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A task-invariant cognitive reserve network

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ABSTRACT

The concept of cognitive reserve (CR) can explain individual differences in susceptibility to cognitive or functional impairment in the presence of age or disease-related brain changes. Epidemiologic evidence indicates that CR helps maintain performance in the face of pathology across multiple cognitive domains. We therefore tried to identify a single, "task-invariant" CR network that is active during the performance of many disparate tasks. In imaging data acquired from 255 individuals age 20–80 while performing 12 different cognitive tasks, we used an iterative approach to derive a multivariate network that was expressed during the performance of all tasks, and whose degree of expression correlated with IQ, a proxy for CR. When applied to held out data or forward applied to fMRI data from an entirely different activation task, network expression correlated with IQ. Expression of the CR pattern accounted for additional variance in fluid reasoning performance over and above the influence of cortical thickness, and also moderated between cortical thickness and reasoning performance, consistent with the behavior of a CR network. The identification of a task-invariant CR network supports the idea that life experiences may result in brain processing differences that might provide reserve against age- or disease-related changes across multiple tasks.

Introduction

The concept of cognitive reserve (CR) explains individual differences in susceptibility to cognitive or functional impairment in the presence of age- or disease-related brain changes (e.g. Stern, 2002). The goal of this study was to better understand the neural implementation of CR. While most fMRI studies of CR have evaluated activation on a particular task, our intention was to identify an aspect of CR that was active across multiple tasks. We approached this by attempting to identify a network of brain areas 1) whose expression correlates with IQ, a proxy of CR, 2) is expressed during the performance of multiple tasks, and 3) whose expression moderates the relationship between brain or pathology status and cognitive performance. We posit that such a network would be a candidate for a task-invariant CR network.

CR refers to the resilience or plasticity of cognitive networks in the face of disruption. It suggests that the brain actively attempts to cope with brain damage by using pre-existing cognitive processes or by enlisting compensatory processes (Stern, 2002). A set of factors including IQ, educational or occupational attainment, exercise and leisure activities may account for differences in CR across individuals. Numerous epidemiologic studies have demonstrated that these variables are related to reduced risk of developing dementia (Meng and D'Arcy, 2012; Valenzuela and Sachdev, 2006; Xu et al., 2015). Similarly, these variables have been related to slower rate of cognitive decline in healthy aging in some, e.g. (Zahodne et al., 2015b), but not all studies, e.g. (Zahodne et al., 2011). Based on these observations, these variables have been employed as proxy measures for CR. In this study, we focused on IQ as a proxy measure of CR because it is readily and reliably obtained in participants of all ages.

To yield insights into the neural implementation of CR, we and many investigators have used task-based fMRI studies to characterize how the functioning brain adapts to structural brain changes in order to maintain cognitive performance (Stern, 2009). These studies measured age-related brain changes such as atrophy (Steffener et al., 2014a), as well as disease-related features such as amyloid plaque or tau tangles (Oh et al., 2017; Rentz et al., 2017) and explored how inter-individual variability in task-related activation can account for differential task performance in the presence of the level of age- or disease-related changes. While these studies have yielded insights into how CR may be neurally implemented, for the most part they have focused on aspects of fMRI activation related

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Table 1A
Participant sample and demographics in main derivation (RANN) sample, N = 255 in total.

Age	<30	30–39	40–49	50–59	6–69	>70
N	35	44	38	40	62	36
NART IQ	113 ± 9	112 ± 9	114 ± 9	115 ± 8	118 ± 9	120 ± 10
Education	15.3 ± 2.3	16.4 ± 2.5	15.9 ± 2.6	15.5 ± 2.3	16.0 ± 2.5	17.3 ± 2.5
Sex	23 F, 12 M	27 F, 17 M	17 F, 21 M	20 F, 20 M	32 F, 30 M	18 F, 18 M
DRS	140.4 ± 2.7	139.8 ± 2.3	139.1 ± 2.9	140.1 ± 3.3	139.7 ± 3.1	139.7 ± 3.0
Mean Cortical thickness	2.69 ± 0.11	2.66 ± 0.09	2.65 ± 0.09	2.59 ± 0.08	2.55 ± 0.11	2.51 ± 0.12

to performance on a single task. Another intriguing possibility is that there exist generic, task-invariant networks that are elicited during the performance of disparate tasks (Stern et al., 2008). A task-invariant CR network would be expressed as a function of CR in the presence of varied cognitive demands. Such a network might allow people who express it to a greater degree to better maintain performance on multiple tasks in the face of age- or disease-related brain changes. Thus, in the present study we attempted to identify a network that was expressed across multiple tasks and whose expression correlates with IQ.

There are important theoretical reasons to test whether generalized neural representations of CR can be identified. In epidemiologic studies, various proxy measures of CR have been associated with lower relative risk of incident AD. In this context, CR allows people to better maintain performance in the multiple domains of cognition affected in AD, as well as activities of daily living, in the face of increasing AD brain pathology. This argues that some aspects of reserve are not task-specific, and suggests the possibility of a task-invariant CR network. In addition, identification of a task-invariant CR network would allow for direct quantification of an individual's level of CR, rather than relying on proxy measures. This would be useful clinically, and also be extremely valuable as an outcome measure in studies designed to enhance CR.

In order to identify a task-invariant CR network, we took advantage of data from the Reference Ability Neural Network (RANN) study (Stern et al., 2014), where healthy individuals age 20 through 80 were each studied with 12 different cognitive activation tasks. We used a multivariate approach, Scaled Subprofile Modeling (SSM) (Alexander and Moeller, 1994; Moeller et al., 1987) to identify a network of brain areas that was expressed during performance of all 12 tasks and whose degree of expression correlates with IQ. Two additional steps tested the network's generalizability. The identified network was tested in held out data to see if its expression correlated with IQ. We then checked to see whether expression of this pattern correlated with IQ in fMRI data obtained during the performance of other tasks.

We then did additional tests to confirm that network expression acted like CR by mitigating the effects of age-related brain changes on cognition. CR could account for cognitive performance over and above that accounted for by brain structure, or could moderate the relationship between brain structure and cognition (Bennett et al., 2003; Jones et al., 2011; Stern et al., 1992). Both influences are conceivable, and can easily be embodied naturally in regression models containing a direct effect of CR on performance and interaction between CR and brain structure. We therefore examined whether expression of the putative task-invariant CR pattern accounted for variance in cognitive performance over that predicted by cortical thickness. In a more demanding approach, we also tested whether the CR pattern moderated the relationship between cortical thickness and cognitive performance. Meeting these demands would provide evidence that the task-invariant network is acting like CR, in helping to mitigate the effect of changes in structure on cognitive performance.

Materials and methods

Subjects

All participants were recruited through random market mailing. All participants were required to be native English speakers, strongly right-handed, and have at least a fourth grade reading level. They were screened for MRI contraindications and hearing or visual impairment that would impede testing. Participants were free of medical or psychiatric conditions that could affect cognition. Careful screening ensured that the older participants did not meet criteria for dementia or mild cognitive impairment (MCI). The primary analyses were conducted on participants from the Reference Ability Neural Network Study (Stern et al., 2014), and included 255 individuals age 20 through 80. Demographic information is presented in Table 1a. Forward application of the derived network was done using data from participants in a second study who underwent fMRI while performing executive and working memory tasks. These included 58 individuals age 20 to 32 and 91 individuals age 50 to 71. Demographic information for this group is presented in Table 1b. There was some partial overlap between participants in these two studies.

fMRI tasks and procedures

All MR images were acquired in the same 3.0T Philips Achieva Magnet with a standard quadrature headcoil that has been used since the start of this study. For the RANN study, MR data were acquired over two 2-h imaging sessions. For the CR study all scans were acquired in one 2-h session. At the start of every session, a scout, T1-weighted image was acquired to determine patient position. In addition to the fMRI studies, all participants received MPRAGE, ASL, FLAIR and DTI scans. For the current study only fMRI and MPRAGE sequence are considered. High-resolution T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) scans were collected axially for each subject (TR = 6.6 ms, TE = 3 ms, flip angle = 8°, field of view (FOV) = 256 × 256 mm, matrix size: 256 × 256 mm, slices: 165, voxel size = 1 X 1 × 1 mm^3). fMRI data were acquired using T2*-weighted gradient-echo planar images (EPI) sequence (TR = 2000 ms; TE = 20 ms; flip angle = 72°; FOV = 224 × 224 mm; voxel size = 2 mm × 2 mm; slice thickness = 3 mm; duration = 3.5 min). A neuroradiologist reviewed each participant's MRI scan and confirm that there were no clinically significant findings for any of the participants.

Task administration and data collection were controlled by a computer running EPrime software, and electronically synchronized with the MR scanner. Task stimuli were back-projected onto a screen located at the foot of the MRI bed using an LCD projector. Subjects viewed the screen via a mirror system located in the head coil. For all tasks except for Picture naming, task responses were made on a LUMItouch response system and behavioral response data were recorded on the task

Table 1B
Participant sample and demographics in replication sample for ECF task, N = 149 in total.

Age	20–31	51–71
N	58	91
NART IQ	114.3 ± 7.5	117.8 ± 9.2
Education	15.7 ± 1.9	16.2 ± 2.4
Sex	18 M, 40 F	44 M, 47 F
DRS	140.0 ± 2.3	139.9 ± 2.6