Identification of a genetic cluster influencing memory performance and hippocampal activity in humans

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Edited by Larry R. Squire, University of California, San Diego, CA, and approved January 18, 2006 (received for review November 25, 2005)

Experimental work in animals has shown that memory formation depends on a cascade of molecular events. Here we show that variability of human memory performance is related to variability in genes encoding proteins of this signaling cascade, including the NMDA and metabotrobic glutamate receptors, adenylyl cyclase, CAMKII, PKA, and PKC. The individual profile of genetic variability in these signaling molecules correlated significantly with episodic memory performance ($P < 0.00001$). Moreover, functional MRI during memory formation revealed that this genetic profile correlated with activations in memory-related brain regions, including the hippocampus and parahippocampal gyrus. The present study indicates that genetic variability in the human homologues of memory-related signaling molecules contributes to interindividual differences in human memory performance and memory-related brain activations.

genes | molecular cascade | learning

During the last three decades, animal studies in both invertebrates and vertebrates have identified genes and signaling molecules important for memory, including protein kinases and phosphatases and transcription factors (1–5). From this work, it appears that many memory-related molecular mechanisms are conserved across species. However, it is still largely unknown whether these molecular pathways are also involved in human memory. The major reason for the lack of translation of the animal findings to humans is that pharmacological manipulation of many of these signaling molecules in humans is not feasible due to either safety issues or lack of pharmacologic specificity. Recent advances in the identification of genetic polymorphisms in the human genome (6, 7) opened, however, new avenues for the examination of complex phenotypes such as human memory. Specifically, correlating the interindividual phenotypic variability with individual patterns of genetic variability in genes relevant to the phenotype of interest can powerfully detect its underlying molecular pathways (8). In the case of human memory, this approach is particularly promising, because twin studies revealed an ≈50% heritability for memory traits (9, 10). In the present study, we used the behavioral genetics approach to investigate the impact of genetic variability in the human homologues of memory-related signaling molecules on episodic memory. Because functional MRI (fMRI) can visualize brain processes involved in early memory formation (11, 12), we used this technique to capture genotype effects on the early phase of episodic memory (i.e., short-term memory) and to validate the genetic findings. In addition to short-term memory-related genes, we also investigated genes implicated in the formation of long-term memory (1–5), because human short-term memory performance is affected by preexisting associative networks stored in long-term memory (13).

A total of 336 healthy human subjects underwent an episodic memory task. Subjects viewed six series of five semantically unrelated nouns presented at a rate of one word per second with the instruction to learn the words for immediate free recall after each series. In addition, subjects underwent an unexpected delayed free-recall test of the learned words after 5 min, which reflects episodic memory (14, 15). Of the 336 subjects who underwent this memory task, a group of 32 individuals with comparable delayed memory performance was selected for the neuroimaging study. The reason for investigating individuals with comparable memory performance was to avoid genotype-unrelated performance effects on brain activations and to instead capture genotype-dependent differences in brain activation patterns. Brain activation as measured by fMRI represents more basic aspects of information processing than do behavioral measurements (16). Therefore, correlations between brain activity and genetic variants may be observed by fMRI also in the absence of phenotypic variability. The search for memory-related genes was done in the remaining group of 304 subjects.

Results

Multilocus Genetic Search. ***First stage.*** To investigate the complex genotype–phenotype relationship, we conducted a linkage-disequilibrium-based multilocus genetic search (17). First, we selected the human homologues of 47 genes with well established molecular and biological functions in animal memory (1–5, 18–35) (Table 1, which is published as supporting information on the PNAS web site). Depending on genomic length, we mapped these genes with 160 SNPs commonly observed in Caucasians to enable haplotype reconstruction and, thereby, to maximize the coverage of a gene's naturally occurring variability. Guided by recent recommendations for the large-scale analysis of complex traits (17), we used a two-stage approach. In the first stage, we used logistic regression models to extract a set of loci influencing human episodic memory under rather liberal statistical criteria ($\alpha = 5\%$). Sixteen variations fulfilled this first criterion. Because nonrandom genetic heterogeneity (i.e., population structure) in outbred populations may lead to spurious associations, we calculated the level of genetic heterogeneity in our study population by genotyping each subject for 318 SNPs located in both genic and nongenic regions and distributed over all autosomes. Structured association analysis (36) revealed that the allele-frequency divergence in our population was low, and that the individual genetic background values were normally distributed (Fig. 1). Eight subjects were identified as outliers (i.e., beyond the 25% or 75% limits of the normal distribution curve). Importantly, the findings of stage 1 remained unchanged after exclusion of these subjects from the statistical analyses. In addition, we included each subject's genetic background value as a covariate in the logistic regression model. Again, the results remained unchanged.

Second stage. In the second stage, the 16 significant variations from stage 1 were stringently evaluated by a permutation-based

Conflict of interest statement: No conflicts declared.

This paper was submitted directly (Track II) to the PNAS office.

Freely available online through the PNAS open access option.

Abbreviations: fMRI, functional MRI; IMAGS, individual memory-related genetic score; MTL, medial temporal lobe.

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www.pnas.org/cgi/doi/10.1073/pnas.0510212103

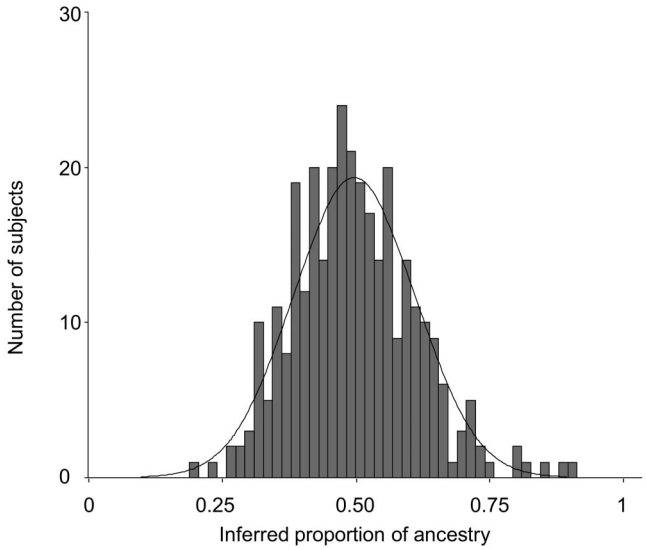

Fig. 1. Genetic structure of the study population. Estimates of the ancestry of study subjects under the *a priori* assumption of $K = 2$ discrete subpopulations. The histogram shows the number of individuals with distinct proportions of ancestry in subpopulation 1. Using 318 unlinked SNPs, structured association analysis revealed low-allele-frequency divergence among populations (Kullback–Leibler distance = 0.23). The superimposed curve indicates normal distribution of the data ($P > 0.1$, Kolmogorov–Smirnov test). Eight subjects were identified as outliers (i.e., outside the 25% or 75% limits of the normal distribution curve). Identical results were obtained under the *a priori* assumption of $3 \leq K \leq 6$ discrete subpopulations.

analysis, which reduced the multiple testing burden and allowed for between-loci interactions (37). This method, termed set association, evaluates sets of polymorphic markers and provides a cluster of significant markers with a single test statistic (37, 38). Seven variations finally contributed to a cluster with significant impact on episodic memory ($P = 0.00008$, Fig. 2). Association due to linkage disequilibrium with SNPs in adjacent genes was excluded (data not shown). We also performed post hoc analyses with 53 SNPs deliberately selected because of their *a priori* unlikely involvement in memory (i.e., SNPs in regions not harboring any genes or SNPs within genes hitherto unrelated to known signaling pathways of memory; Table 2, which is published as supporting information on the PNAS web site). These SNPs were treated statistically in exactly the same manner as our hypothesis-driven SNPs. In the first liberal stage, one of 53 SNPs exceeded the 0.05 significance level. After set-association analysis (stage 2), this SNP was no longer significant (Table 2).

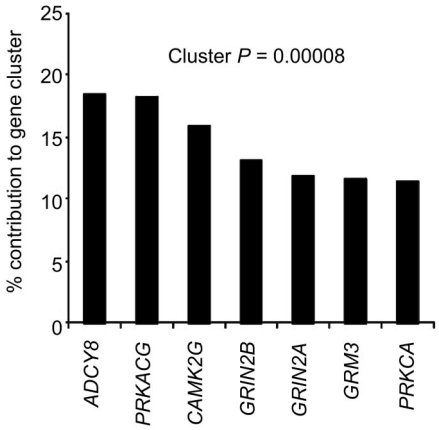

Fig. 2. A cluster of seven genetic variations (i.e., polymorphisms and haplotypes) associated with episodic memory performance. Variations are added to the model according to their relative contribution to overall cluster significance ($P = 0.00008$, as assessed after 50,000 permutations), with the most significant variation added first. Significant SNPs: rs263249 in *ADCY8*, rs3730386 in *PRKACG*, hCV3114928 in *CAMK2G*, multilocus haplotype in *GRIN2B*, rs1868291 in *GRIN2A*, multilocus haplotype in *GRM3*, and hCV11612258 in *PRKCA*.

The seven-SNP cluster was further used for the calculation of an individual's memory-related genetic score, termed individual memory-associated genetic score (IMAGS). Briefly, IMAGS corresponds to the number of memory-associated genetic variations present in a subject weighted by the variations' effect size. The genetic score of individuals carrying none of the seven variations associated with better episodic memory was set equal to 0, which is the minimal possible IMAGS value. Accordingly, IMAGS of individuals possessing one variation was set equal to the corresponding set-association value for the particular variation (e.g., 0.20 for *ADCY8*, 0.12 for *PRKCA*). For two or more variations associated with better episodic memory, set-association statistics of the corresponding variations were added (38). In our study population, IMAGS correlated positively and significantly with memory performance ($\beta = 0.232$, $T = 4.23$, $P = 0.000009$, linear regression analysis).

IMAGS represents physiological variability in genes encoding such well characterized memory-related molecules as adenylyl cyclase (18, 19), PKA (20–22), CAMKII (23–26), NMDA receptor (27–31), metabotrobic glutamate receptor (32, 33), and PKC (34, 35). Importantly, IMAGS did not correlate significantly with immediate recall ($r = -0.058$, $P = 0.3$). Performance in this task requires high levels of attention and motivation along with well functioning working memory. Therefore, the genotype-dependent differences in delayed episodic memory were not caused by genotype effects on confounding factors such as motivation, attention, or working memory. To further demonstrate the specificity of the IMAGS, we randomly selected seven SNPs (rs3744215, rs892200, hCV2522892, hCV347736, hCV1521704, rs3763679, and hCV1341801) from the group of genetic variations that did not emerge as memory-related in the first stage and calculated a negative-control IMAGS (ncIMAGS) in exactly the same way as we did for the IMAGS. We did not observe any significant correlations between ncIMAGS and delayed memory performance ($\beta = 0.026$, $T = 0.473$, $P = 0.6$, linear regression analysis).

Individual Genetic Variability Is Linked to Human Brain Function. In an additional experiment, we aimed at linking the individual genetic variability to human brain functions during different memory tasks and therefore investigated the impact of the IMAGS on memory-related brain activations using fMRI. Importantly, the fMRI study was performed in an independent group of 32 study participants with comparable memory performance who have not been included in the genetic search and therefore were not part of the sample used for IMAGS calculation. Because the IMAGS was associated with human episodic memory, which depends on the medial temporal lobe (MTL) (14, 15, 39), and because the components of the IMAGS are related to the signaling cascade involved in the formation of hippocampus-dependent memory in vertebrates (1, 3, 4), we hypothesized that the IMAGS might affect information processing in the human MTL during the formation of episodic memory. Neuroimaging studies have found that the MTL is activated during the formation of episodic memory (11), especially during associative learning (12, 40). We therefore investigated the impact of the IMAGS on MTL activations during the learning of face-profession associations (40). Specifically, subjects were instructed to imagine a presented person acting in a scene of the written profession. This episodic memory task led to robust

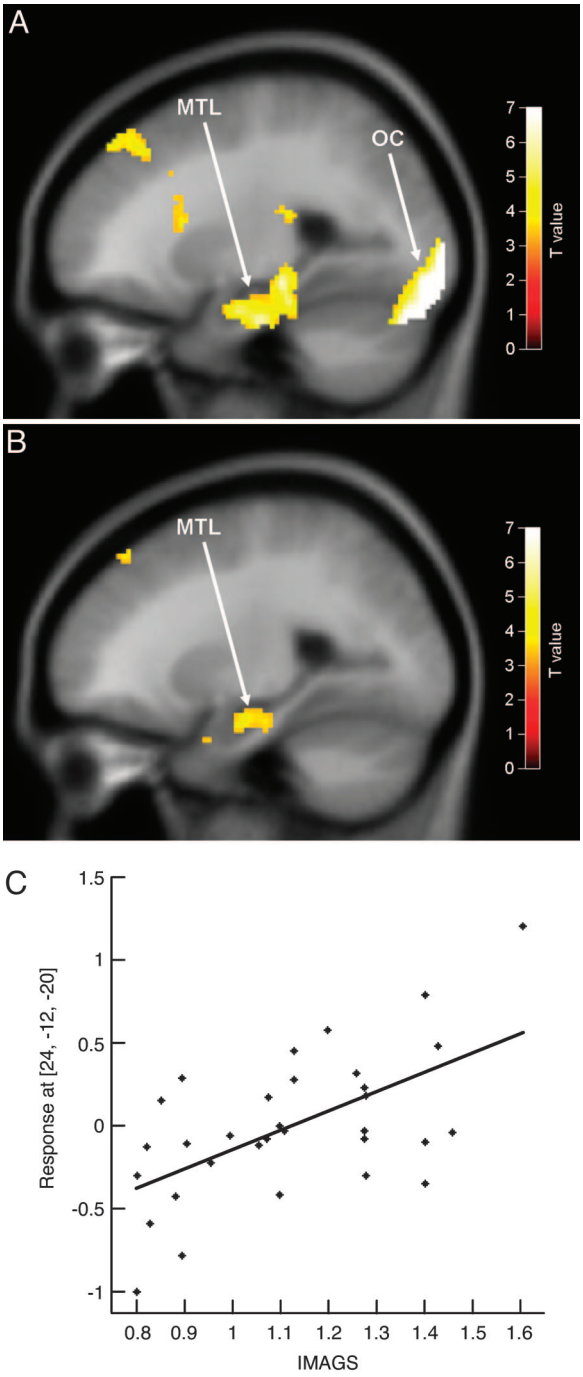

Fig. 3. fMRI of episodic memory. (*A*) Over all subjects, learning face-profession associations as compared to the head-contour baseline task led to robust activations of MTL structures, including the hippocampus and parahippocampal gyrus. Furthermore, there was a strong activation of the occipital cortex (OC), including the lingual gyrus and the fusiform gyrus. (*B*) Regression analysis revealed a significant positive correlation between the IMAGS and learning-induced brain activations in the MTL, including the hippocampus and parahippocampal gyrus. (*C*) Scatter plot illustrating the positive correlation between IMAGS and learning-induced brain activations in the hippocampus at coordinate position [24, −12, −20].

activations of MTL structures, including the hippocampus and parahippocampal gyrus (Fig. 3*A*), as compared to the baseline task. Local maxima in the hippocampal gyrus were located at coordinate position (24, −28, −12) and (22, −12, −24) and in the parahippocampal gyrus at (22, −18, −28) and (22, −32, −20) [$P_{\text{uncorrected}} < 0.001$; $P < 0.05$, false discovery rate (FDR) corrected]. Importantly, in the same memory-related MTL regions, we found positive correlations between learning-induced brain activations and the IMAGS (Fig. 3*B*). Local maxima were located in the hippocampal gyrus (24, −12, −20) and in the parahippocampal gyrus (16, −20, −20) and (28, −26, −20), ($P_{\text{uncorrected}} < 0.001$; $P < 0.05$ FDR corrected). Thus, the higher the IMAGS, the higher was the activity in the MTL during the formation of episodic memory (Fig. 3*C*). The episodic memory task as compared to the baseline task also led to a large activation of the occipital cortex with local maxima in the lingual gyrus (16, −98, −12) and in the fusiform gyrus (28, −88, −26) ($P_{\text{uncorrected}} < 0.001$; $P < 0.05$ FDR corrected, Fig. 3*A*). This activation is likely to reflect visual processing of faces in the learning condition, as compared to the baseline condition during which subjects viewed only head contours. This finding is in line with the reported role of the fusiform gyrus in face processing (41). There was no IMAGS-dependent difference in blood oxygenation in the occipital cortex (Fig. 3*B*), indicating that the IMAGS did not affect face processing, which is not directly related to episodic memory formation. Furthermore, we did not observe IMAGS-dependent differences in MTL blood oxygenation levels during a working memory task as compared to the baseline task (data not shown; see *Methods*). Together, these findings indicate that IMAGS-dependent differences in MTL activities are specific to the formation of episodic memory. As expected based on the matching for recall performance, there was no significant correlation between IMAGS and fMRI recall performance in this group of 32 subjects. Therefore, the impact of IMAGS on brain activity can be fully attributed to an individual's genetic load with memory-related variations. Furthermore, IMAGS did not show significant correlations with age, gender, reaction latencies, or accuracies in the fMRI tasks or any of the neuropsychological measurements of memory, intelligence, spatial cognition, and executive functions ($P > 0.05$, for all variables) in this fMRI group. In addition, we did not observe any significant correlations between negative-control IMAGS and learning-induced brain activations (data not shown).

Discussion

In the present study, we used a behavioral genetics approach to investigate the impact of genetic variability in the human homologues of memory-related signaling molecules on human episodic memory. This approach depends on the correlation between interindividual phenotypic variability and individual patterns of genetic variability in genes relevant to the phenotype of interest. As such, it can powerfully detect molecular pathways related to the phenotype (8); however, any mechanistical explanations of such genetic association findings remain rather speculative. Nonetheless, our results indicate that the human genes encoding adenylyl cyclase 8 (*ADCY8*), the γ catalytic subunit of cAMP-dependent protein kinase (*PRKACG*), the γ subunit of calcium/calmodulin-dependent protein kinase II (*CAMK2G*), 2a and 2b subunits of the ionotropic NMDA glutamate receptor (*GRIN2A, GRIN2B*), metabotropic glutamate receptor 3 (*GRM3*), and protein kinase C α (*PRKCA*) are important for human memory function, because variability among these genes was specifically associated with memory performance and with activation in memory-related brain regions. Thus, the genes described herein appear to form a cluster with strong impact on human memory performance. However, it is not possible to draw conclusions concerning potential molecular interactions between the corresponding gene products.

Can one conclude that genes that did not emerge as memory-associated from this study are not important for human memory? We believe this conclusion would be erroneous. It is important to stress that the genetic loci described in the present

study represent a positive list of memory-associated variations, and that the nonsignificant results presented herein do not justify exclusion of the corresponding loci as memory-related genetic factors. There are several reasons, both genetic and statistical, for this. For example, some genes might require the analysis of additional SNPs to capture their entire variability. Even after complete resequencing of these genes along with their regulative regions, some may still not be associated with memory, because they may be highly conserved and may lack physiologically meaningful genetic variability. However, a lack of physiologically meaningful genetic variability by no means implies a minor importance of these genes for certain phenotypes. Furthermore, some genetic loci might be associated with other forms or stages of memory as those investigated in the present study. In addition, the IMAGS accounted for 5% of the overall variance (and ≈10% of the genetically determined variance, assuming a heritability of 50% for this particular phenotype). Thus, the genes presented herein accounted for a significant percentage of variance; however, 90% of the genetically determined variance remain to be discovered.

As in any genetic association study, significant associations may be a consequence of type I statistical error. We believe this possibility is unlikely in the present study. First, we followed current recommendations and used a two-stage analytical approach, including the application of a first selection under liberal statistical criteria followed by the set-association procedure, which controls for multiple testing by extensive permutation. Second, we excluded hidden population structure by analyzing 318 SNPs and by applying the structured association method. Third, we excluded association due to linkage disequilibrium with genes other than those observed by analyzing SNPs in the respective 5′ and 3′ adjacent genomic regions. Fourth, the reported associations reached highly significant levels ($P < 0.00001$). Fifth, we selected negative-control SNPs and also generated a negative-control genetic score, which yielded nonsignificant results. Finally, IMAGS, which represents an individual's compound genetic score, correlated significantly with activation levels in memory-related brain regions in an independently examined sample.

Taken together, the present results indicate that genetic variability in human homologues of memory-related signaling molecules contributes to interindividual differences in episodic memory and episodic memory-related brain activations. Future steps must include complete resequencing of the associated genes to identify the functionally relevant polymorphic sites and to elucidate their functional consequences. Additional studies are also needed to discover memory-related genes not included in the present study and, in combination with neuroimaging, to assess the impact of genetic variability on different stages and forms of memory, such as autobiographic or implicit memory.

Methods

Subjects. Memory testing and genotyping were done in a total of 336 healthy young Swiss subjects [232 females, 104 males; mean age 22.8 ± 0.2 (standard error) years]. After a complete description of the study to the subjects, written informed consent was obtained. The ethics committee of the Canton of Zurich, Switzerland, approved the study protocol.

Blood Sampling and Genotyping. We collected 18-ml blood (2 × 9 Monovette EDTA tubes; Sarstedt) from each donor by venous puncture. Genomic DNA was extracted by using the QIAamp DNA blood maxi kit (Qiagen, Valencia, CA). To analyze the genetic structure of our population, we used 318 SNPs located in both genic and nongenic regions and distributed over all autosomes (including the 160 memory-related SNPs). High-throughput genotyping was done by the Amplifluor method. Please contact the authors for the detailed list of examined SNPs and corresponding primers.

Statistics. ***Stage 1.*** Genetic variability in 47 memory-related genes was assessed by genotyping 160 SNPs and reconstructing haplotypes. Analysis of linkage disequilibrium and haplotype reconstruction was done with POWERMARKER Version 3.22 (www.powermarker.net). We used forward and backward logistic regression models, controlled for age, gender, education, and immediate recall performance, to examine the influence of SNPs and haplotypes on episodic memory performance. SNPs were entered by using the additive model, and haplotypes were included as binomial categorical variables (42). At this stage, 16 SNPs and haplotypes fulfilled the criterion of $P \leq 0.05$.

Stage 2. Variations fulfilling the criterion of stage 1 were further evaluated by the SUMSTAT program (Rockefeller University, New York), which has been developed for statistical analysis with the set-association method (37). Unlike some conventional methods of data reduction (e.g., factor analysis), the set-association method uses relevant sources of genetic information such as allelic association and Hardy–Weinberg disequilibrium (HWD). Information is combined over multiple markers and genes in the genome, quality control is improved by trimming SNPs with high HWD values, and permutation testing limits the overall false-positive rate (37). Specifically, for each marker, a contingency χ^2 statistic testing the association of genotype with phenotype status is calculated. These χ^2 statistics are then ranked from largest to smallest. Progressively larger sums (S_j) are then calculated over the j largest χ^2 statistics. For example, S_1 is the largest χ^2 statistic of association. S_2 is the sum of the largest and second largest. S_3 is the sum of the largest, second largest, and third largest, and so on. The empirical significance level (P_j) for each S_j is evaluated by permutation methods carried out under the null hypothesis of no genetic association. The smallest of the empirical significance levels (i.e., P_{jmin}) identifies the best and most parsimonious model predicting phenotype status. Importantly, the set-association method has been shown to be of superior power compared with conventional locus-by-locus analyses and to successfully capture statistical interactions among genes (37, 38, 43–45). In this study, we used the maximum possible number of permutation tests ($n = 50{,}000$) to calculate the genetic cluster's significance.

Calculation of population structure was done by using the STRUCTURE program (46), following the developers' instructions (36).

Power of the sample. The power of our sample to detect correlations of $|R| \geq 0.2$ at $\alpha \leq 0.05$ is >90% (47).

fMRI. ***Subjects.*** Twenty-one females and 11 males, mean age 22.5 ± 2.5 (standard error) years, participated in this study.

Episodic memory task. Stimuli consisted of 16 face-profession pairs for associative learning and 24 head contours for the baseline condition. The learning condition consisted of four blocks with four trials of 6 s each. Consequently, each block lasted 24 s and was announced by an instruction slide. The instruction for associative learning of the face-profession pairs was to imagine the presented person acting in a scene of the written profession. Subjects indicated by button press whether they found it easy or difficult to imagine a scene. For recall testing of the learned face-profession associations, the faces were presented alone with the instruction to recall each person's occupation. The baseline condition consisted of four blocks with six trials of 4 s each. The task was to decide whether the area of the left or right ear of a head contour was larger. The sequence of conditions was counterbalanced across subjects.

Working memory. The experiment included one fMRI time series with a two-back task for the assessment of working memory and a baseline task (x-target) for the assessment of concentration.

The two-back task required subjects to respond to a letter repeat with one intervening letter (e.g., **S** –f –**s** –g). The x-target task required subjects to respond to the occurrence of the letter x. Each task was given in five blocks of 26 s each. Blocks were announced by an instruction slide. Stimuli were 50 upper- or lowercase letters typed in black on a white background. Thirteen upper- or lowercase letters were presented per block for the duration of 2 s each.

Data acquisition. Magnetic resonance (MR) measurements were performed on a 3-T Philips (Eindhoven, The Netherlands) Intera whole-body MR scanner equipped with a transmit–receive body coil and a commercial eight-element head coil array. Functional data were obtained from 32 transverse slices parallel to the AC–PC plane covering the whole brain with a measured spatial resolution of $2.8 \times 2.8 \times 4$ mm^3 (acquisition matrix 80×80) and a reconstructed resolution of $1.7 \times 1.7 \times 4$ mm^3. Data were acquired by using a SENSE-sshEPI (48) sequence with an acceleration factor of $R = 2.0$. Other scan parameters were Echo time = 35 ms, Repetition time = 3,000 ms, and $\theta = 82°$.

Analysis of fMRI data. Image pre- and postprocessing and the statistical analyses were performed with SPM2 (Wellcome Department of Imaging Neuroscience, University College London, London). Standard preprocessing procedures were applied, i.e., realignment, normalization, and spatial smoothing (8 mm) (49). On the single-subject level, data were analyzed according to the fixed-effects model (SPM2). The six head movement parameters were included in the model as confounding factors. Data were high-pass-filtered with a specific filter value for each fMRI time series. This value was determined according to 2× (stimulus onset asynchrony)× repetition time. On the second level, within-subject contrasts were entered into a random effects analysis (SPM2), which accounts for variance among subjects (50). We also analyzed the correlation between the within-subject encoding contrasts (learning–baseline) and IMAGS (simple regression, SPM2). Threshold was set at a $P < 0.001$ level, uncorrected for multiple comparisons. SPM2 coordinates refer to standard brains from the Montreal Neurological Institute.

Neuropsychology. In addition to the fMRI experiment, subjects underwent detailed neuropsychological testing. Memory functions were assessed with the Wechsler Memory Scale Revised in German; intelligence with the Hamburg Wechsler Intelligence Test; spatial thinking with the Luria Mental Rotation Test; and executive functions with a verbal (S-words) and a nonverbal (five-point) fluency task, the Kramer Card Sorting Test, and the Stroop Test.

We thank Katharina Henke and Christian Mondadori for scientific advice and help with the fMRI study. We also thank Frank Jessen for constructive comments on the manuscript. This work was supported by grants from the Swiss National Science Foundation (PP00B-68859 and PP00B-106708); by the Helmut-Horten Stiftung; the Hermann-Klaus Stiftung; the Hartmann-Müller-Stiftung; the EMDO-Stiftung; the Olga Mayenfisch Stiftung; the Baugarten Stiftung; and the Stiftung für Wissenschaftliche Forschung, Universität Zürich.

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