Distinguishable Brain Activation Networks for Short- and Long-Term Motor Skill Learning

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Submitted 12 July 2004; accepted in final form 17 January 2005

Floyer-Lea, A. and P. M. Matthews. Distinguishable brain activation networks for short- and long-term motor skill learning. J Neurophysiol 94: 512–518, 2005. First published February 16, 2005; doi:10.1152/jn.00717.2004. The acquisition of a new motor skill is characterized first by a short-term, fast learning stage in which performance improves rapidly, and subsequently by a long-term, slower learning stage in which additional performance gains are incremental. Previous functional imaging studies have suggested that distinct brain networks mediate these two stages of learning, but direct comparisons using the same task have not been performed. Here we used a task in which subjects learn to track a continuous 8-s sequence demanding variable isometric force development between the fingers and thumb of the dominant, right hand. Learning-associated changes in brain activation were characterized using functional MRI (fMRI) during short-term learning of a novel sequence, during short-term learning after prior, brief exposure to the sequence, and over long-term (3 wk) training in the task. Short-term learning was associated with decreases in activity in the dorsolateral prefrontal, anterior cingulate, posterior parietal, primary motor, and cerebellar cortex, and with increased activation in the right cerebellar dentate nucleus, the left putamen, and left thalamus. Prefrontal, parietal, and cerebellar cortical changes were not apparent with short-term learning after prior exposure to the sequence. With long-term learning, increases in activity were found in the left primary somatosensory and motor cortex and in the right putamen. Our observations extend previous work suggesting that distinguishable networks are recruited during the different phases of motor learning. While short-term motor skill learning seems associated primarily with activation in a cortical network specific for the learned movements, long-term learning involves increased activation of a bihemispheric cortical-subcortical network in a pattern suggesting “plastic” development of new representations for both motor output and somatosensory afferent information.

INTRODUCTION

The acquisition of a new motor skill follows two distinct stages with continued practice: first, there is an early, fast learning stage in which performance improves rapidly within a single training session; later, there is a slower learning stage in which incremental gains in performance are seen over several sessions of practice (Ungerleider et al. 2002). The latter stage involves processes of practice-independent learning known as consolidation (Karni and Sagi 1993; Maquet et al. 2003; Walker et al. 2003).

Functional imaging studies have highlighted dynamic changes in cortical and subcortical regions with motor skill learning. During the early stages of learning, the dorsolateral prefrontal (DLPFC), premotor (Ghilardi et al. 2000; Grafton et al. 1992, 2002; Jueptner et al. 1997b) and ipsilateral lateral cerebellar cortices show relatively greater activity (Eliassen et al. 2001; Jenkins et al. 1994; Penhune and Doyon 2002). Increased relative activation in the cerebellar dentate nucleus and basal ganglia characterizes later stages of short-term motor sequence learning (Doyon et al. 2002). While some studies of short-term motor learning have found increases of activation in the motor cortex associated with learning (e.g., Grafton et al. 1997; Hazeltine et al. 1997), decreasing or unchanged activation in this area has been more commonly reported (e.g., Doyon and Ungerleider 2002; Jenkins et al. 1994; Toni et al. 1998). There have been fewer studies in humans of the effects of long-term practice on patterns of brain activation during performance of a motor task. Karni et al. (1995) trained subjects on a motor sequence task for 3 wk and found increased activation over time, which was interpreted as evidence for enlargement of the primary motor cortical functional representation specifically for the trained sequence. This suggests that there may be distinct mechanisms for altered brain motor representations with short- and long-term learning.

The results of Karni et al. are supported indirectly by invasive electrophysiological studies in animals, which have shown plasticity in the functional organization of the primary motor cortex with motor skill training or chronic changes toafferent input (Kaas 2000; Nudo et al. 1996; Rioult-Pedotti et al. 1998). The degree to which primary motor cortex organization occurs may also depend on context or stimulus type (Hazeltine et al. 1997). Reorganization of the somatotopic representation in the primary motor cortex also has been shown in humans after amputation (Cohen et al. 1991; Karl et al. 2001) and after lesions caused by stroke or trauma (Chen et al. 2002). Transcranial magnetic stimulation studies showed that repetition of even very simple movements rapidly causes measurable changes in the excitable cortical field (Classen et al. 1998).

To test further how the representation of the same motor task varies with the stage of learning, we used a well-characterized learning task in which subjects tracked a continuously changing, visually presented target by varying the force exerted on a pressure sensor held in the right hand. This task is controlled for force, velocity, and frequency of movements, so improvements in performance are due to learning of the timing and accuracy of the movement sequence. Changes in activation
METH O D S

Motor learning task

Subjects held a magnetic resonance–compatible pressure sensor in their right hand between the thumb and fingers (Fig. 1). The arm was held in a semi-pronated position, supported by an armrest and secured to prevent arm or wrist movement. As the arm and wrist were held immobile, subjects used the muscles of the thenar eminence and the finger flexor muscles to perform the isometric task. Subjects viewed a large screen on which the movement sequence was presented from a distance of 2 m by means of prism glasses.

Two vertical bars were shown on the screen as shown in Fig. 1B. A red bar on the left side of the screen indicated the target force. A second blue bar on the right side of the screen gave a continuous measure of the subject’s response. The subjects were asked to try to maintain the two bars at equal height on the screen at all times. An increase in applied pressure caused an increase in the response bar height. The force applied to the pressure sensor was sampled at 100 Hz and projected to the screen at the maximum refresh rate of the system, using a multislice gradient-echo EPI sequence (TR, 3,000 ms; TE, 30 ms; 21 × 6 mm axial slices providing whole brain coverage; FOV, 256 × 192 mm; matrix, 64 × 64).

The experiment was implemented as a block design with three conditions: sequence, random, and rest. During the sequence blocks, subjects performed four repeats of an 8-s sinusoidally varying sequence of force changes (Fig. 1C). The force required to equalize the target and response bars therefore changed continuously, smoothly, and (when learned) predictably throughout a sequence block. In the random blocks, subjects followed 28 s of pseudo-random changes in force, constrained so that the changes were always smooth, and so that the mean movement frequency distribution over a full cycle was the same as that in random sequence blocks. During the rest blocks, subjects made no movements and were shown a sinusoidal moving pattern with computer variation of the response bar in simulation of the output with activity. This matched visual input during rest to that during movement blocks and was designed to prevent mental rehearsal of the pattern to be learned during the rest periods. Ten blocks of each condition were performed, with instructions shown on the screen for 3 s before each condition, giving a total experimental duration of 16 min.

The tracking error, measured as a percentage of the maximum force, was recorded throughout the experiment with a sampling rate of 100 Hz. The mean absolute tracking error was calculated for each condition. All subjects were trained outside the scanner for a period of 10 min on a randomly varying tracking sequence before each of the scanning sessions. Tracking performance over this period was measured to ensure that subjects achieved and maintained a stable baseline performance level before the start of the learning experiments. The maximum force level was set at 20 N, which all subjects were able to match easily.

Short-term motor learning group

Fifteen healthy right-hand dominant subjects participated in the short-term motor learning study (8 women and 7 men; mean age, 25.4 yr; range, 20–31 yr). These subjects were scanned during a single session while they learned a sequence that they had never been exposed to. Data from these subjects were analyzed to show changes in activation patterns in the brain due to within-session learning of a novel sequence.

Long-term motor learning group

A further seven healthy right-hand dominant subjects participated in the long-term practice study (4 women and 3 men; mean age, 28.6 yr; range, 22–34 yr). All subjects gave informed consent according to a protocol approved by the local ethics committee. These subjects participated in two sessions, during each of which there were two periods of functional MRI (fMRI) scanning.

Before the first scanning session, these subjects were given one 10-min practice session outside the magnet with two distinct sequences (A and B). They were scanned while performing each of these sequences. Data from these scans was analyzed to show the effect of prior exposure to the sequence on performance and further within-session activation changes.

These subjects went on to complete training on one of the sequences for 3 wk and formed the long-term learning group. Four subjects were trained on sequence A and three on sequence B. Training consisted of 15 min of practice each day, 5 days/wk under conditions controlled to maintain a relaxed environment in quiet room, free from distractions. Short rest periods were given during practice to prevent fatigue. Subjects lay supine for the training sessions and viewed a monitor screen placed near their feet. The arm was secured in the same position as during the scanning sessions. The mean tracking error (root mean square deviation expressed as a percentage of target force) was calculated for each practice block.

After this training period, subjects participated in another set of two scans. During the first of these scans, they performed the sequence on which they had been trained previously and, during the second scan, they performed the untrained sequence. Data from these scans was analyzed to show the effect of long-term learning on performance and brain activation.

Image acquisition

Data acquisition was performed on a 3 Tesla Varian Inova MRI system, using a multislice gradient-echo EPI sequence (TR, 3,000 ms; TE, 30 ms; 21 × 6 mm axial slices providing whole brain coverage; FOV, 256 × 192 mm; matrix, 64 × 64). Four “dummy” scans were added at the beginning of the image sequence to reach steady-state magnetization. A T1-weighted structural image also was acquired for each subject with a notional resolution of 1.5 × 1.5 × 3 mm3 (IR 3D
Turbo Flash; TR, 30 ms; TE, 5 ms; TI, 500 ms; flip angle, 15°; FOV, 256 × 256; matrix, 256 × 256) to allow functional image registration for precise localization of activations and to define individual regions of interest.

Data analysis

fMRI time series analysis was carried out using tools from the FMRIB Software Library (www.fmrib.ox.ac.uk/fsl). The following processing steps were used prior to statistical analysis: motion correction (Jenkinson et al. 2002), spatial smoothing with a Gaussian kernel having a value of 5 mm at half-maximum and nonlinear high pass filtering (using Gaussian-weighted least square fitting with sigma = 50). Statistical analysis was carried out using the general linear model (GLM) with local autocorrelation correction. The first five learning blocks, the second five learning blocks, and the first and second five random blocks were used as distinct temporal explanatory variables. Periods when the instructions were on screen, together with the subject movement parameters, were also included in the GLM to model out effects due to these factors, but were not considered as contrasts of interest. In addition to mean activation maps for the performance of the task over the entire scan, within-session changes were analyzed by comparing the first half of the scanning session with the second half.

Cluster detection, which includes intrinsic correction for multiple comparisons (Poline et al. 1997), was used to threshold the images to a corrected threshold of \( P < 0.05 \). The number of voxels constituting a significant cluster is determined by Gaussian random field theory and depends on the intrinsic smoothness of the data as well as the chosen thresholding level (Worsley et al. 1992). The significance level of the clusters are intrinsically corrected for multiple comparisons. Registrations of EPI functional images to high resolution and into standard space (Talairach and Tournoux 1988) were carried out using an affine transformation with 12° of freedom (Jenkinson and Smith 2001).

Group mixed effects analyses were performed (Woolrich et al. 2005). Group mean activation maps were produced for the short-term learning and for the prior exposure groups. A paired contrast was performed to define differences in brain activation associated with long-term learning. For this analysis higher-level EVs were the effects of training (before vs. after), together with a variable indicating each individual subject, forming a paired mixed effects analysis performed using FLAME (www.fmrib.ox.ac.uk/fsl; Woolrich et al. 2005). Z (Gaussianized T/F) statistic images were corrected for multiple comparisons using cluster detection, with clusters determined by \( Z \geq 2.3 \) and a corrected cluster significance threshold of \( P = 0.05 \) (Forman et al. 1995; Friston et al. 1994; Worsley et al. 1992). Activation maps were overlaid on the group mean high resolution image and the anatomical location of clusters reported using macroscopic anatomical boundaries approximating the expected cytoarchitectural boundaries (Crespo-Facorro et al. 2000; Geyer et al. 2000).

Because we were particularly interested in changes in the primary motor cortex in the extended practice group, a further region of interest (ROI) analysis was performed in this area. Anatomical masks of the hand area of the motor cortex (Yousry et al. 1997) were created from each subject’s high-resolution T1 image. The number of activated voxels and the mean percentage signal change within this ROI were recorded for each subject for the trained sequence, the untrained sequence, and the random movement conditions before and after training.

This protocol was part of a series approved by the Oxford Research Ethics Board. Informed, written consent was obtained from all participants.

RESULTS

Behavioral results

Short-term learning was assessed in the short-term learning group from the rapid decrease in errors over the first several minutes of tracking a novel sequence. Error decreased by a mean of 36% over the first five tracking blocks of the short-term training period (\( P < 0.001 \)), and performance was maintained relatively constant over the second half of the experiment (Fig. 2A).

In the long-term learning group, extended training over 3 wk induced a further decrease in the tracking error, with subjects improving from a mean error of 7.0% to 4.6% as shown in Fig. 2, B and C (34% mean decrease, \( P < 0.01 \)). This long-term learning was specific to the sequence trained. No significant changes were found in performance of the untrained sequence or in the random movement condition. The maximum, minimum, and median force levels did not change significantly over any of the training trials.

FIG. 2. A: tracking error over the short-term learning task decreased significantly between the 1st and 2nd half of the experiment (\( P < 0.01 \)). B: tracking error during each condition before and after training. Training on a sequence induced a further specific significant reduction in the tracking error for that sequence alone (\( P < 0.01 \)). C: steady improvement in tracking accuracy can be seen during the practice sessions outside the scanner. All error bars represent SD.
Within-session changes in brain activation during fast motor learning

Changes in brain activity with short-term learning of a novel sequence were assessed from the short-term learning group. Images acquired over the first half of the tracking sequence were contrasted with those from the second half, when performance had improved. This contrast showed a time-dependent decrease in activation in the anterior cingulate, dorsolateral prefrontal, posterior parietal (in or near the intraparietal sulcus), bilateral primary motor, and the cerebellar cortex (Table 1). A time-dependent increase in activation was found in the left cerebellar dentate, the left putamen, and left thalamus (Fig. 3A). A recently developed connectivity-based map of thalamic architecture (Behrens et al. 2003; www.fmrib.ox.ac.uk/connect) allows localization of the maximum thalamic activation to a region with highest probability of direct connectivity with the premotor cortex, corresponding approximately to the ventral lateral nucleus.

Within-session changes in brain activation after prior exposure

The first set of scans performed by the long-term learning group were acquired after 10 min of practice outside the magnet on the specific sequence later used during the scanning session. A contrast of fMRI data acquired during the second half of their sequence training in the MRI scanner relative to the first half showed only decreases in activity in the left primary sensorimotor and left posterior parietal cortices (Fig. 3B). A decrease in activity over the training trial also was found more anteriorly in the premotor cortex during performance of the random movement condition over the same period (Fig. 3C). No increases in activation were found in the second relative to the first half of the experiment with use of either the training or random sequences.

Changes in brain activation caused by long-term learning

Brain activation patterns were directly contrasted before and after 3 wk of extended training to characterize activation changes associated with long-term learning. Significant increases in brain activation after long-term learning specific to the sequence learned were found in the right striatum and in the left precentral and postcentral gyri in a region overlapping primary sensorimotor cortex activation with the main effect of hand grip (Fig. 3D). There were no significant decreases in activation due to the extended training. Contrasts of brain activation before and after extended training did not reveal significant brain activity changes associated with tracking of the untrained or the random sequences.

An ROI-based analysis in the hand region of the primary motor cortex (Yousry et al. 1997) was performed to assess the

<table>
<thead>
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<th>Region</th>
<th>Brodmann’s Area</th>
<th>Max Z</th>
<th>Position</th>
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<tbody>
<tr>
<td>Left dorsolateral prefrontal cortex</td>
<td>46</td>
<td>−6.5 decrease</td>
<td>42, 18, 44</td>
</tr>
<tr>
<td>Left posterior parietal cortex</td>
<td>5/7</td>
<td>−4.4 decrease</td>
<td>−28, −44, 70</td>
</tr>
<tr>
<td>Left primary motor cortex</td>
<td>4</td>
<td>−4.3 decrease</td>
<td>−38, −22, 58</td>
</tr>
<tr>
<td>Right primary motor cortex</td>
<td>4</td>
<td>−4.3 decrease</td>
<td>34, −28, 60</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>23/24</td>
<td>−3.8 decrease</td>
<td>2, 4, 32</td>
</tr>
<tr>
<td>Right cerebellar cortex I/Crus II</td>
<td>6.2 decrease</td>
<td>−34, −80, −34</td>
<td></td>
</tr>
<tr>
<td>Right cerebellar dentate</td>
<td>N/A</td>
<td>5.5 increase</td>
<td>28, −56, −34</td>
</tr>
<tr>
<td>Right putamen</td>
<td>N/A</td>
<td>5.6 increase</td>
<td>26, 2, 6</td>
</tr>
<tr>
<td>Right thalamus</td>
<td>N/A</td>
<td>5.7 increase</td>
<td>14, −18, 6</td>
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Within-Session Activation Changes After Previous Sequence Exposure

<table>
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<th>Max Z</th>
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<tr>
<td>Left premotor cortex</td>
<td>4</td>
<td>−4.2 decrease</td>
<td>−34, −10, 66</td>
</tr>
<tr>
<td>Left primary sensory cortex</td>
<td>1/2/3</td>
<td>−3.6 decrease</td>
<td>−42, −30, 64</td>
</tr>
<tr>
<td>Left posterior parietal cortex</td>
<td>5/7</td>
<td>−4.2 decrease</td>
<td>−16, −64, 62</td>
</tr>
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Activation Changes After Extended Practice

<table>
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<th>Brodmann’s Area</th>
<th>Max Z</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left primary motor cortex</td>
<td>4</td>
<td>5.02 increase</td>
<td>−20, −16, 72</td>
</tr>
<tr>
<td>Left primary sensory cortex</td>
<td>1/2/3</td>
<td>5.17 increase</td>
<td>−32, −30, 62</td>
</tr>
<tr>
<td>Right putamen</td>
<td>N/A</td>
<td>4.1 increase</td>
<td>28, −10, 16</td>
</tr>
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</table>

N/A, not applicable.
magnitude of activation changes associated with long-term sequence learning. Extended training was associated with an increase in both the mean percentage signal change and the number of significantly activated voxels during performance of the trained sequence (Fig. 4). These increases were specific for tracking the trained sequence: no significant changes were found in the same ROI with either the untrained sequence or the random movement condition before and after the extended training.

**Discussion**

Our results confirm that there are distinct patterns of brain activation changes related to fast, short-term and to slow, long-term motor learning. As we have described in more detail elsewhere (Floyer-Lea and Matthews 2004), during a first training session with a novel sequence, there are rapid within-session changes in activation in several cortical and subcortical regions. Smaller within-session, short-term activation changes are seen when there is an earlier short period of training with the specific movement sequence immediately before the scanning session.

Prenomotor cortex activation changes are seen with a random movement sequence, as well as with the training sequence, implying that activity changes in this region are not specific for learning a particular sequence. They may relate to more general aspects of skill acquisition for this type of task. In contrast, the prefrontal and parietal changes appear specific for the sequence being learned and are attenuated by prior exposure to the sequence. Greater activation in the prefrontal cortex during an initial learning period also has been reported in other studies in which subjects learn new motor sequences (see e.g., Jenkins et al. 1994) and may be involved in the acquisition or encoding of explicit knowledge of the task (Hazeltine et al. 1997). Further evidence that the prefrontal cortex is involved in learning characteristics of specific action plans, rather than the task more generally, comes from studies showing that patients with prefrontal lesions are unimpaired on a tracking task which does not involve learning a specific sequence of movements (Gomez Beldarrain et al. 2002).

As described in previous reports, short-term learning also involves increased activity in the cerebellar dentate region, the thalamus, and the putamen (Doyon et al. 1996, 2002; Jueptner et al. 1997a; Nezafat et al. 2001). These subcortical activation changes are specific for a particular movement sequence and may be a critical element in development of greater movement automaticity with short-term learning. Evidence for the importance of the cerebellum in motor learning has been provided in both lesion (Baizer et al. 1999; Doyon et al. 1997, 1998) and imaging (Doyon et al. 2003) studies. Muscimol inactivation in the dentate nucleus impairs performance of a learned, but not a novel sequence (Lu et al. 1998). The basal ganglia, thalamus, and cortex are linked in multiple anatomical loops (Alexander et al. 1986), which have been shown to be important for motor skill learning (Nakahara et al. 2001). The activation changes seen in the putamen and thalamus are consistent with the notion that cortical and subcortical structures function in an integrated circuit to achieve greater motor control with learned movements.

With extended practice of a motor sequence and long-term learning, there is an increase in activation in the primary sensorimotor cortex contralateral to the trained hand. Both the observations here and from a previous study (Karni et al. 1995) show that this activation change is specific for the motor sequence learned. A potential confound to interpretation of the earlier report of this phenomenon is that there were changes in performance with the long-term learning (Karni et al. 1995). Changes in performance can be associated with altered brain activation independent of learning. In our paradigm, although the accuracy of tracking increased during learning, the timing and force generation in the isometric task were unchanged. This is an important aspect of the experimental design. Increased motor cortical activation is associated with increased force production (Dettmers et al. 1995). We therefore can more unequivocally interpret the increases in activation seen in this study in terms of brain functional changes independent of changes in motor performance.

By analogy to electrophysiologically mapped changes with skill learning in nonhuman primates, we interpret these cortical activation changes as evidence for representation of the specific movement pattern in the primary motor cortex (Nudo et al. 1996). However, somatosensory feedback also is important in motor task learning (Asanuma and Pavlides 1997; Kaelin-Lang et al. 2002; Pavlides et al. 1993). The somatosensory cortex is a major source of afferents to the primary motor cortex (Asanuma et al. 1968). The observation of increased primary somatosensory cortical activation in a region consistent with representation of hand movements (Kleinschmidt et al. 1997) is consistent with the notion that the full movement representation involves both somatosensory and motor cortex.

The motor cortex is anatomically connected to the subcortical nuclei by the motor basal ganglia loop, which projects between the motor and premotor cortex and the posterior putamen (Alexander et al. 1986). Increases in activation in both
the motor cortex and putamen after long-term training in the task suggest that this motor loop becomes more active after a motor sequence is practiced extensively. An important aspect of the task used in this experiment was that it was isometric and that all sequences demanded activation of the same muscle groups. Sequences differed in relative timing and magnitudes of force generation. While there is compelling evidence that force may be encoded in the primary motor cortex (Dettmers et al. 1995; Georgopoulos et al. 1992; Thickbroom et al. 1998), timing of movements particularly involves processing within subcortical structures. The putamen specifically has been implicated in processing movement timing (Lewis et al. 2004; Nenadic et al. 2003; Thaut 2003). Increased activation in the motor cortex–putamen circuit described here may mediate the distinctions in motor activation timing critical to encoding the movement sequences. Previous work also has concluded that the striatum has a role in the long-term storage of well-learned movement sequences (Doyon and Ungerleider 2002) and that cortical–subcortical networks are involved in “automatic” movements (Floyer-Lea and Matthews 2004).

In summary, our observations extend previous work to suggest that distinguishable functional brain networks are recruited during fast, short-term and slower, long-term motor learning. Novel task performance is associated with prominent prefrontal and parietal activation. In early short-term learning, improvement in task performance and development of automaticity (Floyer-Lea and Matthews 2004) seems to be mediated in part by plasticity, allowing increased activity in a subcortical circuit including the cerebellar dentate, thalamus, and putamen. Long-term learning is associated with distinct functional changes consistent with plasticity in the primary somatosensory and motor cortex that increases representation for the specific movement sequence learned and with the increased activation of the motor cortical–basal ganglia loop, which encompasses the putamen. The observation of changes in both somatosensory and motor cortex suggests the importance of afferent feedback to this form of predominantly implicit motor learning. Fast, short-term and slow, long-term motor learning are likely to be mediated by at least partially distinct mechanisms of plasticity.

GRANTS

P. M. Matthews thanks the Medical Research Council (United Kingdom) for personal and program grant support. A. Floyer-Lea gratefully acknowledges a Wellcome Trust postgraduate studentship.

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