Transfer of Learning After Updating Training Mediated by the Striatum

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Science **320**, 1510 (2008);
DOI: 10.1126/science.1155466

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.

MRE11 by either MRN component or by MDC1 (Fig. 3C). However, upon immobilization of NBS1 or MRE11, the accumulation of the downstream factors MDC1 and 53BP1 was strongly impaired in the absence of H2AX (Fig. 3C). Recruitment of MDC1 by $ATM^{1300-3060}$ was similarly decreased, suggesting that phosphorylation of H2AX is an important step in recruiting and maintaining these factors at sites of damage (*17*, *19*).

To finally test whether individual repair factors are sufficient to induce a physiological DDR, we assessed the effect of immobilization on cell cycle progression (Fig. 4). Upon targeting of NBS1, MRE11, MDC1, or ATM, but not Chk1 or Chk2, to chromatin, cells accumulated in G_2 phase as determined by staining of pericentromeric heterochromatin with an antibody to phosphoS10H3 (Fig. 4A) (*20*). Cell cycle delay was confirmed by increased phosphorylation of retinoblastoma protein at Ser^{807}/Ser^{811} (fig. S6). Furthermore, the cell cycle delay was sensitive to the presence of Chk2 and required ATM activity, suggesting involvement of the checkpoint kinase Chk2 (Fig. 4A). $H2AX^{-/-}$ cells were resistant to G_2/M delays upon immobilization of repair factors (Fig. 4B). This observation is in line with the finding that cells lacking H2AX manifest a G_2/M checkpoint defect after exposure to low doses of irradiation (*21*).

We report here that activation of cellular DNA damage response pathways does not require DNA damage but can be triggered by stable association of single repair factors with chromatin. Our observations suggest that the physical interaction of DNA repair factors with chromatin is a key step in activation of the DDR signaling cascade, and that the observed buildup at DNA damage foci probably contributes appreciably to establishing the cellular response to damaged DNA (*4*). Our observation that immobilized downstream factors can recruit upstream components indicates that activation of a full DDR involves amplification via formation of multiple repair complexes and perpetuation of γH2AX phosphorylation. A critical role for signal amplification on DNA is also suggested by the findings that in the absence of γH2AX or MDC1, several repair factors, including NBS1 and 53BP1, are recruited to sites of double-strand breaks, but do not accumulate and are not efficiently retained (*16*, *19*). Our observation of phosphorylation of several key components of the DDR, including H2AX, NBS1, and ATM, and the appearance of cell cycle delays upon tethering indicate that the observed cellular response mimics to a large extent the physiological DDR. Given the apparent importance of the physical interaction of DNA repair factors with chromatin, it will be essential to uncover the precise role of higher-order chromatin structure and chromatin-remodeling complexes in triggering the DDR.

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22. We thank J. Lukas and Y. Shiloh for reagents and comments; A. Belmont, T. Paull, and M. Kastan for reagents; S. Snyder for technical assistance; and M. Kruhlak for help with microscopy. Imaging was performed at the National Cancer Institute (NCI) Fluorescence Imaging Facility. E.S. was supported by a fellowship from the Human Frontier Science Program. This research was supported by the Intramural Research Program of the NIH, NCI, and Center for Cancer Research.

Supporting Online Material

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Materials and Methods
Figs. S1 to S7
References

14 April 2008; accepted 1 May 2008
Published online 15 May 2008;
10.1126/science.1159051
Include this information when citing this paper.

Transfer of Learning After Updating Training Mediated by the Striatum

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Process-specific training can improve performance on untrained tasks, but the magnitude of gain is variable and often there is no transfer at all. We demonstrate transfer to a 3-back test of working memory after 5 weeks of training in updating. The transfer effect was based on a joint training-related activity increase for the criterion (letter memory) and transfer tasks in a striatal region that also was recruited pretraining. No transfer was observed to a task that did not engage updating and striatal regions, and age-related striatal changes imposed constraints on transfer. These findings indicate that transfer can occur if the criterion and transfer tasks engage specific overlapping processing components and brain regions.

Task-specific performance enhancement and altered patterns of brain activity have been demonstrated after training on complex executive tasks (*1*, *2*). Training can also improve performance on untrained transfer tasks (*3*), but the magnitude of gain is considerably smaller and often there is no transfer at all (*2*). One current hypothesis is that transfer will occur if the criterion and transfer tasks involve overlapping processing components and engage, at least in part, the same brain regions (*4*). In the present study, we studied learning and transfer of a specific skill: updating. Updating is a basic executive function (*5*, *6*) related to measures of intelligence (*7*) and working memory, in particular to working-memory tasks that require manipulation of information (*6*). Updating has been associated with the striatum (*8*), and, in a recent computational model (*9*), striatal neurons serve a gating function for updating in working memory.

To map training-induced changes in brain activity, functional magnetic resonance imaging (fMRI) was used before and after 5 weeks of computer-based updating training (*10*). A test of letter memory served as the updating criterion task (*5*). It consisted of 10 lists of randomly presented letters (A to D), and the task was to recall the four last presented letters. The *n*-back task (*11*) with three levels of load (1, 2, and 3) was used as the transfer task. This task differed from letter memory in terms of memorial content (letters versus numbers), set size, presentation rate, and response format (*10*). These differences are important given that previous research has indicated that even subtle procedural variations can reduce the degree of transfer (*12*), but, critically, *n*-back requires updating and hence shares a basic process with letter memory. A Stroop test was also included. Letter memory and Stroop tap different executive processes (*5*, *6*) and activate specific neural systems (*13*), but transfer could be mediated through a common frontoparietal network (*13*, *14*). Alternatively, no transfer to Stroop should be observed if transfer specifically depends on training-induced

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changes in a striatal updating system. In a second experiment, we used the same basic procedure to investigate training effects in older adults (*10*). Task-specific training gains and altered patterns of brain activity after training on complex executive tasks have been demonstrated in older adults (*15*, *16*), but transfer to untrained tasks tend to be more difficult to demonstrate in older than in younger adults (*12*, *17*–*19*). It is well established that age-related changes are prominent in the striatum (*20*, *21*), which could impose constraints on transfer of updating training to untrained task performance.

In experiment 1, the training and control groups were comparable on relevant background characteristics (table S1), and the groups were indistinguishable on letter memory before training (table S2). The training group showed considerably larger gains in letter memory, as revealed by a significant group-by-session interaction ($F_{1.20}$ = 26.45, $P < 0.001$). Further, the effect size for the training group was significantly larger than for the control group (Fig. 1A) [$t(20) = 5.14$, $P < 0.001$]. Evaluation of performance on the Stroop task did not reveal any significant training-related changes in performance (table S2). For the *n*-back task, there was a significant group-by-session interaction ($F_{1.20}$ = 10.32, $P < 0.01$) for 3-back, and the effect size for trained participants was significantly greater than for controls (Fig. 1A) [$t(20) = 4.05$, $P < 0.001$]. No significant interaction was found for 1- and 2-back, reflecting pretraining ceiling effects (table S2). Analyses of the *n*-back imaging data were therefore restricted to 3-back.

The hypothesis that transfer will occur if the criterion and transfer tasks initially engage similar processes and brain circuits predicts overlapping activity before training. We tested this prediction with a conjunction analysis of pretraining activity ($N = 22$) for letter memory and 3-back and observed joint activation in left striatum ($x = –16$, $y = –2$, and $z = 16$; $x = –20$, $y = 4$, and $z = 14$) along with common frontoparietal activation (Fig. 2A). In addition, a direct comparison of letter memory and 3-back at pretest revealed several differences in brain activity, as expected from differences in task demands (fig. S1). A similar conjunction analysis of letter memory with the Stroop task did not reveal any overlap in striatal regions, despite overlap in frontoparietal regions (Fig. 2A). Analyses of pre- and post changes in the fMRI data for letter memory revealed relatively greater activity after training in left striatum ($x = –26$, $y = –4$, and $z = –4$; $t = 4.32$) (see table S3 for other areas), along with decreased frontoparietal activity (table S3). In the analyses of transfer effects, training-related increases were seen in left striatum ($x = –30$, $y = 4$, and $z = 6$; $T = 4.74$) and frontal cortex for 3-back (see table S3 for other areas), but no significant changes were found for Stroop. On the basis of these findings of posttraining activity increases in left striatum for both letter memory and 3-back, we conducted a conjunction analysis to assess commonalities in between-session activation changes for these tasks. This analysis revealed overlap in left striatum ($x = –28$, $y = 8$, and $z = –2$; $T = 3.91$). Critically, the striatal region showing training-related increases for both letter memory and 3-back overlapped with the striatal region that was jointly activated at the pretraining session for these two tasks (Fig. 3A). This overlap in activity fell within the associative striatum (*22*).

In experiment 2, the older training and control groups were comparable on relevant background characteristics (table S1), and the two groups performed at similar levels on letter memory at pretraining (table S2). Both groups improved their performance in the posttraining session,

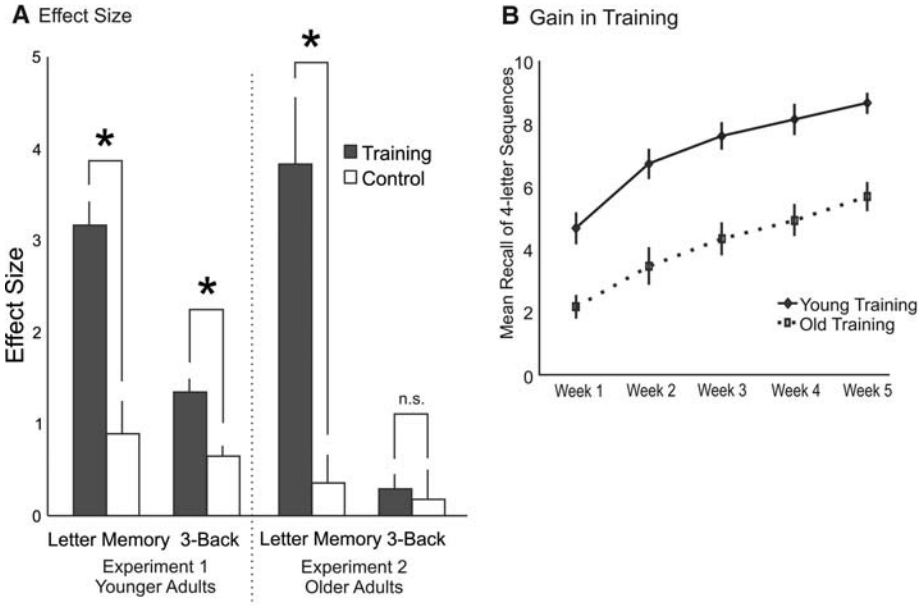

Fig. 1. (**A**) Letter memory and 3-back performance for training and control groups. The histograms denote mean effect sizes. (**B**) Training gains in younger and older adults during the 5-week intervention period. Error bars indicate SEM. Asterisks indicate statistical significance; n.s., not significant.

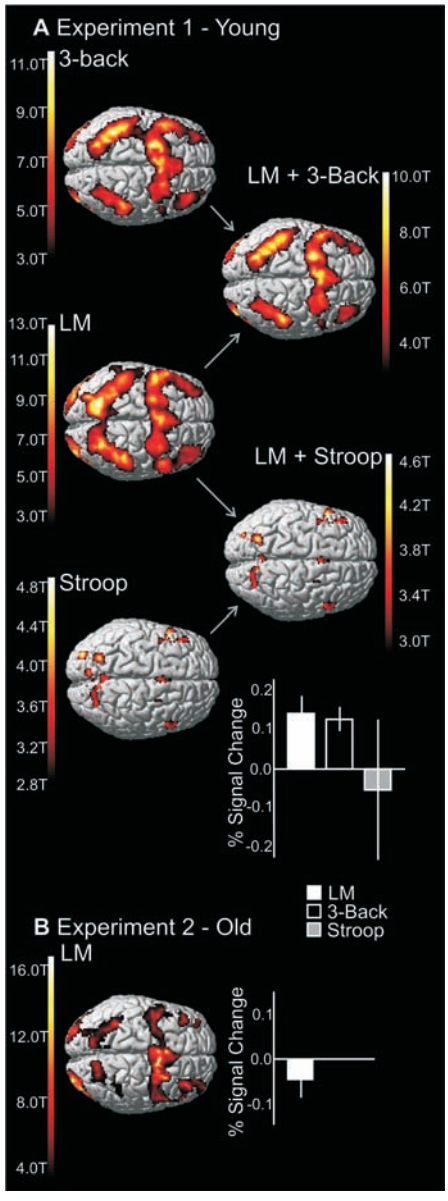

Fig. 2. (**A**) Brain maps to the left (dorsal view) show activation of bilateral parietal cortex and lateral and medial frontal cortex for all tasks at pretraining. Conjunction analyses of the letter memory (LM) task with Stroop and 3-back revealed overlapping frontoparietal activation patterns for the criterion task and both transfer tasks (cortical maps to the right). The bar graph (bottom) shows the striatal activation profile across tasks at pretraining and reveal overlapping activations in LM and 3-back (plotted at peak $x = –20$, $y = 4$, and $z = 14$). (**B**) Brain map to the left shows activation of bilateral parietal cortex and lateral and medial frontal cortex for LM pretraining. The bar graph shows no significant striatal activation in LM for older adults (plotted at peak $x = –24$, $y = 10$, and $z = –2$, where selective training-related increases were found). Error bars indicate SEM.

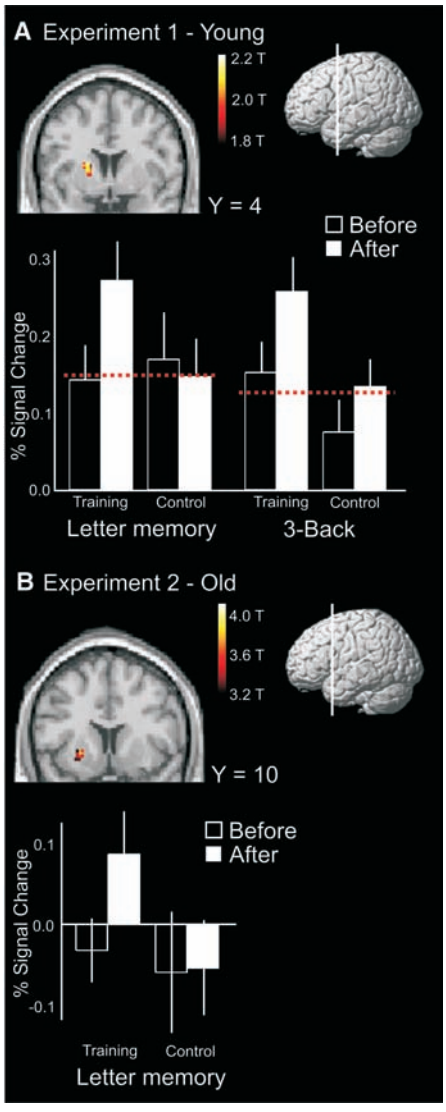

Fig. 3. (**A**) Left striatum (peak $x = -20$, $y = 4$, and $z = 14$) was activated before training and showed a training-related increase for both letter memory and 3-back in younger adults. The bar graph shows the activation profiles across tasks and sessions. The red line indicates mean baseline bold values for the striatal region (mean of trained before, controls before, and controls after). (**B**) Left striatum (peak $x = -24$, $y = 10$, and $z = -2$) showed a training-related increase for letter memory in older adults. Error bars indicate SEM.

but the increase in performance was larger for the trained group compared with controls as indicated by a significant group-by-session interaction ($F_{1,17} = 20.56$, $P < 0.001$). Further, the effect size was significantly larger for the old training group compared with controls (Fig. 1A) [$t(17) = 4.53$, $P < 0.001$]. However, the older adults showed no transfer to 3-back (Fig. 1A). This finding is in keeping with prior findings of limited transfer for older adults (*12*, *17*–*19*). Furthermore, a comparison of the learning curves from experiments 1 and 2 showed that the trained older adults had significantly lower performance at the beginning [$t(24) = 3.38$, $P < 0.005$] as well as at the end of training [$t(24) = 4.99$, $P < 0.001$] compared with the trained younger adults, and the final level of letter memory performance in the trained older group was below the level reached by younger adults after 2 weeks of training (Fig. 1B). These behavioral findings indicate age-related neural constraints on updating learning and transfer, which was supported by the fMRI analyses. Specifically, the striatum was not significantly activated during letter memory in the pretraining session for older adults, although they did activate frontoparietal regions ($N = 19$) (Fig. 2B). Analyses of prepost changes for letter memory revealed training-related activity increases in left striatum for trained older adults relative to controls ($x = -24$, $y = 10$, and $z = -2$; $T = 4.17$) (Fig. 3B; see table S3 for other areas), but no significant changes were found for the 3-back transfer task.

Our findings reveal a critical role for the striatum in mediating transfer of learning after updating training. Transfer after other forms of training, taxing different executive processes, will likely depend on other brain regions. The striatal region where a common training-related increase was seen for the letter memory and 3-back tasks was also activated at pretraining for these tasks. By contrast, no striatal activation was observed for the Stroop task, and updating training did not influence Stroop performance. Some previous research has found striatal activation during the Stroop task (*23*), but this is not a typical finding (*24*, *25*) and the Stroop task should not tax updating. Thus, although a similar frontoparietal cortical system was activated for all three tasks examined, the transfer effect apparently required that both the criterion and transfer tasks engaged a specific processing component (i.e., updating) and associated brain systems (i.e., striatum). Even though this conclusion is based on a limited regime of tasks, the observed selectivity in the neural basis of transfer is consistent with numerous behavioral findings of limited transfer. The hypothesis that a basis for transfer is that training and transfer tasks recruit overlapping neural systems (*4*) may thus be too general.

The finding of substantial performance increments on the criterion task for the older participants is consistent with previous demonstrations of enhanced performance after executive training in advanced age (*15*). However, there were pronounced age-related performance deficits on the updating criterion task and, most critically, on the magnitude of transfer to the 3-back task. Also, the older adults did not show significant striatal activation before training. These results indicate that restricted transfer of learning after updating training in older age may reflect deficient striatal functioning (*21*, *24*). Importantly, the differences in task characteristics and associated brain activity (fig. S1) and the finding of pronounced task differences in training-related frontal changes (table S3) converge with the observation of significant improvement on letter memory along with no transfer to 3-back in older adults. Although the distinction between training and transfer tasks remains to be defined precisely, collectively our findings illustrate the distinct nature of the current criterion and transfer tasks.

A key role for the striatum in learning and transfer of an updating skill is consistent with much previous work. A recent study identified striatum as being responsible for allowing only relevant information into working memory (*26*). Anterior parts of the striatum form an associative network with dorsolateral frontal regions (*22*, *27*). Neurons in the striatum may regulate updating in working memory by affecting dopaminergic modulation of the prefrontal cortex (*9*, *28*), and increased striatal dopamine release has been observed during performance of tasks requiring specific executive processes (*29*).

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30. The authors thank M. Andersson for support with statistical analyses, A.-K. Johansson for helping in collecting the data, and the staff at the MRI center. This work was funded by grants from the Swedish Research Council and the Joint Committee for Nordic Research Councils in the Humanities and the Social Sciences to L.N. for a Nordic Center of Excellence (NCoE) in Cognitive Control and by grants from the Swedish Research Council and Swedish Brain Power to L.B.

Supporting Online Material

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Materials and Methods
Fig. S1
Tables S1 to S3

22 January 2008; accepted 15 May 2008
10.1126/science.1155466