Neural predictors of individual differences in response to math tutoring in primary-grade school children

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Edited* by Michael I. Posner, University of Oregon, Eugene, OR, and approved March 29, 2013 (received for review December 19, 2012)

Now, more than ever, the ability to acquire mathematical skills efficiently is critical for academic and professional success, yet little is known about the behavioral and neural mechanisms that drive some children to acquire these skills faster than others. Here we investigate the behavioral and neural predictors of individual differences in arithmetic skill acquisition in response to 8-wk of one-to-one math tutoring. Twenty-four children in grade 3 (ages 8–9 y), a critical period for acquisition of basic mathematical skills, underwent structural and resting-state functional MRI scans pretutoring. A significant shift in arithmetic problem-solving strategies from counting to fact retrieval was observed with tutoring. Notably, the speed and accuracy of arithmetic problem solving increased with tutoring, with some children improving significantly more than others. Next, we examined whether pretutoring behavioral and brain measures could predict individual differences in arithmetic performance improvements with tutoring. No behavioral measures, including intelligence quotient, working memory, or mathematical abilities, predicted performance improvements. In contrast, pretutoring hippocampal volume predicted performance improvements. Furthermore, pretutoring intrinsic functional connectivity of the hippocampus with dorsolateral and ventrolateral prefrontal cortices and the basal ganglia also predicted performance improvements. Our findings provide evidence that individual differences in morphometry and connectivity of brain regions associated with learning and memory, and not regions typically involved in arithmetic processing, are strong predictors of responsiveness to math tutoring in children. More generally, our study suggests that quantitative measures of brain structure and intrinsic brain organization can provide a more sensitive marker of skill acquisition than behavioral measures.

math learning | intervention | prediction | multimodal neuroimaging | educational neuroscience

Mathematical problem solving skills are crucial for academic and professional success (1–3). Fluency with basic arithmetic provides a foundation upon which more complex skills are built (4–6). In the past two decades, math-tutoring programs designed to improve basic arithmetic fluency have been developed and tested in classroom and one-to-one tutoring settings (7–10). Children in these programs, however, show significant individual differences in math learning in response to tutoring (11). Critically, very little is known about the behavior and brain mechanisms that drive these individual differences. An understanding of the behavior and brain mechanisms underlying math learning could contribute greatly to our understanding of general cognitive development (12). It may also explain individual differences in response to instruction, thereby increasing the chances of identifying children who require different approaches or more intensive intervention. Here we use a validated one-to-one math-tutoring paradigm (10, 13, 14) to investigate the behavioral and neural predictors of individual differences in arithmetic skill acquisition.

Our study focuses on primary-grade school children between the ages of 8 and 9, an important period for learning and mastering arithmetic skills. Behavioral studies of primary-grade school children by Fuchs and colleagues have shown that the combination of computer-aided intervention and one-to-one tutoring can significantly improve mathematical abilities (6, 9). Critically, they found that interventions emphasizing number knowledge and speeded practice with efficient counting strategies can improve math skills in primary-grade school children (9, 10, 13). Number knowledge is an important foundation in the development of arithmetic competence because it leads to efficient counting procedures and reasoning strategies for consistently pairing a problem with its correct answer. The inclusion of speeded practice to generate many correct responses then leads to more direct retrieval of arithmetic facts (15). For example, Fuchs and colleagues found that one-to-one number knowledge tutoring combined with speeded practice on counting strategies compared with number knowledge tutoring with games was more effective at increasing automatic retrieval and arithmetic fluency. Findings supporting the efficacy of combining number knowledge tutoring with speeded practice have been replicated in multiple studies (6, 16). The neural basis of individual responses to these successful math-tutoring interventions, however, remains poorly understood. This study characterizes the neurobiological mechanisms predicting improvements in performance resulting from one-to-one math tutoring and to compare neural and cognitive predictors of responsiveness with academically relevant tutoring.

Functional neuroimaging studies in adults have consistently implicated a number of parietal and temporal brain regions in mathematical problem-solving tasks, including the intraparietal sulcus (IPS), the superior parietal lobule, the angular gyrus, the supramarginal gyrus, and the lingual and fusiform gyri in the inferior temporal cortex (17–20). In contrast, children, compared with adults, rely less on these posterior parietal and temporal cortical areas for solving arithmetic problems and more on the medial temporal lobe (MTL) memory systems critical for learning and memory as well as prefrontal cortex (PFC) regions important for working memory and cognitive control mechanisms that are necessary for accurate problem solving (21). Notably, recent work on the development of fact retrieval in children has highlighted the role of a distributed network of interconnected prefrontal and MTL areas including the right hippocampus, left ventrolateral prefrontal cortex (VLPFC), and bilateral dorsolateral prefrontal cortex (DLPFC) (22, 23), a system overlooked in most previous studies in adults. In parallel, studies of declarative memory have emphasized the role of the hippocampus and prefrontal cortex in learning more generally (24–26). Critically, it is currently not known if these systems mediate skill acquisition in math learning through tutoring.

Author contributions: K.S. and V.M. designed research; K.S. performed research; C.T., M.R.-L., L.F., and V.M. contributed new reagents/analytic tools; K.S., A.G.S., and D.D.J. analyzed data; and K.S., A.G.S., and V.M. wrote the paper.

The authors declare no conflict of interest.

*This Direct Submission article had a prearranged editor.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1222154110/-/DCSupplemental.

We conducted a math-tutoring study in a well-characterized sample of 24 children aged 8–9 y, all in grade 3 of elementary school, with varying levels of mathematical abilities. Our overall study design is illustrated in Fig. 1. Each child underwent structural and resting state functional MRI scanning before math tutoring along with an extensive battery of neuropsychological assessments. They subsequently went through an intensive 8-wk one-to-one tutoring program focused on number knowledge tutoring with speeded practice on efficient counting strategies. Tutoring was designed to facilitate fluency in arithmetic problem solving (9, 10, 13, 14). Before and after tutoring, we recorded arithmetic strategy use as well as speed, accuracy, and performance efficiency of arithmetic problem solving in each child using standardized procedures (23). In addition to standard regression analyses, we used a machine learning approach (27, 28) to investigate behavioral and neural predictors of performance gains with tutoring. We first conducted prediction analyses using neuropsychological assessment scores to investigate behavioral measures that predict performance improvements on arithmetic problems with math tutoring. We then used voxel-based morphometry (VBM) to investigate regional gray matter volume that predicts performance improvement with tutoring. We then used resting-state functional MRI (fMRI) data to investigate functional circuits that predict performance improvements with tutoring. We hypothesized that prefrontal and parietal regions involved in arithmetic (29) as well as MTL areas involved in declarative memory (22) would predict performance improvements in children who received one-to-one tutoring. Finally, we examined the specificity of our findings using 16 age- and grade-matched children who served as a no-contact comparison group.

Results

Participants. Demographic information and cognitive profile data for the tutoring and no-contact comparison groups are shown in Tables S1 and S2, respectively.

Eight Weeks of One-to-One Math Tutoring Improves Arithmetic Performance, with Some Children Improving More than Others. Performance on the arithmetic verification task improved significantly after tutoring (Fig. 2). Performance gains were observed for both accuracy [$F(1, 23) = 17.25$, $P < 0.001$, $\eta_p^2 = 0.43$] and reaction time [$F(1, 23) = 19.28$, $P < 0.001$, $\eta_p^2 = 0.46$]. To better assess simultaneous changes in accuracy and reaction time, we computed a composite measure of performance efficiency (30). Performance efficiency showed significant increases after tutoring [$F(1, 23) = 51.43$, $P < 0.001$, $\eta_p^2 = 0.69$]. All 24 children individually showed increases in efficiency after tutoring. The mean improvement in performance efficiency was 67%, ranging from 8% to 198%. In addition, there was a significant increase in use of retrieval strategies after tutoring [$F(1,18) = 6.57$, $P = 0.02$, $\eta_p^2 = 0.27$] (Fig. 2). In contrast, the no-contact comparison group did not show gains in accuracy [$F(1, 15) = 0.62$, $P = 0.44$, $\eta_p^2 = 0.04$), reaction time [$F(1, 15) = 2.78$, $P = 0.12$, $\eta_p^2 = 0.16$], performance efficiency [$F(1, 15) = 2.78$, $P = 0.16$, $\eta_p^2 = 0.16$], or retrieval strategy use [$F(1,15) = 0.47$, $P = 0.50$, $\eta_p^2 = 0.03$] after 8 wk (Fig. S1).

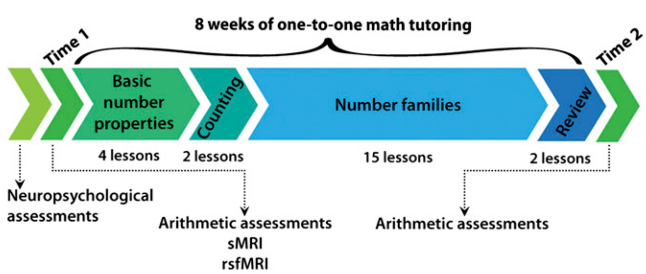

Fig. 1. Study design. Each child first underwent an extensive battery of neuropsychological assessments. At time 1, each child performed two arithmetic tasks, one designed to assess strategy use and the second designed to assess accuracy and reaction time during problem solving. Structural MRI (sMRI) and resting-state fMRI (rsfMRI) scans were also acquired at time 1. At time 2, the two arithmetic tasks were repeated to assess changes in arithmetic strategy use, accuracy, and reaction time. Between time 1 and time 2, children went through an intensive 8-wk, one-to-one tutoring program focused on conceptual aspects of number knowledge and speeded practice on efficient counting strategies and systematic learning of number families. Together, these training components were designed to facilitate fluency in arithmetic problem solving.

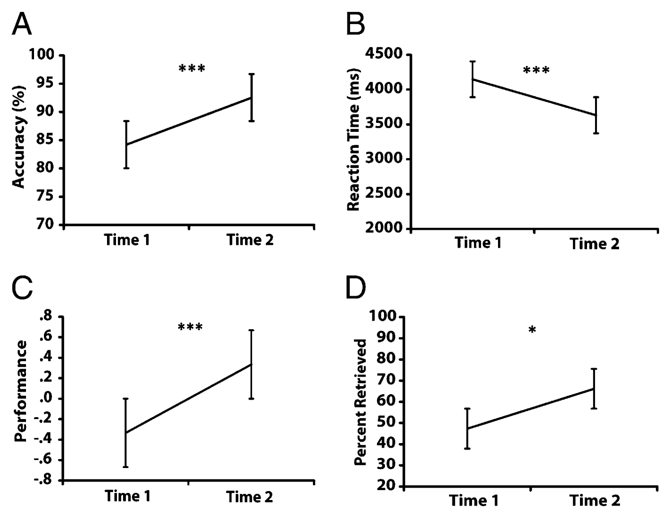

Fig. 2. Eight weeks of one-to-one math tutoring improves arithmetic performance, with some children improving more than others. Participants solved arithmetic problems with significantly (*A*) higher accuracy, (*B*) faster reaction time, (*C*) higher performance efficiency, and (*D*) greater use of retrieval strategies after undergoing 8 wk of one-to-one math tutoring. The mean improvement in performance efficiency was 67%, ranging from 8% to 198%. Performance efficiency is a composite standardized measure obtained by combining accuracy and reaction time for each child. Time 1 and time 2 denote before and after tutoring measures respectively (**P* < 0.05, ****P* < 0.001).

Behavioral Measures Do Not Predict Individual Differences in Arithmetic Skill Acquisition in Response to 8 wk of One-to-One Math Tutoring. To investigate whether behavioral measures predict individual differences in arithmetic skill acquisition, we examined the relation between behavioral measures acquired before tutoring and changes in arithmetic skills with tutoring. None of the behavioral measures included in the extensive battery of neuropsychological assessments conducted before tutoring, including assessments of intelligence quotient (IQ), working memory or math and reading abilities, were associated with arithmetic problem solving performance improvements. Critically, neither the numerical operations ($r = -0.38$, $P = 0.07$) nor the math reasoning ($r = -0.14$, $P = 0.54$) subtests of the Wechsler Individual Aptitude Test (WIAT)-II were related to changes in performance efficiency with tutoring (Fig. S2). Further, none of the working memory subscores (digit recall: $r = -0.03$, $P = 0.89$; block recall: $r = -0.11$, $P = 0.59$; backward digit recall: $r = 0.06$, $P = 0.75$; count recall: $r = 0.28$, $P = 0.19$), nor a composite working memory score ($r = -0.08$, $P = 0.69$), were related to changes in performance efficiency with tutoring. To test whether multiple behavioral measures together were related to changes in arithmetic skills with tutoring, we used multivariate stepwise regression with change in performance efficiency as the dependent variable and neuropsychological assessments listed in Table S1 as independent variables. This multivariate analysis did not reveal any significant behavioral correlates of arithmetic skill acquisition ($P > 0.46$).

To further examine the predictive ability of behavioral measures, we used a machine learning approach: balanced cross-validation combined with linear regression (*SI Materials and Methods*). Results from this analysis were consistent with the results from the correlation analysis, namely: neither the numerical operations [$r(pred,actual) = 0.18$, $P = 0.28$] nor the math reasoning [$r(pred,actual) = -0.13$, $P = 0.57$) subtests of the WIAT-II nor the working memory subscores [digit recall: $r(pred,actual) = -0.21$, $P = 0.66$; block recall: $r(pred,actual) = -0.07$, $P = 0.44$; backward digit recall: $r(pred,actual) = -0.23$, $P = 0.73$; count recall: $r(pred,actual) = -0.01$, $P = 0.68$], nor a composite working memory score [$r(pred, actual) = -0.13$, $P = 0.35$], assessed before tutoring predicted changes in performance efficiency with tutoring.

Gray Matter Volume in Hippocampus Predicts Individual Differences in Arithmetic Skill Acquisition in Response to 8 wk of One-to-One Math Tutoring. To investigate whether regional gray matter volume predicts individual differences in arithmetic skill acquisition, we conducted a VBM analysis using T1-weighted MRI images acquired before tutoring. We then performed a whole-brain regression analysis using the VBM derived gray matter volume as the independent variable and change in performance efficiency with tutoring as the dependent variable. Gray matter volumes of the right hippocampus, right thalamus, and right cerebellum were correlated positively with changes in performance efficiency with tutoring (Fig. 3 and Table S3). In addition to whole-brain VBM, we performed additional analyses using an observer-independent cytoarchitectonically defined region of interest (ROI) encompassing the right hippocampus. Consistent with findings from the voxel-wise whole-brain analysis, a significant positive correlation was found between gray matter volume of the right hippocampus ROI and changes in performance efficiency with tutoring ($r = 0.54$, $P < 0.01$). These results remained significant even after covarying out pretutoring performance efficiency levels ($r = 0.55$, $P < 0.01$). To further examine the effect of pretutoring performance efficiency levels on our results, we excluded seven participants who had high pretutoring performance. The results remained unchanged even after excluding these seven participants from the analysis. Additional analyses revealed that among these three brain regions, the gray matter volume of the right hippocampus was the most related to performance gains. Specifically, gray matter volume within the right hippocampus cluster, compared with the thalamus and cerebellum cluster, explained the most variance observed in performance gains ($P < 0.01$). In the no-contact comparison group, this right hippocampus cluster was not correlated with changes in performance efficiency after 8 wk ($r = 0.30$, $P = 0.26$) (Fig. S3).

To further examine the predictive ability of regional gray matter volume, we used a machine learning approach: balanced cross-validation combined with linear regression (*SI Materials and Methods*). Results from this analysis were consistent with the results from the correlation analysis, namely: gray matter volume in hippocampus [$r(pred,actual) = 0.45$, $P = 0.008$] was most predictive of changes in performance efficiency with tutoring. In the no-contact comparison group, this right hippocampus cluster did not predict changes in performance efficiency after 8 wk [$r(pred,actual) = -0.05$, $P = 0.36$].

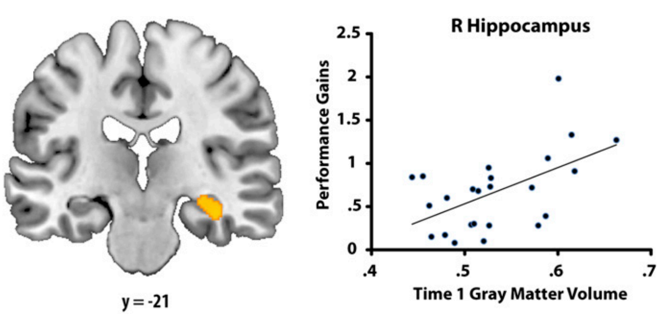

Fig. 3. Gray matter volume in hippocampus correlates with improvement in arithmetic performance in response to 8 wk of one-to-one math tutoring. Gray matter volume of the right (R) hippocampus before math tutoring showed a significant positive correlation with performance gains in arithmetic problem solving after 8 wk of one-to-one math tutoring. Performance gains represent a normed change in arithmetic problem-solving efficiency from time 1 (before tutoring) to time 2 (after tutoring). Results are based on VBM analysis at the whole-brain level (height threshold: $P < 0.01$; extent threshold: $P < 0.05$, 100 voxels). The data plotted in the scatterplot are nonindependent and are shown for visualization purposes only; these results are further bolstered by the machine learning–based prediction and cross-validation analyses.

Intrinsic Functional Connectivity of the Hippocampus Predicts Individual Differences in Arithmetic Skill Acquisition in Response to 8 wk of One-to-One Math Tutoring. To investigate whether functional interactions of the hippocampus predict individual differences in arithmetic skill acquisition, we conducted a whole-brain regression analysis using functional connectivity of the hippocampus as the independent variable and change in performance efficiency with tutoring as the dependent variable. Functional connectivity of the hippocampus with the left DLPFC, left VLPFC, right supplementary motor area, right middle temporal gyrus, and basal ganglia before tutoring showed a significant positive relation with changes in performance efficiency with tutoring (Fig. 4 and Table S4). These effects remained significant even after covarying out individual differences in right hippocampal volume as well as pretutoring performance efficiency levels. No regions showed negative correlations with improvement in performance efficiency with tutoring. To further examine the effect of pretutoring performance efficiency levels on our results, we excluded seven participants who had high pretutoring performance. The results remained unchanged even after excluding these seven participants from the analysis. We then compared the correlation strength of hippocampus connectivity with that of the right thalamus and the right cerebellum, the other two regions identified by the VBM analysis, as well as a fourth ROI encompassing right IPS, voxels consistently implicated in numerical cognition (31). This analysis revealed that, compared with the functional connectivity of the thalamus, cerebellum, and IPS, the functional connectivity of the hippocampus was the most correlated with performance gains ($P < 0.001$) (Fig. 5). In the no-contact comparison group, hippocampus connectivity with multiple target brain regions identified in the tutoring group were not correlated with performance efficiency changes after 8 wk ($P > 0.11$; Fig. S4).

To further examine the predictive ability of functional connectivity of the hippocampus, we used a machine learning approach: balanced cross-validation combined with linear regression (*SI Materials and Methods*). Results from this analysis were consistent with the results from the correlation analysis, namely: functional connectivity of the hippocampus with the left DLPFC [$r(pred,actual) = 0.38$, $P = 0.02$], left VLPFC [$r(pred,actual) = 0.54$, $P = 0.002$], right supplementary motor area, [$r(pred,actual) = 0.67$, $P = 0.002$], right middle temporal gyrus [$r(pred,actual) = 0.78$, $P = 0.002$), and basal ganglia [$r(pred,actual) = 0.75$, $P = 0.002$] predicted performance gains with tutoring. Additionally, compared with the functional connectivity of the thalamus, cerebellum, and IPS, the functional connectivity of the hippocampus was the most predictive of performance gains. In the no-contact comparison group, hippocampus connectivity with multiple target brain regions identified in the tutoring group did not predict performance efficiency changes after 8 wk ($P > 0.21$). These results highlight the specificity of our findings with respect to the tutoring group.

Discussion

This study examines neural predictors of individual responses to math tutoring in children. We used a one-to-one, validated individualized math-tutoring program (10, 16) that emphasized conceptual as well as procedural knowledge important to the development of arithmetic skill. The tutoring program was highly effective in that performance gains were systematically seen in accuracy, reaction time, overall performance efficiency, and retrieval

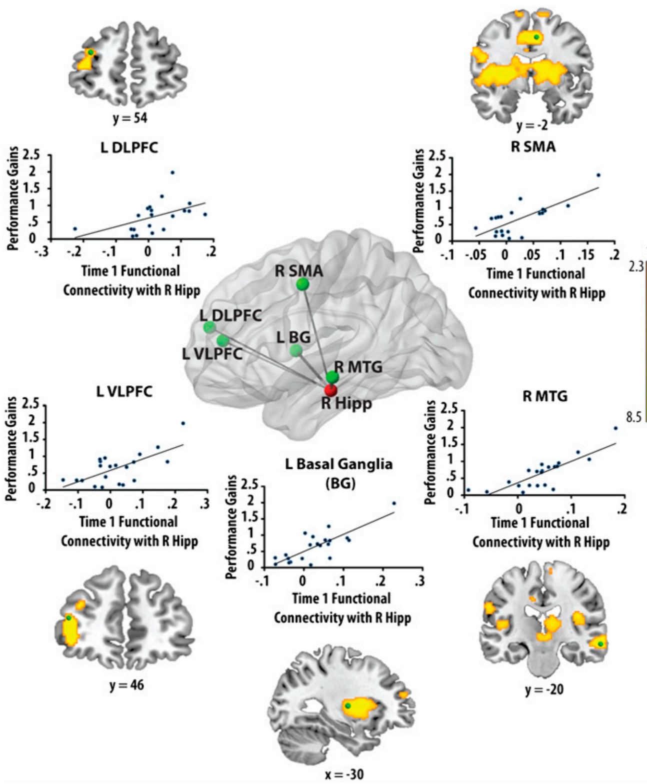

Fig. 4. Functional connectivity of the hippocampus correlates with improvement in arithmetic performance in response to 8 wk of one-to-one math tutoring. Functional connectivity of the right hippocampus (R Hipp) before math tutoring showed a significant positive correlation with performance gains in arithmetic problem solving after 8 wk of one-to-one math tutoring. Performance gains represent a normed change in arithmetic problem-solving efficiency from time 1 (before tutoring) to time 2 (after tutoring). Performance gains were correlated with time 1 hippocampal connectivity with the left dorsolateral prefrontal cortex (L DLPFC), left ventrolateral prefrontal cortex (L VLPFC), right supplementary motor area (R SMA), left basal ganglia (L BG), and right middle temporal gyrus (R MTG). Composite 3D view of connectivity network is shown in the central panel with the right hippocampus seed ROI highlighted in red and voxels showing peak connectivity with the hippocampus highlighted in green. Surrounding panels show brain areas correlated with performance gains with tutoring (height threshold: $P < 0.01$; extent threshold: $P < 0.01$, 128 voxels). Scatterplots in each panel are based on voxels showing peak connectivity. The data plotted in each scatterplot are nonindependent and are shown for visualization purposes only; these results are further bolstered by the machine learning–based prediction and cross-validation analyses.

strategy use. In contrast, the no-contact comparison group showed no such improvements. This corroborates previous classroom-based tutoring studies (10, 14). Critically, we found that individual response to 8 wk of tutoring was predicted by pretutoring measures of brain anatomy and functional connectivity, but not by cognitive and neuropsychological measures. Notably, children who had more gray matter volume in the hippocampus showed greater improvements in problem-solving efficiency. Hippocampal functional connectivity with the PFC and basal ganglia also predicted significant improvements in arithmetic problem-solving skills, and these effects were significant even after covarying out individual differences in hippocampal volume. Importantly, compared with other brain regions typically associated with math performance, including the IPS, hippocampal connectivity emerged as the strongest predictor of performance changes with tutoring. These findings provide evidence for the importance of hippocampal structure and circuitry in early-stage math learning.

We found that children with larger right hippocampus volumes showed greater improvement in arithmetic problem-solving skills with tutoring. Although the role of the hippocampal system in memory encoding and retrieval of individual stimulus items is well known (24–26), its role in learning and acquisition of academically relevant skills such as math has received virtually no attention. Previous studies in adults have emphasized the role of prefrontal and posterior parietal cortices in arithmetic fact learning over a period of about a week (32), but neither pretutoring anatomy nor functional activation in these brain areas have been linked to posttutoring gains. Our findings of hippocampal volume as a significant predictor of posttutoring gains are, however, consistent with emerging evidence from developmental studies, suggesting that during critical stages of arithmetic knowledge acquisition children rely more on hippocampus-based declarative memory systems for fact retrieval. Thus, for example, children show greater activation of the hippocampal memory system compared with adults (21, 33), and Cho and colleagues recently reported differential recruitment of the right hippocampus in relation to greater use of retrieval strategies during arithmetic problem solving (23). However, as with previous studies in adults, this study of early development has relied on cross-sectional and correlational approaches. Our findings of hippocampal volume as a predictor of learning and skill acquisition over time provide evidence of its causal role in skill acquisition and learning in an academically relevant domain. Consistent with this interpretation, it is further noteworthy that children with dyscalculia demonstrate structural deficits in the hippocampus and the entorhinal cortex (34) and they typically have poor skills in retrieving arithmetic facts from memory (35).

The second key finding of our study relates to functional circuits associated with the hippocampal region whose gray matter volume predicted behavioral improvements with tutoring. We used resting state fMRI acquired before tutoring to probe hippocampal circuits and investigate whether hippocampal connectivity predicted performance improvements with tutoring. We found that intrinsic functional connectivity of the hippocampus with multiple PFC regions before tutoring predicted improvements in arithmetic problem-solving skills after tutoring. This included the dorsolateral and ventrolateral PFC, two prefrontal regions important for cognitive control processes that facilitate memory encoding and retrieval (36–38). Hippocampal interactions with these PFC

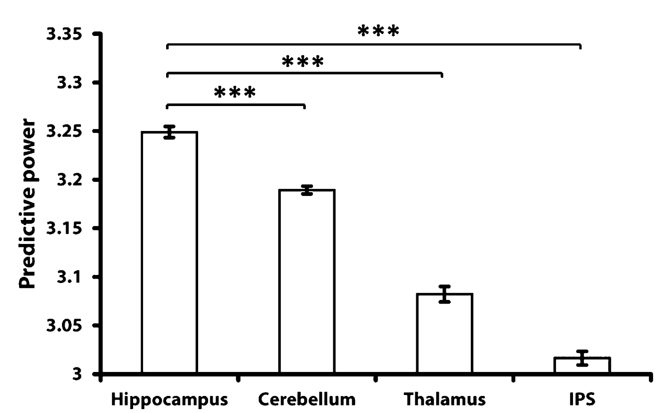

Fig. 5. Functional connectivity of the hippocampus shows highest correlation with improvement in arithmetic performance in response to 8 wk of one-to-one math tutoring. Correlation of right hippocampus functional connectivity before math tutoring with performance gains in arithmetic problem solving after 8 wk of one-to-one math tutoring was higher than the correlation of the right thalamus functional connectivity and the right cerebellum functional connectivity before tutoring with performance gains. The right thalamus and the right cerebellum were the two other regions besides the right hippocampus whose gray matter volume before math tutoring correlated with performance gains in arithmetic problem solving after tutoring. A fourth region encompassing right IPS voxels consistently implicated in numerical cognition also had significantly less correlation than the hippocampus (***$P < 0.001$).

regions are also known to facilitate long-term memory formation (37). Consistent with this view, Cho and colleagues found increased recruitment of the same hippocampal and PFC regions with greater retrieval use (23). In addition to the PFC, hippocampal interactions with the basal ganglia were also predictive of performance improvements with tutoring. In contrast, the no-contact comparison group showed no such effects. These results provide evidence that arithmetic skill acquisition depends on the intrinsic connectivity of the procedural memory subserved by the basal ganglia and declarative memory subserved by the hippocampus-based system. Our findings are consistent with the notion that the hippocampus and basal ganglia form interacting memory systems (39–41) that contribute to skill and knowledge especially during early phases of learning, which rely on both procedural and declarative memory systems (39–43). The most thoroughly studied developmental and schooling-based improvement in arithmetical competency is change in the distribution of strategies used during problem solving (13, 15, 44). With development, the mix of strategies changes such that inefficient strategies, such as counting, are used less frequently, and efficient strategies, especially retrieval, are used more frequently (15, 45, 46). Moreover, the speed and accuracy with which individual strategies are executed improves with development resulting in long-term memory representations that support the use of memory-based problem-solving processes. In our study, before tutoring, 8–9 y old children primarily used inefficient "counting" strategies. At the end of 8 wk of intensive math tutoring, their strategy use shifted to predominant use of retrieval. Our findings suggest that arithmetic skill acquisition during this early period of learning depends on the integrity of hippocampal-prefrontal cortex and hippocampal-basal ganglia functional circuits. Children who exhibited higher intrinsic functional connectivity in these circuits before tutoring showed the greatest performance improvement in math problem solving.

A third important finding of our study is that the brain measures outperformed behavioral measures in predicting performance improvements with tutoring, including domain-general measures, such as IQ and working memory, and domain-specific measures, including standardized measures of numerical operations and verbal math reasoning. Previous behavioral studies have related math achievement with domain-general abilities including working memory and executive functions (47) as well as domain-specific abilities including estimation abilities (48), nonsymbolic arithmetic ability (49), symbolic numerical distance effect (50), and number sense acuity (51, 52). However, it is crucial to point out that our study differs quite radically from the aforementioned ones. The main difference being that these studies examined how behavioral measure at time 1 is correlated with mathematical achievement at time 2 [e.g., number sense acuity at time 1 is correlated with arithmetic math performance years later (51)], which is in contrast to our study in which we examined whether behavior and/or neural measures at time 1 predict amount of arithmetic learning from time 1 to time 2. Even more importantly, our study is unique because between time 1 and time 2 each child underwent a targeted one-to-one math tutoring, as opposed to other studies where the educational factors that could have influenced their outcome were not systematically controlled. The main point of our findings is that the amount of arithmetic learning (and not later arithmetic achievement, as it was for other studies) is best and uniquely predicted by neural measures. Previous longitudinal studies of reading development have demonstrated that neural measures can provide important additional information for the identification of children at risk for low academic performance (53, 54). For example, Hoeft and colleagues reported that patterns of brain activation as well as right superior longitudinal fasciculus white-matter organization predicted future reading gains over 1–2 y in children with dyslexia (53). In contrast, standardized measures of reading and language were not predictive of reading gains. In a longitudinal study of math without focused one-to-one tutoring, a combination of behavioral performance and brain activation during working memory was found to be predictive of future performance in children and adolescents ages 6–16 (55). Our findings extend these studies by showing that performance gains after 8 wk of math tutoring can be predicted by intrinsic brain structure and functional connectivity measures, thereby providing important insights into why some children in primary-grade school gain more from remedial one-to-one tutoring than others.

In conclusion, our study provides strong evidence that individual differences in anatomy and functional circuitry of brain regions associated with memory formation predict math-tutoring outcomes in primary-grade school children. Importantly, the predictive biomarkers for math learning identified in our study are distinct from those identified in prior training studies of language (56) and video game skill acquisition (57, 58) in adults. In particular, our findings of hippocampal structure and hippocampal–prefrontal cortex and hippocampal–basal ganglia functional circuits provide evidence for pathways that predict skill development during tutoring designed to facilitate fact retrieval skills. In contrast, learning a video game, which involves procedural, but not declarative learning, has shown to be predicted by striatal, but not hippocampal volume (57). Our findings have broad implications for understanding neurobiological factors that predict individual differences in arithmetic skill acquisition. Quantitative neuroimaging measures of brain structure and intrinsic brain organization, compared with behavioral measures, can be used to better predict response to intervention and provide insights into brain mechanisms that support efficient learning. Characterization of predictive biomarkers in each child may facilitate the development of targeted training and intervention programs.

Materials and Methods

Participants. Twenty-four children (11 boys, 13 girls) in grade 3 (mean age 8.47 y) participated in a math tutoring study (Table S1), and 16 additional age- and grade-matched children participated as a no-contact comparison group (Table S2 and *SI Materials and Methods*).

Overall Study Design. Fig. 1 illustrates our study design. Demographic, neuropsychological, cognitive, and brain imaging measures were acquired from each participant before tutoring. The neuropsychological and cognitive measures assessed intelligence, working memory, reading, and math problem-solving abilities (*SI Materials and Methods*). After successful completion of the MRI scanning session, children started an 8-wk math-tutoring program. Tutoring sessions occurred three times per week, each ~40–50 min in duration. Response to tutoring was examined using an arithmetic verification task that assessed accuracy and reaction time and an arithmetic production task that assessed retrieval strategy use before and after tutoring. The no-contact comparison group followed an identical protocol, the only exception being that they did not participate in any tutoring sessions.

Tutoring Sessions. Children took part in an 8-wk math-tutoring program adapted from MathWise (10, 14). The tutoring program combined conceptual instruction with speeded retrieval of math facts. Similar to MathWise, the tutoring involved a total of 15–20 h of training, but it was condensed to 8–9 h/wk, with longer lessons to equate overall time on tutoring. The tutoring consisted of 22 lessons of increasing difficulty. The details of each lesson are described in *SI Materials and Methods*.

Tutoring Outcome Measures. Response to tutoring was examined using an arithmetic verification task that assessed accuracy and reaction time and an arithmetic production task that assessed retrieval strategy use on single-digit problems before and after tutoring. Arithmetic verification tasks involving single-digit addition problems were performed during fMRI scanning and emphasized speeded performance, whereas the strategy assessments were performed outside the scanner with other standardized neuropsychological measures and emphasized accuracy. Arithmetic verification and production tasks are described in detail in *SI Materials and Methods*.

Structural MRI. For each subject, a high-resolution T1-weighted spoiled grass gradient recalled inversion recovery 3D MRI sequence was acquired. We conducted a VBM analysis using the T1-weighted MRI scans acquired before tutoring to examine whether regional gray matter volume predicts predict performance improvements with math tutoring. Structural MRI data acquisition and VBM analysis procedure is described in detail in *SI Materials and Methods*.

fMRI. Each subject underwent a resting state scan that lasted 6 min. We performed intrinsic functional connectivity analysis using preprocessed resting state fMRI data acquired before tutoring to investigate functional circuits that predict performance improvements with math tutoring. fMRI data acquisition, preprocessing, and intrinsic functional connectivity analysis procedure is described in detail in *SI Materials and Methods*.

ACKNOWLEDGMENTS. We thank Arron Metcalfe, Teresa Iuculano, and Jennifer Richardson for their assistance; and the anonymous reviewers for their valuable comments and suggestions. This research was supported by National Institutes of Health Grants (HD047520, HD059205, HD057610) and the Netherlands Organization for Scientific Research (446-12-001).

1. Gross J, Hudson C, Price D (2009) *The Long Term Costs of Numeracy Difficulties.* (Every Child a Chance Trust and KPMG, London, UK).
2. Parsons S, Bynner J (1997) Numeracy and employment. *Educ Training* 39(2):43–51.
3. Rivera-Batiz FL (1992) Quantitative literacy and the likelihood of employment among young adults in the United States. *J Hum Resour* 27(2):313–328.
4. Kaufmann L (2002) More evidence for the role of the central executive in retrieving arithmetic facts - a case study of severe developmental dyscalculia. *J Clin Exp Neuropsychol* 24(3):302–310.
5. McCloskey M, Harley W, Sokol SM (1991) Models of arithmetic fact retrieval: An evaluation in light of findings from normal and brain-damaged subjects. *J Exp Psychol Learn Mem Cogn* 17(3):377–397.
6. Fuchs LS, et al. (2006) The effects of computer-assisted instruction on number combination skill in at-risk first graders. *J Learn Disabil* 39(5):467–475.
7. Rittle-Johnson B, Koedinger K (2009) Iterating between lessons on concepts and procedures can improve mathematics knowledge. *Br J Educ Psychol* 79(Pt 3):483–500.
8. Johnson M, Bailey JS (1974) Cross-age tutoring: Fifth graders as arithmetic tutors for kindergarten children. *J Appl Behav Anal* 7(2):223–232.
9. Beirne-Smith M (1991) Peer tutoring in arithmetic for children with learning disabilities. *Except Child* 57(4):330–337.
10. Fuchs LS, et al. (2008) Remediating computational deficits at third grade: A randomized field trial. *J Res Educ Eff* 1(1):2–32.
11. Fuchs LS, Fuchs D, Compton DL (2012) The early prevention of mathematics difficulty: Its power and limitations. *J Learn Disabil* 45(3):257–269.
12. Posner M, Rothbart MK (2007) *Educating the human brain* (American Psychological Association, Washington, DC), p 263.
13. Fuchs LS, et al. Effects of first-grade number knowledge tutoring with contrasting forms of practice. *J Educ Psychol* 105(1):58–77.
14. Powell SR, Fuchs LS, Fuchs D, Cirino PT, Fletcher JM (2009) Effects of fact retrieval tutoring on third-grade students with math difficulties with and without reading difficulties. *Learn Disabil Res Pract* 24(1):1–11.
15. Siegler RS, Shrager J (1984) Strategy choices in addition and subtraction: How do children know what to do. *Origins of Cognitive Skills*, ed Sophian C. (Erlbaum, Hillsdale, NJ), pp 229–293.
16. Fuchs LS, et al. (2004) Enchancing mathematical problem solving among third-grade students with schema-based instruction. *J Educ Psychol* 96:635–647.
17. Menon V, Rivera SM, White CD, Glover GH, Reiss AL (2000) Dissociating prefrontal and parietal cortex activation during arithmetic processing. *Neuroimage* 12(4):357–365.
18. Rickard TC, et al. (2000) The calculating brain: An fMRI study. *Neuropsychologia* 38(3): 325–335.
19. Delazer M, et al. (2003) Learning complex arithmetic—an fMRI study. *Brain Res Cogn Brain Res* 18(1):76–88.
20. Grabner RH, et al. (2009) To retrieve or to calculate? Left angular gyrus mediates the retrieval of arithmetic facts during problem solving. *Neuropsychologia* 47(2):604–608.
21. Rivera SM, Reiss AL, Eckert MA, Menon V (2005) Developmental changes in mental arithmetic: Evidence for increased functional specialization in the left inferior parietal cortex. *Cereb Cortex* 15(11):1779–1790.
22. Cho S, et al. (2012) Hippocampal-prefrontal engagement and dynamic causal interactions in the maturation of children's fact retrieval. *J Cogn Neurosci* 24(9):1849–1866.
23. Cho S, Ryali S, Geary DC, Menon V (2011) How does a child solve 7 + 8? Decoding brain activity patterns associated with counting and retrieval strategies. *Dev Sci* 14(5): 989–1001.
24. Squire LR, Stark CEL, Clark RE (2004) The medial temporal lobe. *Annu Rev Neurosci* 27: 279–306.
25. Suzuki WA (2007) Making new memories: The role of the hippocampus in new associative learning. *Ann N Y Acad Sci* 1097(1):1–11.
26. Wang SH, Morris RGM (2010) Hippocampal-neocortical interactions in memory formation, consolidation, and reconsolidation. *Annu Rev Psychol* 61:49–79, C1–C4.
27. Supekar K, Menon V (2012) Developmental maturation of dynamic causal control signals in higher-order cognition: A neurocognitive network model. *PLOS Comput Biol* 8(2):e1002374.
28. Cohen JR, et al. (2010) Decoding developmental differences and individual variability in response inhibition through predictive analyses across individuals. *Frontiers Human Neurosci* 4(47).
29. Wu SS, et al. (2009) Functional heterogeneity of inferior parietal cortex during mathematical cognition assessed with cytoarchitectonic probability maps. *Cereb Cortex* 19(12):2930–2945.
30. Salthouse TA, Hedden T (2002) Interpreting reaction time measures in between-group comparisons. *J Clin Exp Neuropsychol* 24(7):858–872.
31. Cohen Kadosh R, Lammertyn J, Izard V (2008) Are numbers special? An overview of chronometric, neuroimaging, developmental and comparative studies of magnitude representation. *Prog Neurobiol* 84(2):132–147.
32. Delazer M, et al. (2005) Learning by strategies and learning by drill—evidence from an fMRI study. *Neuroimage* 25(3):838–849.
33. De Smedt B, Holloway ID, Ansari D (2011) Effects of problem size and arithmetic operation on brain activation during calculation in children with varying levels of arithmetical fluency. *Neuroimage* 57(3):771–781.
34. Rykhlevskaia E, Uddin LQ, Kondos L, Menon V (2009) Neuroanatomical correlates of developmental dyscalculia: Combined evidence from morphometry and tractography. *Frontiers Human Neurosci* 3(51).
35. Geary DC, Hoard MK, Byrd-Craven J, DeSoto MC (2004) Strategy choices in simple and complex addition: Contributions of working memory and counting knowledge for children with mathematical disability. *J Exp Child Psychol* 88(2):121–151.
36. Rossi S, et al. (2011) Temporal dynamics of memory trace formation in the human prefrontal cortex. *Cereb Cortex* 21(2):368–373.
37. Simons JS, Spiers HJ (2003) Prefrontal and medial temporal lobe interactions in long-term memory. *Nat Rev Neurosci* 4(8):637–648.
38. Nagel IE, Schumacher EH, Goebel R, D'Esposito M (2008) Functional MRI investigation of verbal selection mechanisms in lateral prefrontal cortex. *Neuroimage* 43(4): 801–807.
39. Delgado MR, Dickerson KC (2012) Reward-related learning via multiple memory systems. *Biol Psychiatry* 72(2):134–141.
40. Poldrack RA, Rodriguez P (2004) How do memory systems interact? Evidence from human classification learning. *Neurobiol Learn Mem* 82(3):324–332.
41. Voermans NC, et al. (2004) Interaction between the human hippocampus and the caudate nucleus during route recognition. *Neuron* 43(3):427–435.
42. Poldrack RA, et al. (2001) Interactive memory systems in the human brain. *Nature* 414(6863):546–550.
43. Dickerson KC, Li J, Delgado MR (2011) Parallel contributions of distinct human memory systems during probabilistic learning. *Neuroimage* 55(1):266–276.
44. Geary DC (1994) *Children's Mathematical Development: Research and Practical Applications* (American Psychological Association, Washington, DC).
45. Ashcraft MH (1982) The development of mental arithmetic: A chronometric approach. *Dev Rev* 2(3):213–236.
46. Siegler RS, Shipley C (1995) Variation, selection, and cognitive change. *Developing Cognitive Competence: New Approaches to Process Modeling* (Lawrence Erlbaum Associates, Hillsdale, NJ), pp 31–76.
47. Geary DC (2011) Cognitive predictors of achievement growth in mathematics: A 5-year longitudinal study. *Dev Psychol* 47(6):1539–1552.
48. Siegler RS, Booth JL (2004) Development of numerical estimation in young children. *Child Dev* 75(2):428–444.
49. Gilmore CK, McCarthy SE, Spelke ES (2010) Non-symbolic arithmetic abilities and mathematics achievement in the first year of formal schooling. *Cognition* 115(3): 394–406.
50. De Smedt B, Verschaffel L, Ghesquière P (2009) The predictive value of numerical magnitude comparison for individual differences in mathematics achievement. *J Exp Child Psychol* 103(4):469–479.
51. Halberda J, Mazzocco MM, Feigenson L (2008) Individual differences in non-verbal number acuity correlate with maths achievement. *Nature* 455(7213):665–668.
52. Jordan NC, Kaplan D, Ramineni C, Locuniak MN (2009) Early math matters: Kindergarten number competence and later mathematics outcomes. *Dev Psychol* 45(3): 850–867.
53. Hoeft F, et al. (2011) Neural systems predicting long-term outcome in dyslexia. *Proc Natl Acad Sci USA* 108(1):361–366.
54. McNorgan C, Alvarez A, Bhullar A, Gayda J, Booth JR (2011) Prediction of reading skill several years later depends on age and brain region: Implications for developmental models of reading. *J Neurosci* 31(26):9641–9648.
55. Dumontheil I, Klingberg T (2012) Brain activity during a visuospatial working memory task predicts arithmetical performance 2 years later. *Cereb Cortex* 22(5):1078–1085.
56. Golestani N, Pallier C (2007) Anatomical correlates of foreign speech sound production. *Cereb Cortex* 17(4):929–934.
57. Erickson KI, et al. (2010) Striatal volume predicts level of video game skill acquisition. *Cereb Cortex* 20(11):2522–2530.
58. Basak C, Voss MW, Erickson KI, Boot WR, Kramer AF (2011) Regional differences in brain volume predict the acquisition of skill in a complex real-time strategy videogame. *Brain Cogn* 76(3):407–414.