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ORIGINAL ARTICLE

Default Mode Network Activity Predicts Early Memory Decline in Healthy Young Adults Aged 18–31

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Abstract

Functional magnetic resonance imaging (fMRI) research conducted in healthy young adults is typically done with the assumption that this sample is largely homogeneous. However, studies from cognitive psychology suggest that long-term memory and attentional control begin to diminish in the third decade of life. Here, 100 participants between the ages of 18 and 31 learned Lithuanian translations of English words in an individual differences study using fMRI. Long-term memory ability was operationalized for each participant by deriving a memory score from 3 convergent measures. Age of participant predicted memory score in this cohort. In addition, degree of deactivation during initial encoding in a set of regions occurring largely in the default mode network (DMN) predicted both age and memory score. The current study demonstrates that early memory decline may partially be accounted for by failure to modulate activity in the DMN.

Key words: aging, deactivations, default mode network, learning, memory

Introduction

Cognitive capacities evolve rapidly during childhood and adolescence and undergo substantial decline as adults age. This pattern is seen in speed of processing (Elliott 1970; Kail 1991), cognitive control (Welsh and Pennington 1988), and long-term memory ability (Dirks and Neisser 1977; Mandler and Robinson 1978; Craik and Byrd 1982; Balota et al. 2000; Drummey and Newcombe 2002; Cycowicz et al. 2003; Craik and Salthouse 2008). A considerable amount of research has focused on those periods in which change is occurring rapidly (e.g., between younger and older children and between college students and individuals over 60 years of age), but there has been less emphasis on how cognitive function behaves within a relatively small age window of adult performance (e.g., between 20 and 30 years of age).

Are cognitive capacities relatively static across age within healthy young adults? Is the period between age-related growth and decline in performance marked by an extended plateau wherein there exists a relatively small amount of change in cognitive abilities (see Craik and Bialystok 2006)? Behavioral evidence suggests that processing speed and memory performance begin to decline not just in older adults, but in people in the third decade of life (i.e., in their 20s) (Salthouse et al. 2004; Park and Reuter-Lorenz 2009; Salthouse 2009). Indeed, these studies typically suggest a linearly decreasing function in speed of processing and various memory capabilities from about age 20.

Evidence from structural neuroimaging reveals declines in gray matter volume within areas of frontal and parietal cortex in healthy young adults (Fotenos et al. 2005; Raz et al. 2005; Pieperhoff et al. 2008). For instance, longitudinal studies by Raz et al. (2005) showed significant volumetric changes in participants measured at 2 different timepoints, with both measurements occurring before the individuals were 30 years of age.

Some of these gray matter changes were best fit by nonlinear functions, but other regions appear to exhibit linear volumetric decreases from age 20 to 80. In sum, studies of cognitive function and brain structure both suggest some degree of linear decline before age 30.

Thus far, studies addressing brain–behavior relationships across age have tended to focus on extreme-group comparisons between healthy young adults typically ranging in age from 18 to 35 years and older adults, defined as people in their 60s or 70s (Velanova et al. 2007; Dew et al. 2011; but see Park et al. 2013). Thus, the neurobiological underpinnings that underlie behavioral changes observed in young adults have not been established, and in fact, have received very little attention in the cognitive neuroscience literature.

In the current study, we characterize brain–behavior relationships in the domain of learning and memory in a sample of healthy young adults between the ages of 18 and 31. Specifically, we asked participants to learn information that they had not previously encountered (foreign language vocabulary), and used functional magnetic resonance imaging (fMRI) to demonstrate that neural activity measured during first-trial learning was correlated with both the participant's age and with memory performance.

Materials and Methods

Participants

One hundred individuals from the St Louis area participated in the experiment. Participants were recruited via Craigslist (www.craigslist.org), as well as flyers posted throughout the greater St Louis community. A total of 14 participants were excluded, including 6 for excessive movement, 6 for failure to comply with task instructions (eyes closed during task or not responding during test), 1 participant who opted out citing illness, and 1 who did not complete the experiment. The remaining 86 participants (36 female) were between 18 and 31 years old (mean, 24.82) and had completed between 10 and 22 years of education (mean, 15). All participants were right-handed native speakers of English with normal or corrected-to-normal vision and no reported history of neurological or psychiatric illness. All participants were consented according to the guidelines of Washington University's Human Research Protection Office and were compensated $25 per hour of participation.

Stimuli

Stimuli consisted of 45 direct Lithuanian–English translations of concrete nouns (e.g., namas—house) from the Grimaldi et al. (2010) norms. Participants reported no prior knowledge of the Lithuanian language. Lithuanian cues were stripped of typographic ligatures and diacritical marks to assure participants enunciated the translations based on spelling to sound correspondences in English. The word pairs varied in character length (Lithuanian: range, 4–9; mean, 5.96; English: range, 3–8; mean, 4.56) and number of syllables (Lithuanian: range, 2–4; mean, 2.4; English: range, 1–2; mean, 1.22). Stimuli were all capitalized and presented in white, 48-point Arial type on a black background.

Procedure

The experiment comprised 4 phases taking place over 3 days (Fig. 1). Phases 1–3 occurred on the first day and involved fMRI. During Phase 1, participants studied 45 Lithuanian–English pairs one at a time in random order. Participants were instructed to study each translation in preparation for a test that would require verbal recollection of the English translation (e.g., "house") when presented with just a Lithuanian cue (e.g., "namas"). All translations were novel to participants in the context of the experiment. Each Lithuanian–English pair was presented for 3.5 s, separated by a jittered interstimulus interval of 1.5–6.5 s. We imaged the blood oxygen level–dependent (BOLD) response as participants studied each cue-target pair across a single scanning run.

Phase 2 was completed while participants remained in the scanner but no MR images were acquired. During Phase 2, participants took iterative cued-recall tests with feedback on the Lithuanian–English pairs; these tests continued until a 100% recall criterion was reached. Specifically, participants were given a Lithuanian cue (e.g., "namas") for 3.5 s and asked to verbally recall its English target (e.g., "house"). If a correct response was spoken, the cue-target pair was not tested again in Phase 2. Regardless of response accuracy, the correct English word was then presented on the screen for 1.5 s. Items were tested in random order with a 1-s interstimulus interval. Following a given test, participants solved arithmetic problems aloud for 30 s to limit the possibility that cue-target pairs were maintained in working memory. Participants then performed an identical test on only cue-target pairs that had not yet been recalled. In this

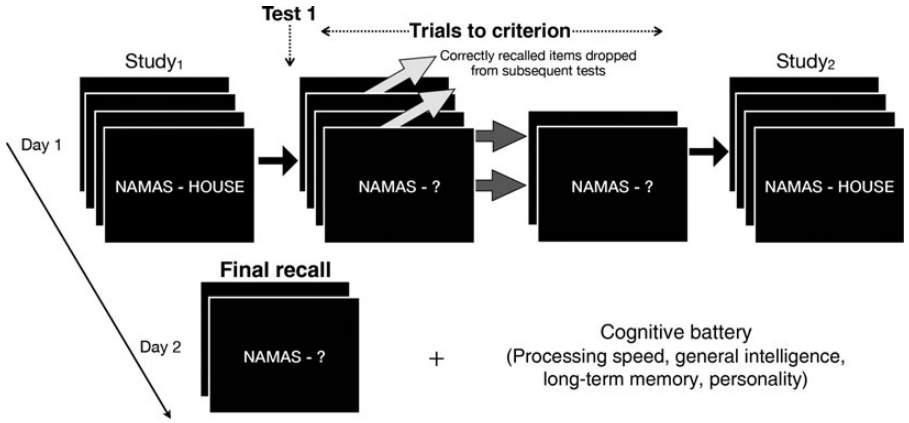

Figure 1. Experimental design. On Day 1, participants studied Lithuanian–English word pairs ($Study_1$) and were subsequently tested until they correctly recalled each item one time. During a second study epoch ($Study_2$), all word pairs were presented once more. Two days later (Day 2), participants took a final test on all word pairs and were administered cognitive and personality batteries (see Materials and Methods).

manner, participants took cued-recall tests with feedback separated by blocks of math problems until every Lithuanian–English word pair was recalled correctly.

Phase 3 was a restudy trial in which the 45 intact Lithuanian–English pairs were again presented to participants in random order. The procedures and instructions for this phase were a direct replica of those used in Phase 1. Both Phase 1 and Phase 3 were preceded by identical 10-min resting-state scans, in which the participant was simply asked to lie as still as possible with their eyes open while fixating a crosshair presented in the center of the screen. The methods and data related to these scans are beyond the scope of this article. Following the restudy scan, participants were instructed not to make a special effort to rehearse any of the cue-target pairs during the intervening delay before Phase 4.

Phase 4 took place 2 days after Phases 1–3 (Phase 3–4 delay; range, 36.5–49.5; mean, 43 h). Participants were given a final cued-recall test on all 45 Lithuanian–English pairs. This final test was a single trial and like the tests in Phase 2. During this final test, each Lithuanian cue was presented in random order for 8 s with a 1-s interstimulus interval. Feedback was not provided to participants during the final test. Phase 4 concluded with a battery of cognitive testing.

fMRI data Acquisition

Functional MR images were acquired by following a standardized set of imaging protocols. To stabilize head position, subjects were situated in the scanner with foam pillows and fitted with a thermoplastic mask that was fastened to the head coil. All images were acquired using a Siemens MAGNETOM Tim Trio 3.0T Scanner (Erlangen, Germany) and a Siemens 12 channel Matrix Head Coil. A T_1-weighted sagittal Magnetization-Prepared Rapid Gradient-Echo structural image was obtained (time echo [TE] = 3.08 ms, time repetition [TR] partition = 2.4 s, time to inversion [TI] = 1000 ms, flip angle = 8°, 176 slices with 1 × 1 × 1 mm voxels) (Mugler and Brookeman 1990). In addition, a T_2-weighted turbo spin echo structural image (TE = 84 ms, TR = 6.8 s, 32 slices with 2 × 1 × 4 mm voxels) was obtained in the same anatomical plane as the subsequent BOLD images to improve alignment to an atlas. An auto-align pulse sequence protocol provided in the Siemens imaging software package was used to align the acquired slices from functional scans in parallel to the anterior commissure-posterior commissure plane and centered on the brain. This plane parallels the slices in the Talairach atlas (Talairach and Tournoux 1988), which is used for subsequent data analysis. Functional imaging was performed using a BOLD contrast sensitive gradient echo echo-planar sequence (TE = 27 ms, flip angle = 90°, in-plane resolution = 4 × 4 mm). Whole-brain Echo Planar Imaging volumes of 32 interleaved, 4-mm-thick axial slices were obtained every 2.5 s. The first 4 image acquisitions were discarded to allow net magnetization to reach steady state.

Noise-cancelling headphones were used to help dampen scanner noise for participants. The headset was equipped with a microphone and allowed participants to communicate with research technicians throughout the scanning procedures. An Apple iMac computer (Apple, Cupertino, CA, USA) running PsyScope software (Cohen et al. 1993) and Adobe Flash Professional CS5.5 (Adobe Systems, San Jose, CA, USA) was used to display visual stimuli. An LCD projector (model PG-C20XU, Sharp) was used to project stimuli onto an MRI-compatible rear-projection screen (CinePlex) at the head of the scanner bore. Subjects viewed this screen through a mirror mounted to the top of the head coil.

fMRI data Preprocessing

Each subject's fMRI data were preprocessed with a standardized stream meant to reduce noise and remove artifacts from the data. This protocol included: 1) correction for movement within and across runs using a rigid-body rotation and translation algorithm (Snyder 1996); 2) mode-1000 intensity normalization, allowing for comparisons across subjects (Ojemann et al. 1997); and 3) temporal realignment of all slices to the temporal midpoint of the first slice using sinc interpolation to account for the slice-time acquisition differences. Functional data were then resampled into 3-mm isotropic voxels and transformed to stereotaxic atlas space (Talairach and Tournoux 1988). To register individuals' data to an atlas, subjects' T_1-weighted images were aligned to a custom atlas-transformed (Lancaster et al. 1995) target T_1-weighted template (711-2B) using a series of affine transforms (Michelon et al. 2003; Fox et al. 2005).

fMRI data Analysis Using the General Linear Model

Preprocessed data were analyzed at the voxel level using a general linear model (GLM) approach (Friston et al. 1994; Miezin et al. 2000). Briefly, the GLM treats the functional data at each timepoint in every voxel as the summation of all effects that are present at that timepoint. Effects may be produced by events in the model and by error. Estimates for the timecourse of effects were derived from the model for each condition by coding each timepoint as a set of delta functions immediately following onset of the events (Ollinger et al. 2001).

Data from each subject consisted of 2 separate runs of 141 frames each (after discarding the first 4 frames to allow for T_1 equilibration) that were concatenated into a single time-series for functional analysis. Run 1 contained the BOLD data corresponding to all $Study_1$ events, while Run 2 contained the BOLD data corresponding to all $Study_2$ events. Thus, GLMs for each participant contained 282 frames and did not differ across subjects. Within each GLM, the $Study_1$ and $Study_2$ conditions were modeled as 8 timepoints each with a 2.5-s TR. However, for the purpose of the analysis shown in Supplementary Figure 4, the $Study_1$ condition was separated into items that were subsequently correctly recalled on Test 1 and items that were not.

In addition to the regressors described above, a trend term accounted for linear changes to the MR signal, and a constant term modeled the baseline signal. Event-related effects are described in terms of percent signal change, defined as the MR signal magnitude divided by a constant term. It is essential to note that this approach makes no assumptions about the shape of the BOLD response. However, this method assumes that all events included in a condition (e.g., $Study_1$) are associated with the same BOLD response within that condition (Ollinger et al. 2001). Image processing and analyses were carried out using in-house software programed in Interactive Data Language (Research Systems, Inc.).

Whole-brain Voxelwise Analysis and Region of Interest Definition

We conducted whole-brain voxelwise analyses that generated images from which we defined our regions of interest (ROIs). All statistical tests were conducted on cross-correlation magnitudes calculated at each voxel. Magnitudes were computed as the inner product of the estimated timecourse of the BOLD response and a vector of contrast weights modeling a γ function with a 2-s delay and a time contrast of 1.25 s (Boynton et al. 1996). Further, 3 additional delays of 1 s were used to account for onset variability of

the hemodynamic response. The delay that produced the largest t-statistic was chosen for each voxel.

First, we computed a voxelwise correlation to assess the relationship between neural activity during $Study_1$ and "Memory Score" (Fig. 4A). Next, we computed a second correlation to determine voxels that showed a significant relationship between $Study_1$ activity and age (Fig. 4B). These images were then Monte Carlo-corrected at a z-value of 2.25 with at least 53 contiguous voxels (familywise $P < 0.05$) (McAvoy et al. 2001). We then created a binary mask for each of these images where statistically significant voxels in the brain were given a value of 1 and all other voxels were given a value of 0. Summing the images resulted in a map with voxel values of 0, 1, and 2, where voxels with a value of 2 correspond to locations where $Study_1$ activity was correlated with both memory score and age. ROIs were then defined using a peak-finding algorithm that searched for locations with voxel value equal to 2 after smoothing the data with a 2-mm blurring kernel. The reason for applying a 2-mm blurring kernel at this stage was to ensure that the final conjunction image represented overlap near the center of mass of the 2 constituent images and not simply spurious overlap around the edges of regions in the constituent images. Spherical regions of 10 mm diameter were created around the peak locations derived from the search algorithm. A total of 7 ROIs emerged from this analysis. We then averaged the activity across each of the 7 regions and plotted that activity against memory score (Fig. 4C) and age (Fig. 4D). Scatterplots are shown to depict the relationship between activity and baseline (% signal change = 0), not as a means of showing a significant pattern of correlation since this was already determined by the statistical images.

Administration of Cognitive Batteries

All computer-based tasks (Computation Span, Switching, and Stroop Switching) were administered on a MacBook Pro (Apple, Cupertino, CA, USA) running Windows 7 Professional (Microsoft Corp., Redmond, WA, USA) and presented to participants using a 20″ Dell Ultrasharp Monitor (Dell systems, Dallas, TX, USA) connected as a display to the laptop. Personality inventories were also completed on the computer, and were administered using Adobe Flash Professional CS5.5. All other tasks were given by paper and pencil according to instructions contained in either the test manual or corresponding research article.

WAIS-IV: Digit Symbol

Participants were instructed to fill in the box below each number with the appropriate symbol using the legend at the top of the page (Wechsler 2008) . They were informed that the experimenter would keep track of the time and they would complete the trials in sequence until they either finished or time was called (participants had 2 min to do the task). The experimenter then completed the demo boxes and had participants complete the sample boxes. If the participant had no questions, they were told to start. Participants were not allowed to correct mistakes or skip items during the test.

WAIS-IV: Symbol Search

Participants were told that their task was to search for the 2 symbols indicated on each trial in the corresponding search set (Wechsler 2008). If a symbol was found in the search set, they marked through it with a line. If neither of the symbols were in the search set, they marked through "NO." The experimenter then completed the demonstration items and had the participants complete the sample items. Participants were informed that the experimenter would be keeping track of time and they would complete the trials in sequence until they either finished or time was called (participants had 2 min to do the task). Participants were not allowed to correct mistakes or skip items during the task.

Trail Making A and B

Participants connected orbs in increasing numerical order for Trails A (Reitan 1958; Corrigan and Hinkeldey 1987; Lezak et al. 2004; Tombaugh 2004). Trails B consisted of connecting orbs in increasing numerical and alphabetical order, alternating between the two (i.e., 1 A 2 B 3 C. . .). The experimenter completed a demonstration before having the participant complete each trail. Participants were informed that they would be timed. Participants were also instructed to correct any mistakes they made during the task.

CVLT-II: Part 1

This section includes List A Immediate Free Recall Trial 1 through List A Short Delay Cued Recall (Delis et al. 2000). The experimenter read a list of 16 words to the participant, who was then asked to recall all the words they could remember (in any order). There was a 20-min delay between the end of the California Verbal Learning Test (CVLT)-II Part 1 and the beginning of CVLT-II Part 2.

WASI-II: Matrix Reasoning

Participants were shown Sample A and told that their task was to select the item from the array that best completed the matrix for each problem (Wechsler 2011). Participants were then asked to complete Sample items A and B (SA and SB). If both were correct, the experimenter skipped to Item 4 and credit was given for Items 1–3. If it seemed that the participant was taking longer than normal or did not have an answer on a particular problem the experimenter would prompt them for a response (e.g., "Do you have an answer?") to move them along. The task was terminated when the participant received 3 consecutive scores of 0 (incorrect).

CVLT-II: Part 2

This section includes List A Long Delay Free Recall through List A Long Delay Yes/No recognition (Delis et al. 2000). Participants did not complete the Forced-Choice Recognition portion of CVLT-II. Participants were asked to recall the list of 16 words the experimenter had read to them during CVLT-II Part 1. Instructions were read directly from the CVLT packet.

WASI-II: Vocabulary

Participants were asked to define a series of vocabulary words. Responses were recorded and scored on the spot using the Wechsler Adult Scale of Intelligence (WASI-II) manual (see WASI manual for more specific guidelines on assigning scores for each item) (Wechsler 2011). Administration of the task was discontinued if the participant received 3 consecutive scores of 0 points.

Computation Span

Participants read math problems aloud and responded whether they were correct or incorrect (e.g., is 5 + 7 = 12?) (Conway et al. 2005). They were asked to remember the second number in each equation to recall later in order. The number of digits to remember increased by one every 3 trials. Participants had to get 2 of 3 trials right on each span in order to advance to next span length. A participant's CSPAN was the longest span in which they had at least 2 trials correct.

Consonant/Vowel Odd/Even Switching

Participants saw a number and letter and had to either decide if the number was even or odd, or decide if the letter was a consonant or vowel (Tse et al. 2010). Participants were instructed to respond as quickly as they could without sacrificing accuracy.

Stroop Switching

Depending on whether the cue was "word" or "color," participants had to indicate the word spelled by the text (word) or the color of the text (color) (Hutchison et al. 2010). Participants were instructed to respond as quickly as they could without sacrificing accuracy.

Personality Inventories

The Zimbardo Time Perspective Inventory (ZTPI, Zimbardo and Boyd 1999), Need for Cognition Scale (NFC, Cacioppo et al. 1984), Narcissistic Personality Inventory (NPI, Ames et al. 2006), Ten-Item Personality Inventory (TIPI, Gosling et al. 2003), and Vividness of Visual Imagery Questionnaire (VVIQ, Marks 1973) were also administered to participants at the end of the session. Discussion of these inventories is beyond the scope of the paper.

Analysis of Cognitive Batteries

Analysis of the cognitive batteries was performed with the goal of obtaining 4 separate scores for each participant: 1) processing speed, 2) long-term memory, 3) general intelligence—matrix reasoning, 4) general intelligence—vocabulary.

Processing Speed

The behavioral measures that comprise this score include both "Switch" and "Non-switch" reaction times for the "Consonant/Vowel Odd/Even Switching" and "Stroop Switching" tasks, reaction times from Trails A and Trails B, as well as the "symbol search" and "digit symbol" sub-sections from the WAIS-IV. All data were converted to z-scores based on performance across individuals for the purpose of averaging across the measures to produce a composite. Z-scores for reaction time data were multiplied by negative one so that faster reaction times produced positive z-values. Reversing the sign allowed us to average the reaction time data and the performance data from the WAIS-IV to create a measure of processing speed.

Long-term Memory (CVLT-II)

Final scores from the CVLT-II included 16 separate memory measures, some of which were not strongly correlated within subjects. As a result, we submitted each score of each subtest of the CVLT-II to a factor analysis to determine the measures that accounted for the greatest amount of variance that loaded onto a single component. Seven separate measures loaded onto the first component, accounting for 40.82% of the total variance. These included "short-delay free recall," "long-delay free recall," "short-delay cued recall," "long-delay cued recall," "trial 1–5 performance," "subjective clustering," and "recognition discrimination." Each of these measures was z-scored and averaged within participants to obtain an overall "Long-term memory" score.

General Intelligence—Matrix Reasoning and Vocabulary (WASI-II)

Each of the WASI-II subtests was scored according to the instruction manual, and participant's scores were converted to z-scores.

Results

Long-term memory performance was measured as a function of 3 indices: Test 1 performance, Trials to Criterion, and Final Recall performance. On average, participants correctly recalled 6.7 items on Test 1 (range 0–22), took 9.4 test trials (range 4–22) to learn all 45 word pairs, and recalled 30.1 (range 10–45) items at Final Recall (Fig. 2A). Across participants, these indices were strongly intercorrelated, such that participants who recalled

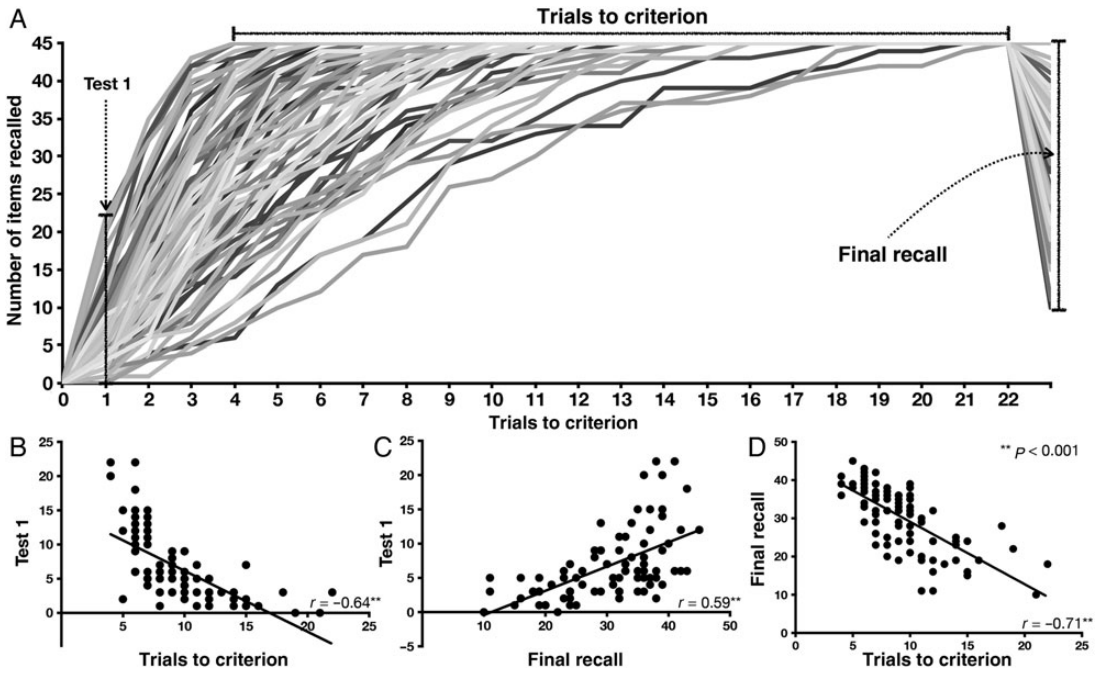

Figure 2. Behavioral data reveal striking individual differences. (*A*) Learning curves for each of the participants ($n = 86$) are plotted along with performance on the final test. (*B–D*) Each behavioral measure is shown plotted against one another, demonstrating robust correlations across participants.

more items on Test 1 also learned the pairs in fewer trials, and remembered more of the English associates on a final test (Fig. 2*B–D*). These outcomes were combined into a single measurement, referred to here as a memory score, as a means of approximating a given person's overall memory performance.

There was a significant negative relationship between memory score and age of the participants ($r = -0.30$, $P < 0.01$), such that the older participants performed more poorly (Fig. 3). Correlations between age and Test 1 ($r = -0.24$, $P < 0.05$), Trials to Criterion ($r = 0.25$, $P < 0.05$), and Final Recall ($r = -0.29$, $P < 0.01$) were also significant (Supplementary Fig. 1); older participants performed less well on Test 1, took longer to learn the items, and remembered fewer items at Final Recall. Age was also significantly negatively correlated with a combined measure of processing speed ($r = -0.24$, $P < 0.05$, Supplementary Fig. 2, see Materials and Methods), but showed no significant relationship with measures of either fluid or crystallized intelligence as measured by the WASI-II. In addition, age was not correlated with performance on the CVLT.

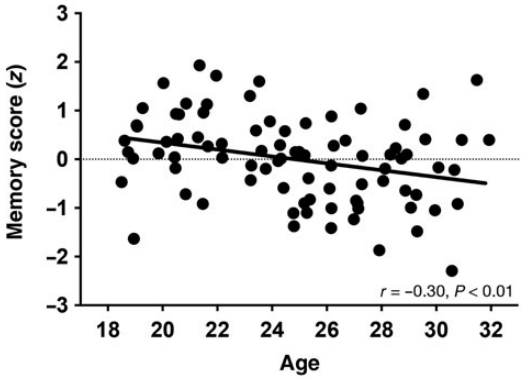

Figure 3. Memory score versus age. Scatterplot of memory score versus age reveals a significant negative correlation ($r = -0.30$, $P < 0.01$).

Thus far, we have shown that some of the variance in memory performance can be accounted for by the age of our participants. Next, we examined whether neural activity during $Study_1$ learning predicted either memory score or age, and the degree to which common brain regions predicted both variables. Interestingly, voxelwise correlation maps depicting the relationship between $Study_1$ neural activity with both memory score and age (Fig. 4*A*,*B*; Tables 1 and 2) revealed considerable overlap between regions in the ventromedial prefrontal cortex (vmPFC), posterior cingulate cortex (PCC), and angular gyrus, all core members of the default mode network (DMN) (Raichle et al. 2001). These regions, along with others present in either the memory score or age map alone, show patterns such that neural activity is negatively related to memory performance and positively related to age. In other words, within these regions, both high performers and younger adults show less activity during initial study of material. Examination of the magnitude of neural activity reveals that high-performing and young participants did not simply show less activity during $Study_1$, but deactivated these regions below baseline (Fig. 4*C*,*D*). Both lower performing and older participants deactivated the regions to a lesser degree or simply failed to significantly modulate them (see Discussion). Whole-brain correlation maps corresponding to the 3 separate measures going into the composite memory score all revealed prominent members of the DMN as well (see Supplementary Fig. 3). In addition, these correlations also hold when only incorrect items (items not recalled on Test 1) are analyzed (Supplementary Fig. 4), suggesting that it is a person-level difference not simply driven by differences in task success.

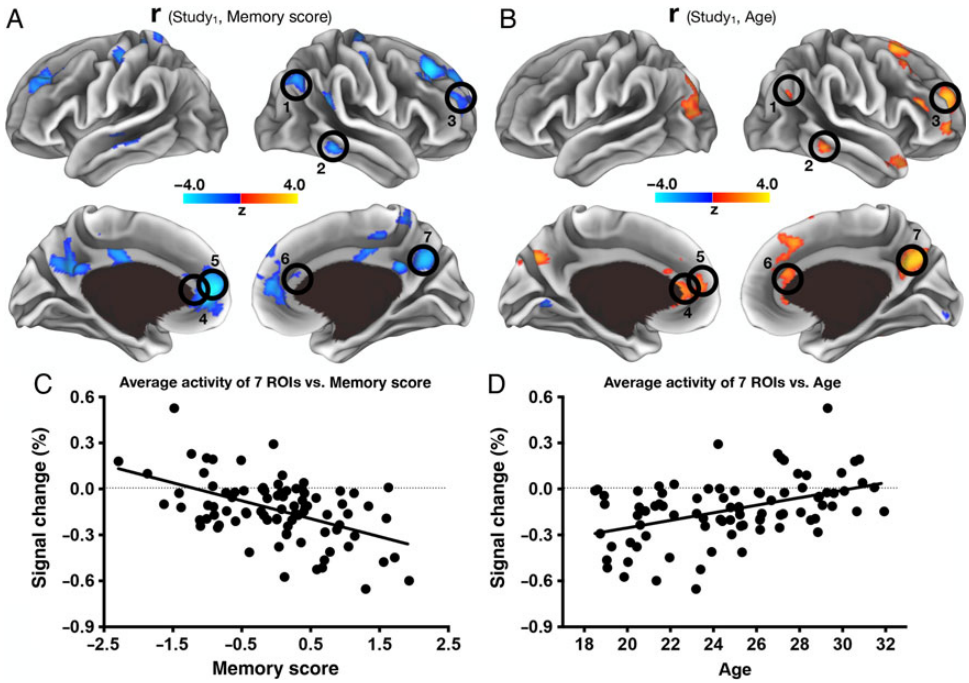

Figure 4. Neural activity from a common set of regions correlates with both memory score and age. (*A* and *B*) Correlation maps, corrected for multiple comparisons, depict voxels that show a significant relationship between activity during $Study_1$ and memory score (*A*), and $Study_1$ and age (*B*). Circled regions are common to both maps. Data are projected onto the Conte69 fiducial surface using Connectome Workbench (http://humanconnectome.org) (Van Essen et al. 2012). (*C* and *D*) Scatterplots depict the relationship between the average activity of the 7 overlapping regions (*y*-axis) and memory score (*C*) and age (*D*).

Table 1 Regions showing a significant relationship between $Study_1$ activity and age, peak stereotactic coordinate in MNI space, and z-statistic

Region	Peak coordinate (x,y,z)			z-Statistic
Ventromedial PFC	−6	34	3	3.90
Posterior cingulate cortex	8	−59	31	3.57
Superior frontal cortex	23	55	20	3.17
Precuneus	4	−67	37	3.16
Dorsolateral PFC	36	34	20	3.02
Medial cerebellum	−11	−76	−31	2.98
Superior frontal cortex	20	20	60	2.97
Lateral cerebellum	−25	−73	−36	2.84
Anterior temporal cortex	56	12	−25	2.81
Dorsomedial PFC	3	37	28	2.79
Middle frontal gyrus	33	19	56	2.74
Fusiform gyrus	41	−35	−25	2.72
Anterior cingulate cortex	6	30	43	2.70
Lateral occipital cortex	−42	−81	18	2.68
Anterior PFC	40	57	−3	2.67
Angular gyrus	50	−67	43	2.62
Inferior temporal	61	−40	−11	2.61
Superior occipital gyrus	−35	−87	27	2.60
Fusiform gyrus	49	−46	−18	2.54
Angular gyrus	51	−67	32	2.50
Dorsolateral PFC	36	33	41	2.45
Superior temporal gyrus	45	17	−28	2.44
Ventromedial PFC	−8	54	9	2.43
Superior occipital gyrus	−35	−80	39	2.38
Angular gyrus	−52	−72	32	2.28
Precuneus	12	−76	46	2.26
Medial cerebellum	−6	−93	−23	−2.80
Lingual gyrus	2	−70	−5	−2.78
Medial cerebellum	−18	−90	−24	−2.51

PFC, prefrontal cortex.

Table 2 Regions showing a significant relationship between $Study_1$ activity and memory score, peak stereotactic coordinate in MNI space, and z-statistic

Region	Peak coordinate (x,y,z)			z-Statistic
Ventromedial PFC	−9	54	7	−3.96
Superior frontal gyrus	21	35	42	−3.51
Anterior PFC	22	52	14	−3.30
Precentral gyrus	−36	−22	52	−3.29
Superior frontal gyrus	−25	38	38	−3.17
Temporo-parietal junction	62	−47	24	−3.16
Posterior cingulate cortex	6	−62	36	−3.16
Dorsal premotor cortex	28	−7	46	−3.10
Posterior cingulate cortex	7	−46	63	−3.04
Intraparietal sulcus	39	−52	30	−3.00
Dorsomedial PFC	14	51	30	−3.00
Middle cingulate cortex	1	−19	41	−2.95
Inferior temporal cortex	58	−40	−12	−2.91
Posterior cingulate cortex	−7	−56	29	−2.90
Anterior temporal cortex	−61	−15	−9	−2.90
Angular gyrus	44	−71	42	−2.87
Ventromedial PFC	9	46	3	−2.83
Posterior cingulate cortex	3	−44	30	−2.82
Postcentral gyrus	−36	−30	69	−2.75
Superior parietal lobule	−28	−46	70	−2.74
Cingulate cortex	1	−11	32	−2.62
Precentral gyrus	−47	−14	54	−2.61
Medial PFC	−1	63	15	−2.61
Posterior cingulate cortex	−12	−56	42	−2.60
Fusiform gyrus	48	−37	−19	−2.58
Precentral gyrus	28	−18	73	−2.55
Precentral gyrus	40	−15	53	−2.54
Dorsomedial PFC	6	56	38	−2.54
Precentral gyrus	−18	−45	74	−2.52
Medial PFC	0	40	19	−2.48
Anterior PFC	−21	47	29	−2.45
Posterior cingulate cortex	1	−54	50	−2.42
Precentral gyrus	36	−13	68	−2.38
Middle frontal gyrus	−23	50	−1	−2.36
Dorsolateral PFC	35	33	38	−2.36
Middle temporal gyrus	−65	−35	0	−2.32

PFC, prefrontal cortex.

Seven overlapping ROIs were thus identified in the voxelwise analyses, all of which showed a relationship between neural activity and both memory score and age (Fig. 5A; Table 3). That is, we observed a significant correlation among the 3 variables of interest (neural activity during $Study_1$, memory performance, and age). A mediation analysis tested whether average BOLD deactivation in the set of regions common to the age and memory score correlation mediates the relationship between age and memory performance. Indeed, BOLD deactivation in the 7 ROIs was found to mediate the relationship between age and memory performance (Fig. 5B; Sobel test, $z = 3.29$, $P < 0.001$).

Discussion

We have shown that task-evoked fMRI activity relates to aging in a sample of healthy, neurologically normal young adults. Our data suggest that there is a relationship between age and memory performance in young adults, which is mediated by widespread cortical deactivation, predominantly in regions of the DMN. Here, we discuss the implications for understanding the functional role of deactivations and their relationship to memory performance. We then consider features of the task that may have contributed to its predictive power. In addition, we consider whether the effects seen here in the DMN might help elucidate understanding of disorders, such as Alzheimer's disease (AD), that are strongly related to both age and memory. We end by discussing potential limitations of the current study and provide concluding remarks.

The Relationship Between DMN Deactivation, Long-term Memory, Attention, and Aging

Shulman et al. (1997) identified a set of regions that tend to deactivate during situations calling for attention to the external environment, regardless of the specific cognitive task. This set of regions was subsequently labeled the DMN (Gusnard and Raichle 2001; Raichle et al. 2001) due to its hypothesized role in the human default mode of thought (e.g., during daydreaming, reminiscing, and other situations in which focused attention to the external environment is not required); that is, the network was hypothesized to be active much of the time (in the default mode of thought) but transiently deactivated or suppressed in situations requiring that attention be focused away from oneself and onto the external environment. Resting-state functional connectivity MRI subsequently confirmed that this set of regions indeed comprises a network in that the regions co-fluctuate during periods of unconstrained cognition (Power et al. 2011; Yeo et al. 2011).

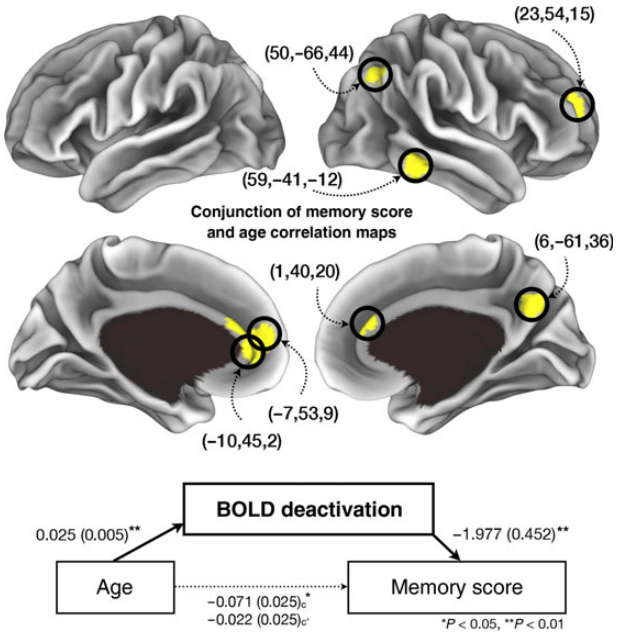

Figure 5. BOLD deactivation in overlapping regions mediates the relationship between memory score and age. (*A*) Regions of interest (ROI) whose activity relates to both memory score and age are projected onto the Conte69 fiducial surface using Connectome Workbench (http://humanconnectome.org) (Van Essen et al. 2012) along with stereotactic coordinates in MNI space. (*B*) Diagram of a mediation model depicts the relationship between age (predictor), BOLD deactivation (mediator), and memory score (outcome). Shown beside the arrows are unstandardized regression coefficients and their standard error (in parentheses).

Table 3 Regions showing a significant relationship between $Study_1$ activity and both age and memory score, peak stereotactic coordinate in MNI space

Region	Peak coordinate (x,y,z)		
Posterior cingulate cortex	6	−61	36
Ventromedial PFC	−10	45	2
Medial PFC	−7	53	9
Anterior PFC	23	54	15
Medial PFC	1	40	20
Lateral temporal cortex	59	−41	−12
Angular gyrus	50	−66	44

PFC, prefrontal cortex.

Although considerable debate has ensued regarding the exact role of the DMN in cognition, many empirical regularities have emerged. Within the memory literature, the degree of deactivation within the DMN has been linked to successful encoding [although the direction of the effect—more deactivation for subsequently remembered items than subsequently forgotten items—has led some researchers to interpret the pattern as indicative of involvement in forgetting, not remembering (see Otten and Rugg 2001; Wagner and Davachi 2001; Kim et al. 2010)]. Older adults tend to deactivate the network less than younger adults, which has led to the hypothesis that the DMN is a source of the long-term memory deficits that occur with age (Lustig et al. 2003). In a lifespan study, Park et al. (2013) found that the decrease in memory performance between middle-aged and older adults was accompanied by a decrease in the robustness of DMN deactivation from middle to old adulthood.

The present data extend this body of work by suggesting that those who more robustly deactivate the DMN during an encoding phase may better allocate attentional resources during the learning epochs and therefore more effectively encode the stimuli. Importantly, this robustness of deactivation differs widely across individuals and tends to weaken across the early adult (18–31 years) lifespan.

The Lithuanian–English Task may Encourage Unique Processing Demands Compared with Learning Familiar, Semantically Rich Information

The sensitivity of the Lithuanian–English task performance to aging effects within this sample may at first seem to contradict the lack of effect in other measures, most notably the CVLT. Although speculative, we hypothesize that features of the present task may have allowed the emergence of subtle behavioral deficits that may not be apparent in other tasks.

To understand this distinction, it is helpful to consider the influential theory forwarded by Craik and Byrd (1982) that older adults exhibit memory deficits to the extent that the situation requires attentional resources (what Craik referred to as "processing power," p. 112) (Lindenberger and Mayr 2014). That is, when the external environment does not provide cues or reminders to guide performance, and the person instead has to initiate top-down control to execute the task, aging effects are more readily observed. Craik posited that different encoding and retrieval tasks can vary along this continuum of requiring subject-initiated processing power or being guided by external, environmental cues.

The task developed for the present study was designed to place great demands on these subject-initiated processes. For English speakers, there is no obvious meaning that can be ascribed to the Lithuanian words; the stimuli do not easily afford elaborative processing, and there is no obvious link between the phonological representations and their translation equivalent. Furthermore, the stimuli were presented relatively quickly, placing additional stress on the brain's cognitive capacities. Finally, the cued-recall tests presented just the Lithuanian word and required that the subject generate the English translation, a task that requires more attentional resources than other types of memory tasks (e.g., recognition memory or a stem completion test).

With these ideas in mind, one can begin to reconcile the lack of correlation between the CVLT and age with the observed correlation between the Lithuanian–English task and age (Supplementary Fig. 2). The CVLT uses semantically related words organized into 4 categories, affording individuals the opportunity to use meaning and category membership to organize the information as they attempt to memorize the words. In contrast, the novel Lithuanian word is devoid of any semantic or categorical content and must instead be mapped in an apparently arbitrary manner to the corresponding English word. In addition, learning novel stimulus pairings discourages the learner from being able to use contextual cues present when learning a list of words.

Does the Relationship between Age and Deactivation Lend Insights into Early Progression of AD?

Previous studies comparing younger and older adults have found age differences similar to the ones we report here (Lustig et al. 2003; Sperling et al. 2009); older adults deactivate regions of the DMN less than younger adults in attention-demanding tasks and also have memory impairment relative to young adults.

However, a major focus in studies of older adults is not just on the healthy aging process, but also on pathologies like AD. Thus, groups of older adults tend to be broken up into subgroups based on the severity of their cognitive impairment, often measured by the Clinical Dementia Rating scale. Recent work suggests that neuropathological markers for AD [i.e., Amyloid beta, Tau, as measured via cerebral spinal fluid measures and amyloid plaques measured in vivo via Pittsburgh Compound B or PiB Imaging (Klunk et al. 2004)] can be detected a decade before onset of dementia (see Bateman et al. 2012). Further, attenuated task-induced deactivations and PiB binding co-localize in core regions of the DMN (i.e., PCC and vmPFC).

A natural question is whether insults detected with PiB imaging are preceded by, or perhaps even caused by, physiological aberrations present during task performance. In other words, is the failure to deactivate DMN regions during attention-demanding tasks a precursor to greater PiB binding, or alternatively, does the presence of amyloid plaques lead to decreased deactivations and impaired memory performance? A study from Cirrito et al. (2005) using mouse models of AD suggests that changes in neuronal activity precede the manifestations of tangles and plaques, lending at least some support to the idea that aberrant neurophysiology may precede detectable biomarkers of AD in humans. The present results may have the potential to inform disease progression in AD (Seeley et al. 2009; Spreng and Turner 2013), although this link is speculative. A necessary first step is better understanding of the healthy progression of reduced DMN deactivations from young to old adults, with a view to establishing a normative function of decline by which individuals who deviate from this function are either more or less likely to develop AD. Of course, metrics like these would be used in addition to behavioral and genetic markers to one day create predictive models that optimize early detection.

Limitations

Any study that focuses on the relationship between 2 measures in the context of individual differences runs the risk of failing to account for lurking variables that may sufficiently explain the relationship, often in a less interesting manner. With this concern in mind, we evaluated a wide variety of cognitive, personality, and education-related variables collected in this study to ensure these other variables could not account for the relationship between $Study_1$ activity, age, and memory score; they could not. For instance, measures like intelligence quotient (IQ) as measured by the WASI-II (see Supplementary Fig. 2) were unrelated to the age of the participant.

Another limitation that can sometimes be problematic for fMRI studies focusing on individual differences is small sample size (Yarkoni 2009; Mar et al. 2013). Although we collected data from 100 participants (with a final $n = 86$; see Materials and Methods), replication will be critical to determine the robustness of the finding. Indeed, the hope is that future research will continue to place boundary conditions on the findings presented here with the goal of providing experimental constraints that speak to the likelihood of observing such an age × brain × behavior relationship to develop a framework for understanding such individual differences.

Conclusions

In the current study, we show widespread heterogeneity in a sample of 18- to 31-year olds on a measure of memory performance as well as BOLD deactivation during the initial study period. Thus, aging effects that have been demonstrated previously in the behavioral literature may relate to an individual's ability to deactivate regions, largely in the DMN. However, future studies should determine the degree to which these results generalize across different learning materials and task parameters. Importantly, aging and memory performance effects may be most visible in young adults in learning situations that require rapid acquisition of novel information with very little semantic context. In these scenarios, attentional demands on encoding may be appropriately sensitive to reveal interesting differences that have yet to be discovered.

Supplementary material

Supplementary Material can be found at http://www.cercor.oxfordjournals.org/ online.

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