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$k_{\text{undock},2} = 0.06 \text{ s}^{-1}$ and $k_{\text{undock},2}^{\text{PSP}} = 0.04 \text{ s}^{-1}$, etc. (see Fig. 4). The numerical solution of this set of coupled differential equations is plotted in Fig. 2. The fitted solution uses $k_{\text{cleav}} = 0.12 \text{ s}^{-1}$, $k_{\text{lig}} = 0.24 \text{ s}^{-1}$, and the fact that 7% of the enzymes are not active. The fit determines the equilibrium constant $k_{\text{cleav}}/k_{\text{lig}} = 0.5$ to better than $\pm 30\%$ and places an upper limit on $k_{\text{lig}} \leq 0.8 \text{ s}^{-1}$. [See (25) for a full description of this numerical work.]

Finally, we propose a model for the memory effect based on slow transitions between different structural configurations of loops A and B. The structures of these loops in the undocked state determined by NMR (16, 17) are different from those in the docked state determined by x-ray crystallography (18). We propose that loops A and B can adopt different conformations in the undocked state. If each loop has two possible conformations that favor a deeply docked and a loosely docked state, respectively, then their four combinations lead to four undocking rates, as are observed. The slow transition time between these loop conformations determines the memory time of the undocking rates. If only one of the two loops undergoes such transitions, it would require four different metastable conformations of this loop to give the four undocking rates.

Indeed, both NMR studies of loops A and B have given evidence of metastable alternating conformations, such as sharp resonance peaks for protonated and unprotonated species of A10 in loop A (16) and weak resonances detected between bases in loop B (17), but well-defined alternate structures were not proposed. Future research should test this hypothesis with a series of mutations that alter the structures of loops A and B to favor certain docked states at the expense of others.

Our single-molecule results demonstrate a tight coupling of structural dynamics and catalytic function in the hairpin ribozyme. Strikingly, the hairpin ribozyme—one of the simplest RNA enzymes—shows very complex structural dynamics, with four docked states of distinct stabilities and a strong memory effect. Our observations would be difficult to obtain by ensemble methods because the less stable conformational states are nonaccumulative. This work highlights the power of single-molecule approaches in characterizing complex structural dynamics.

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23. The hairpin sequence we used is based on the optimized SV5 EH4 hairpin ribozyme (12). The 2'OMeA-1 substrate was used when measuring the docking and undocking rates independent of cleavage. Cy5-labeled RzA and biotin-labeled RzB were synthesized by the RNA synthesis facility of the University of Vermont. Cy3 was coupled to the 3' end of RzA postsynthetically, via a primary amine attached to the 3'-most phosphate. All single-stranded RNAs used in the experiment were purified by gel electrophoresis and C_{18} reversed-phase high-performance liquid chromatography as described (12) to >95% purity. To form the ribozyme, we annealed RzA to RzB by heating to 80°C for 1 min and then slowly cooling to 22°C in 50 mM tris-HCl (pH 7.5) and 12 mM $MgCl_2$. These standard buffer conditions were used in all experiments. In single-molecule experiments, an oxygen scavenger system (7) was added to the buffer to show photobleaching.
24. The distance between the 3' and 5' ends of RzA in the docked state was estimated using a recent crystal structure (18). The distance in the undocked state was estimated under the assumption that the structures of the two domains are similar to those in the docked state but are coaxially stacked. The distance in the S-free state was estimated under the assumptions that domain B has a similar structure as in the docked state, whereas the single-stranded overhang is a random coil with complete flexibility between adjacent nucleotides. These distances compare very well with a previous measurement by time-resolved FRET (13).
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Supporting Online Material
www.sciencemag.org/cgi/content/full/296/5572/1473/DC1
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Figs. S1 to S5
References

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Functional Neuroanatomical Differences Between Adults and School-Age Children in the Processing of Single Words

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A critical issue in developmental cognitive neuroscience is the extent to which the functional neuroanatomy underlying task performance differs in adults and children. Direct comparisons of brain activation in the left frontal and extrastriate cortex were made in adults and children (aged 7 to 10 years) performing single-word processing tasks with visual presentation; differences were found in circumscribed frontal and extrastriate regions. Conceivably, these differences could be attributable exclusively to performance discrepancies; alternatively, maturational differences in functional neuroanatomy could exist despite similar performance. Some of the brain regions examined showed differences attributable to age independent of performance, suggesting that maturation of the pattern of regional activations for these tasks is incomplete at age 10.

A fundamental objective in basic and clinical neuroscience is to understand the development of the functional organization of the human brain. Such knowledge can not only

illuminate normal functional anatomical development (1) but also create a context for understanding the consequences of early perturbations to the developing brain (2, 3) or

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aberrant organizations thought to underlie developmental disorders of cognition (4). Such knowledge can also serve as a context for developing clinical interventions to treat these disorders.

Because of difficulties in matching anatomy and performance across age groups (5), developmental functional magnetic resonance imaging (fMRI) studies of cognition [reviewed in (5, 6)] have employed indirect strategies for group comparison (7–9) or have not opted to perform comparisons (10–12). We used a multistep strategy to overcome these barriers in an event-related fMRI study of children and adults performing single-word language tasks (13).

The first step was to develop a comparable task base for adults and children. All tasks used were controlled (that is, effortful) visual lexical (single-word) processing tasks (14). In these tasks, participants were required to generate a single-word verbal response to a visually presented word (15). These lexical processing tasks were chosen because they are similar to those previously studied in adult populations (16, 17), [for review, see (18–20)], and the neural processes underlying these tasks are thought to undergo substantial development between childhood and adulthood (21). For example, specialization in certain left extrastriate regions is thought to occur as readers become literate (18). Likewise, frontal cortex maturation, apparently related to the development of control processes (22, 23), appears to be relatively protracted as compared to that of other cortical regions, continuing beyond adolescence [reviewed in (22)]. Hence, the current study focused on the comparison of left frontal and left extrastriate activations between normal, native English-speaking, right-handed children 7 to 10 years old ($n = 19$ children, 10 of whom were female; mean age 9.3) and adults 18 to 35 years old ($n = 21$ adults, 11 of whom were female; mean age 25.5) (13). Because fMRI runs consisted of an event-related design (24–26) with overt verbal response (26), both accuracy and reaction time (RT) could be related to the fMRI measures on a trial-by-trial basis. Although children were, on average, slower and less accurate than adults, there was a substantial overlap with adult performance measures.

The second step in the strategy, for the purpose of direct statistical comparisons between functional activations in adult and child brains, was to perform voxel-by-voxel

analysis of variance (ANOVA) on all imaging data in a common stereotactic space (27, 28). This ANOVA included time as a within-

subject factor and age group as a between-subject factor. A “main effect of time” image (Fig. 1) showed multiple activations, includ-

Fig. 1. Statistical activation maps derived from whole-brain fMRI of adults and children performing visual lexical processing tasks in an event-related design. Images are sagittal sections positioned with the front of the brain pointing toward the viewer's left, across all 40 participants (21 adults and 19 children) incorporated into the ANOVA. The color scale corresponds to ANOVA-derived z scores. The first column shows the main effect of time image for the two groups generated from ANOVA with group (adult and child) \times time (seven levels; each MR frame is 3 s in duration) for all trials with correct responses collapsed across the three controlled lexical tasks (14). The top slice is a sagittal cut through the left hemisphere at the Talairach coordinate of $x = -49$; the bottom is a section through the left hemisphere 20 mm medial to the top slice, at $x = -29$. The column labeled interaction is the group \times time interaction from the same ANOVA. In considering this ANOVA, active regions in the time image reflect locations whose activity is probably similar between the two groups. Circles in the time image highlight selected regions that have a robust main effect of time across groups but no statistically significant group \times time interaction. These regions are analyzed further in this study. Regions in the interaction image reflect locations that are significantly different between the two groups. Circles in the interaction image highlight selected regions in the left frontal and extrastriate cortex analyzed further in this study (13).

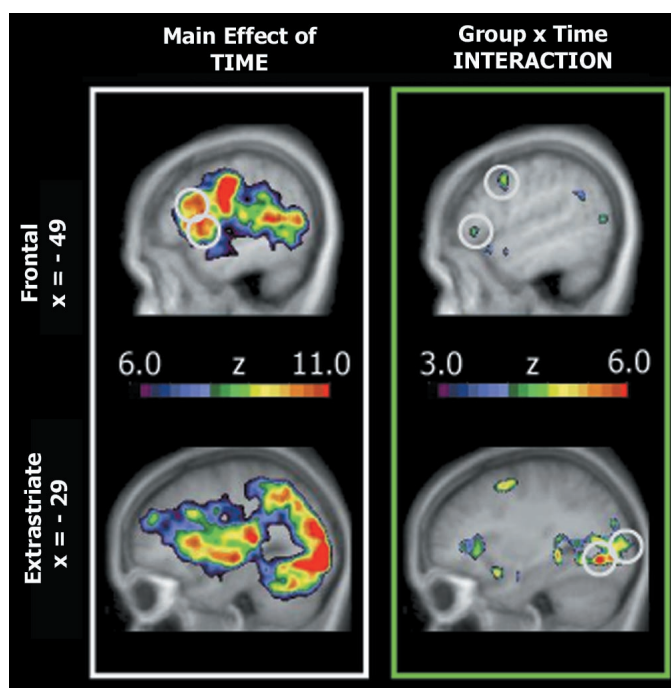


Fig. 2. Demographics and task performance characteristics of the four subgroups tested. Of the initial 19 children and 21 adults, 10 from each were placed into subgroups based on performance parameters (30). Green dotted lines show statistically equivalent groups, as derived from ANOVA and Scheffé tests at $P < 0.05$. The mean (of the median RTs for correct trials across all three tasks) RTs for the matched children, matched adults, and nonmatched adults were not statistically different. By contrast, the RT for the nonmatched children fell outside of the Scheffé-derived grouping. In all other respects assessed, no significant difference was observed between the within-age-category subgroups. Intelligence quotient (IQ) data were collected on children only (13). Both matched adults and matched children performed accurately, but the former group was significantly more accurate. However, only the correct trials were incorporated into the statistical analysis. A chi-square test revealed no significant differences in gender composition among the subgroups. n , number of participants; age, mean age of participants in subgroup; % correct, percentage of trials per run with correct response collapsed across all three tasks; f, female; m, male.

	Children		Adults	
	Non-Matched	Matched	Matched	Non-Matched
n	9	10	10	11
gender	5 f / 4 m	5 f / 5 m	4 f / 6 m	7 f / 4 m
age	9.38	9.22	24.49	25.93
% correct	80.78	81.11	92.06	98.12
RT (msec)	2388	1481	1326	1222
Verbal IQ	118	125	---	---
Performance IQ	113	115	---	---
Full Scale IQ	120	123	---	---

..... ANOVA / Scheffé groupings, $p < 0.05$

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ing activations as expected in the left frontal and left extrastriate cortex, suggesting that the children and adults had similar activity in these regions (7–9). However, a “group \times time interaction” image (Fig. 1) revealed regions of difference between adults and children in the left frontal and left extrastriate cortex [among other regions (13)] as well. From these two images, six regions of inter-

est (ROIs)—four in the left frontal cortex and two in the left extrastriate cortex—were defined (13, 29).

The third step in the strategy addresses a fundamental question raised by the differences found in the interaction image. Are these functional anatomical differences between the groups due to maturational stage, or do they simply reflect the overall slower and less

accurate performance of the children on these tasks? This question was addressed by using an analysis sensitive to the effects of both age and performance.

Because of the overlap in performance discussed above, it was possible to create two separate comparison subsets of child and adult data: one in which child and adult performance were very similar (“matched”) and one in which there were clear performance differences between adults and children (“nonmatched”) (30). Several demographic and performance characteristics of these subgroups are depicted in Fig. 2. If the task-related activity in a region were affected by neither age nor performance, it would have similar activity for adults and children in both the matched and nonmatched subgroups (age/performance-independent region). A region where performance has an effect would exhibit minimal if any differences between the matched subgroups but significant differences between the nonmatched subgroups (performance-related region). Critically, a region where the activity is affected by the age of the person irrespective of performance would have dissimilar activity between the matched subgroups, and this difference would replicate in the nonmatched subgroups (age-related region).

Activity in the six ROIs was characterized using the above criteria (Fig. 3). Activity in two frontal regions (–47, 9, 22, BA 9 and –51, 7, 6, BA 44) (13) was age/performance-independent. Activity in one left frontal cortex region [more anterior and ventral to the above regions (–37, 23, 6, BA 45/47)] and in the more posterior left extrastriate cortex region (–27, –87, 4, BA 18) was performance-related, both regions showing greater activation in children in the nonmatched group. One left frontal and one left extrastriate region were found to be age-related. The left extrastriate age-related region (–29, –71, –6, BA 18) again demonstrated more robust activity in children than in adults. In contrast to this extrastriate region, the frontal region (–49, 3, 40, BA 44/6) showed significantly greater activation in adults than in children. Analysis of the time course data in this region for the children alone revealed that children (both overall and in both subgroups) did not have a significant activation in this location.

The different patterns of performance and age-related patterns found have several implications for the comparison of adult and child functional anatomy. The age/performance-independent regions, by definition, behave similarly in children and adults. The performance-related regions appear to be affected by time on task and not by age. Time-on-task effects are common in functional neuroimaging data, including activations in similar frontal and extrastriate regions (31). Thus, it seems reasonable to conclude that

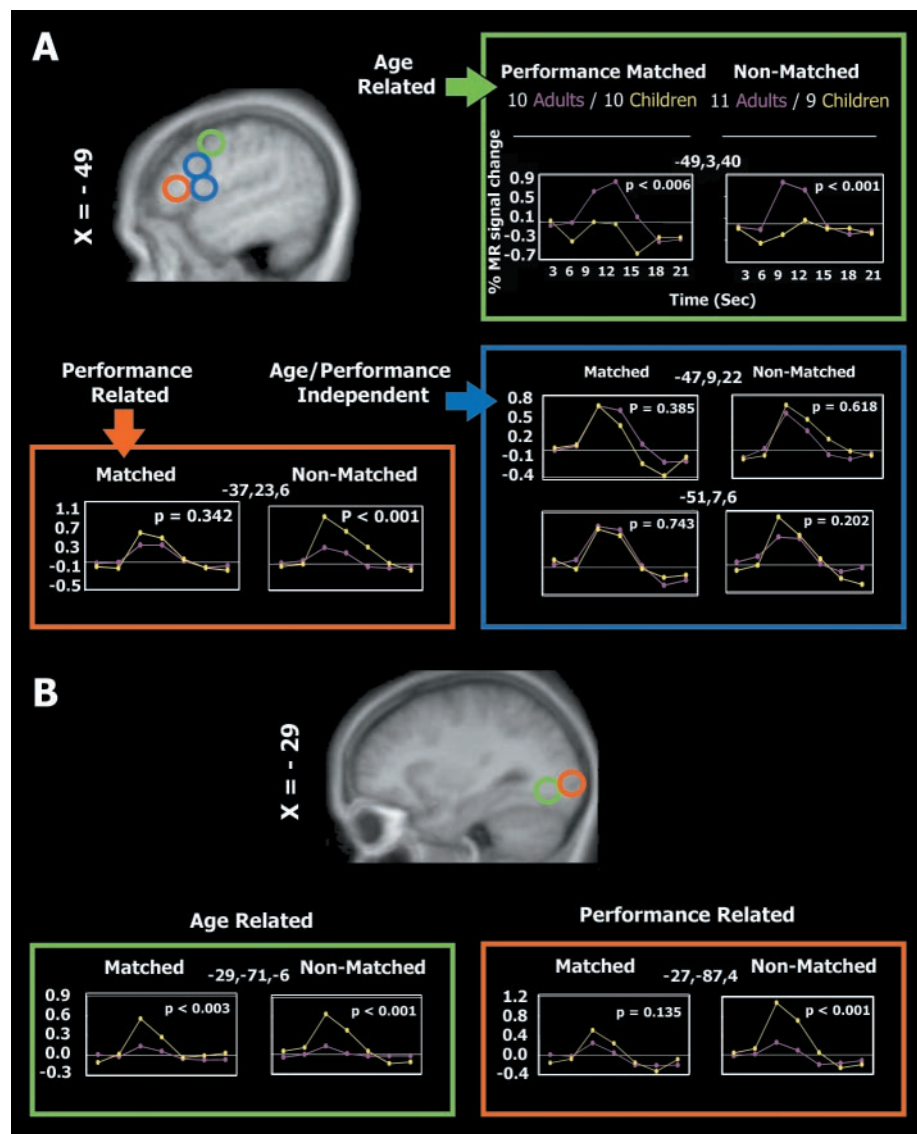


Fig. 3. Three developmental relationships observed in left frontal and left extrastriate regions. The hemodynamic response function time courses for adults and children, and the P values derived from the group \times time interaction, are shown for six regions derived from the ANOVA. Four of the regions are derived from the interaction image in Fig. 1, and two regions are derived from the time image in Fig. 1. The percentage of MR signal change is plotted against time in seconds. The time courses and P values for the performance matched and for the performance nonmatched subgroups are shown for each region. The numeric coordinates (such as –49, 3, 40) indicate the location of the center of mass of the relevant region of activation in a standard atlas space (13). Age-related regions (green) denote areas where activation depends on the person’s age, not performance; performance-related regions (orange) denote areas where activation depends on the person’s performance, not age; age/performance-independent regions (blue) denote areas where activation is independent of the person’s age or performance. (A) Left frontal cortex. Four frontal ROIs are delineated with circles in stereotactically accurate locations on a sagittal view of the averaged high-resolution structural image from 20 matched participants (10 children and 10 adults). The time course for each ROI is depicted. (B) Left extrastriate cortex. One age-related region and one performance-related region are depicted.

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age/performance-independent and performance-related regions are functioning similarly in adults and children.

However, it should be noted that the performance-related regions are an example of how performance mismatch might lead to a false attribution of such differences between age groups to effects of maturation per se. Although issues of group performance mismatch are relevant throughout the functional neuroimaging literature when development, aging, or pathology is studied, our results suggest that these issues can and should be addressed to avoid the confounding of performance effects with group-related functional anatomical differences.

Age-related regions, on the other hand, do most plausibly reflect effects of brain maturation per se and indicate that the brain of a (7-to-10-year-old) child uses, in part, a different functional neuroanatomy than that of an adult performing the same tasks. There are several potential explanations for such effects.

One explanation is that the left dorsal age-related region is immature in children and is incapable of producing sufficient processing to aid in the performance of this task. In the absence of activation of the left dorsal frontal region, the child's brain adopts an alternative strategy that includes greater use of a left extrastriate region [as well as other regions, not detailed here (13)]. By "strategy," we refer to the tactic used by the brain to solve a problem and not necessarily to an overt or volitional approach used by the participants. This scenario does not lead to the assertion that the frontal lobe as a whole is not mature or not accessible, because the bulk of the lateral frontal cortex highlighted here shows no age-related differences (Fig. 1).

Alternatively, it could be that because of experience, children have not yet incorporated the processing resources of this left frontal region into a strategy for performing the types of tasks used here, but do so for other tasks. Recently published work suggests that this latter alternative may be the case (32).

Recent developmental studies have suggested that child brains may have a more widespread (9) or less focal lexical processing system than adult brains have. Such a regressive model does not appear to account for the full set of differences between adults and children found in this study. Although the extrastriate differences might be explained in such a framework, the addition of an age-related frontal activation in adults seems to be counter to this suggestion. In fact, when performance is matched, the majority of differences between adults and children disappear, and those that remain reflect response differences in discrete anatomical regions.

The results presented here strongly suggest that the functional neuroanatomy under-

lying controlled lexical task performance is still developing during early school years. Several points follow: Through study of older children and through longitudinal studies, the transition of age-related regions from immaturity to mature patterns of activity can be delineated. Through study of younger children, further age-related differences will likely be found. And, perhaps most important, when the functional neuroanatomy of children who have brain pathology is studied, the normal developmental context (at the time of injury and the time of study) needs to be taken into account.

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- Three tasks were used: verb-, rhyme-, and opposite-generate. For example, in the case of opposite generation, when the participant was presented with the word "short," an appropriate response would be "tall." For this report, analysis has been collapsed across the three tasks. Analysis of differential task activation across children and adults revealed only one left hemisphere region. This region was outside of the left frontal and left extrastriate cortex. Each participant performed one run of each type of task, and each run consisted of 21 trials (13). To make these tasks tractable for 7-to-10-year-old children, words were drawn from available U.S. first grade reading lists.
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- Although it is an expressed concern that the child brain is too variable in size and shape to be compared directly with the adult brain (5), we have viewed the feasibility of such a comparison as an empirical issue (33). We have demonstrated that pediatric brains and adult brains can be placed into a standard stereotaxic space (28) with comparable reliability and that significant differences in anatomy seen with the methods used are of such a size that, in simulation, they do not have negative effects on fMRI studies (33).
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- A peak-finding algorithm was used to obtain center-of-mass coordinates for activated regions (13, 34) for the time and interaction images. For region-of-interest analyses, a 10-mm sphere centered on the location of the center of mass of the statistical effect in the image was used. An activated region was defined as having a significant positive main effect of time or a significant interaction between the factor "age group" and time. The larger list of all regions of differential activation is available in table S1 (13). For the purposes of this study, we chose regions based on earlier lexical processing studies emphasizing left lateral frontal and left extrastriate regions (16, 17). Guided by the output of the peak search program, and by visual inspection of the interaction image, we found the regions corresponding to the two highlighted extrastriate and two highlighted regions in the frontal cortex. Peak search and visual inspection of the time image and comparison to the interaction image motivated us to find the frontal regions from the time image that appeared to be absent in the interaction image.
- To generate subgroups of adults and children with matched (and nonmatched) performance, a scatter plot was created with each person plotted by accuracy (the percent of correct trials collapsed across three tasks) versus RT (the mean of median RT for correct trials for each task). Visualization of that scatter plot revealed apparent "natural" boundaries. We used 95% mean accuracy and 2000-ms mean RT as boundaries. Nonmatched adults had >95% accuracy and <2000-ms RTs. Matched adults and children had <95% accuracy and <2000-ms RTs. Nonmatched children had <95% accuracy and >2000-ms RTs. Groupings were verified by performance of a K-means cluster analysis on the mean RTs of all children, which yielded two subgroups identical to the matched and nonmatched subgroups derived as detailed above. To equate as well as possible for accuracy differences, only trials with correct verbal responses were entered into the statistical analysis, addressing the accuracy discrepancy between matched adults and matched children. There was no significant correlation in children between age and RT ($r = 0.026$, $P = 0.916$), age and accuracy ($r = -0.077$, $P = 0.753$), verbal intelligence quotient (VIQ) and RT ($r = -0.236$, $P = 0.331$), nor VIQ and accuracy ($r = 0.254$, $P = 0.295$).
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- This study was approved by the Washington University Human Studies Committee. We thank R. Coalson and E. Brandling-Bennett for technical assistance; L. Counts for research subject coordination; T. Spevack and L. Blackburn for neuropsychological testing; and R. Buckner, G. Shulman, and members of our laboratory for helpful comments on the manuscript. Supported by NIH grants NS51281 (S.E.P.), NS32979 (S.E.P.), and NS55582 (B.L.S.) and by the McDonnell Center for Higher Brain Function (S.E.P. and B.L.S.). B.L.S. is a Scholar of the Child Health Research Center of Excellence in Developmental Biology at Washington University School of Medicine (HD01487). T.T.B. is an NSF Graduate Research Fellow.

Supporting Online Material

www.sciencemag.org/cgi/content/full/296/5572/1476/DC1

Materials and Methods

Fig. S1

Table S1

References

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