence that enhanced engagement of a task-related functional brain network can moderate cognitive decline associated with structural brain changes in aging. We identified a brain network exhibiting differential activation between single and dual task conditions on a set-shifting task. Critically, this differential activation moderated the relationship between structural brain change and change in task-switching performance over 5 years. Individuals showing greater increases in neural activation from single to dual conditions better preserved cognitive flexibility despite accumulating structural brain change, suggesting a neural implementation of cognitive reserve. While structural declines impaired performance, functional upregulation of a specific brain network buffered against deleterious effects. Such proximal candidates for the neural implementation of CR present alternate valuable research in addition to the evaluation of traditional epidemiological CR proxies such as educational or occupational attainment.

Ethical approval

The participants provided their written informed consent to participate in this study and the Columbia University Institutional Review Board approved all study procedures.

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CRediT authorship contribution statement

Fatemeh Hasanzadeh: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Christian Habeck:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Data curation, Conceptualization. **Yunglin Gazes:** Resources, Data curation, Conceptualization. **Yaakov Stern:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Funding acquisition, Data curation, Conceptualization.

Declaration of Competing Interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2024.10.008.

Data availability

The dataset including demographic, behavioral and neuroimaging measures, along with analytical scripts used to produce the results presented in the manuscript are available at Dryad (datadryad.org), final DOI:10.5061/dryad.qz612jmrm.

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