Lateralization of Cerebral Blood Flow Velocity Changes During Cognitive Tasks
A Simultaneous Bilateral Transcranial Doppler Study

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Background and Purpose—Transcranial Doppler ultrasonography (TCD) permits the assessment of cognitively induced cerebral blood flow velocity (BFV) changes. We sought to investigate the lateralization of BFV acceleration induced by a variety of cognitive tasks and to determine the influence of age, gender, IQ, and quality of the performance on the relative BFV changes.

Methods—Simultaneous bilateral TCD monitoring of BFV in the middle cerebral arteries (MCAs) was performed in 90 normal right-handed volunteers during 13 verbal and visuospatial tasks and their preceding rest periods.

Results—All tasks induced a significant bilateral BFV increase in the MCAs compared with the preceding rest periods. Five verbal tasks showed a significant left-hemispheric BFV acceleration. Linguistic tasks that required active or creative processing of the verbal stimuli, such as sentence construction or word fluency, elicited the most asymmetric response. Five visuospatial tasks revealed a significant right-hemispheric BFV shift. Paradigms that combined visuospatial attention and visuomotor manipulation showed the most lateralized acceleration. Older volunteers (aged >50 years) showed higher relative BFV changes, but lateralization was not influenced by age. Gender, IQ, and performance quality did not reveal significant effects on BFV change.

Conclusions—Bilateral TCD is a noninvasive technique that has the potential to connect the particular change in flow pattern of the MCA distribution with selective cognitive activity and thus offers specific functional information of scientific and clinical value. (Stroke. 1999;30:2152-2158.)

Key Words: blood flow velocity • cognition • neuropsychological tests • ultrasonography, Doppler, transcranial

Transcranial Doppler ultrasonography (TCD) is a noninvasive diagnostic tool with high temporal resolution that allows a continuous and bilateral monitoring of blood flow velocity (BFV) of the basal cerebral arteries. Functional TCD (fTCD) research examines BFV changes during the performance of mental tasks. There is growing evidence to support the hypothesis of a relationship between mental activity and BFV measured by TCD and that BFV is more rapid when subjects engage in cognitive activities compared with rest periods.1–17 Evidence has accumulated that the diameter of the large cerebral arteries does not change significantly under a variety of physiological stimuli.18–22 Assuming that the diameter of the basal cerebral arteries remains unchanged with time, BFV changes under successive mental conditions are necessarily related to volume flow changes. Hence, changes in cerebral BFV reflect changes in cerebral metabolism due to cerebral activation.

The aim of the present study is to investigate the change in the flow pattern of the MCA distribution during 13 mental tasks selected to induce lateralized cognitive activity and metabolic demand. Tasks with high lateralizing power are of interest to fundamental and clinical research and may even be useful for the individual patient.10 Because the MCA carries approximately 80% of the flow volume received by the cerebral hemisphere23 and is very easy to monitor by TCD in most patients, we have focused on this artery. In addition, we will evaluate the influence of demographic variables and quality of performance on BFV changes.

Subjects and Methods

Subjects
Ninety normal volunteers (38 men and 52 women; mean±SD age 36±13.3 years, range 18 to 62 years) participated in the study. All subjects were right-handed, as measured by the Edinburgh Handedness Inventory (Laterality Index, mean±SD 90.2±15.9%).24 A Dutch version of the National Adult Reading Test25 measured a mean±SD IQ of 102±7.6. The mean±SD years of education was 13.8±2.3). State anxiety was measured by the Dutch version of the Spielberger State Anxiety Questionnaire, which showed low-state anxiety scores in all subjects (mean±SD 30.3±5.4).26 None of the subjects took psychoactive medication, had an active medical disease, or had a history of cardiovascular, neurological, or psychiatric disorders. They all refrained from drinking caffeine-containing beverages or smoking for at least 12 hours before the study. All
Flemish-Dutch speaking subjects had normal or corrected-to-normal vision and were experimentally naïve about TCD procedures. No reading disorders were reported. In 11 additional subjects, TCD measurement was not possible because of an insufficient signal through the temporal bone window.

TCD Apparatus
A commercially available 2-MHz pulsed-wave TCD unit (Multidop X2 hardware, DWL version 2.53j of TCD 7 software, DWL Elektronische systeme GmbH) continuously and simultaneously monitored BFV of the MCA. Two dual 2-MHz transducers, fitted on an elastic headband (DWL 4038) and placed on the left and right temporal skull window, transmitted the ultrasonic signal and received the echoes. Details of the insonation technique, and the correct insonation of the MCA have been described elsewhere.27 Starting from an insonation depth of 50 mm, depth and angles of insonation were adjusted to obtain the highest signal intensity of the M1 segment of the MCA (insonation depth ranged from 42 to 56 mm). The outline or envelope of the velocity spectrum and mean maximal BFV were calculated by the standard algorithm implemented on the instrument with use of a fast Fourier transform. The TCD unit allowed continuous-wave Doppler recording of the intracranial artery with online calculation of mean flow velocity in centimeters per second.

Procedure
All tests were performed in a quiet room without any visual or auditory stimulation and with illumination held constant. The subjects were seated in a comfortable chair in front of a computer screen. The basic principles of the equipment and the general design of the study were explained to promote a relaxed atmosphere and reduce possible anxiety. After written informed consent was obtained, demographic data were noted, and the Edinburgh Handedness Inventory and the Spielberger State Anxiety Inventory were as- sessed. The 2 TCD probes were fixed over the left and right temporal regions of the subject’s head and adjusted to obtain optimal signals. Blood pressure, respiratory rate, hematocrit, or end-tidal CO2 were not monitored. There is ample evidence that these variables do not change in a significant way during the course of the experimental procedure.2,7,14–16 Following an initial 6-minute rest phase, subjects were confronted with 6 verbal and 7 visuospatial tasks, most of which were presented on a computer screen. All tasks were performed in 1 session of approximately 1.5 hours. The order of the tasks was rotated from subject to subject, thus beginning with a different task each time without changing the remainder of the sequence. The nature of each task was explained and the subjects were familiarized with the task requirements by means of 2 practice items. Each activation condition lasted 120 seconds. The subjects were instructed to work as accurately as possible. The speed of the stimulus presentation was individualized to reduce frustration with stimulus pacing (either too slow or too fast) and to maximize the individual’s mental activity. As soon as the subjects gave a response, the next item was shown. To obtain a stable measurement during activation, only the middle 60 seconds of each 120-second activation condition were used to determine the mean BFV for that task. Each activation phase was preceded by a 120-second rest period. During the 120-second rest periods, subjects were asked to look at an illuminated blank computer screen, to relax and breathe regularly without falling asleep, and to “think of nothing.” They were not allowed to move or speak, nor were they spoken to. The first 60 seconds of each rest period served as a recovery period in which posttask activation could subside.3 Only the last 60 seconds of the rest period served as the baseline measurement for the subsequent activation phase.

Cognitive Tasks
We selected cognitive tasks that had demonstrated potential for lateralized cognitive activity (and lateralized hemodynamics) in previous functional imaging or TCD research. In addition, we also added some tasks that have never been used in this research before.

The order in which the tasks are described represents the sequence presented to the first volunteer.

(1) Reading. Subjects were instructed to read a list of 50 words aloud. The list was a Dutch version of the National Adult Reading Test.25 Because the entire list had to be read (and scored), this task was of variable duration.

(2) Verbal Similarities (List). Subjects were requested to select those 2 words from a list of 6 that belong to a close superordinate semantic category (eg, reckless, crucial, obliging, dynamic, profitable, energetic). Subjects had to indicate their choice on the computer screen by pointing out the words with both index fingers simultaneously to avoid unilateral activation of the motor cortex.

(3) Visuospatial Design Comparison. This task involved the comparison of very similar complex molecule-like designs (Figure 1a). Subjects had to detect subtle differences between 2 designs and had to indicate these with both index fingers simultaneously.

(4) Syntactic Sentence Construction. The words of a sentence were shown in a mixed-up order. Subjects were asked to whisper a grammatically correct sentence using as many words as possible (eg, radio-exploited-this-in-1-the-station-morning-the-heard-had-a-on-that-bomb). Whispering minimizes the acoustic interference on the TCD signal by preventing voice artifacts caused by the conduction of the normal voice spectrum via the cranial bones to the temporally placed probes.

(5) Visuospatial Cube Construction. Simple to complex diagrams of unfolded cubes were presented (Figure 1b). One of the ribs was marked with an asterisk; letters marked 5 other ribs. Subjects were requested to refold the cube in their imagination and decide on which rib (letter) the asterisk would touch by indicating the answer with both index fingers simultaneously.

(6) Verbal Similarities (Pairs). Subjects were asked to decide whether 2 simultaneously presented nouns were semantically similar (eg, tarry-linger) or different (eg, reputation-concentration). They responded by pressing a button held in the left hand (different) or right hand (similar) that activated a red or green light, respectively. Left- and right-handed responses were balanced over the 2-minute period to avoid disproportionate activation of 1 motor cortex.

(7) Mental Rotation (Alphanumeric). This task was based on previous positron emission tomography research.28 Alphanumeric stimuli were presented in either “normal” or “backward” (ie, mirror image) form. The stimuli were also presented in 1 of 3 orientations: 120°, 180°, and 240°. Subjects had to decide whether the stimulus was shown in its normal or backward (mirror) form (Figure 1c). The subjects responded by pressing hand-held buttons (cf verbal similarities [pairs], above).

(8) Syntactic Sentence Comparison. Pairs of sentences differing only in syntactic complexity (eg, active versus passive voice) were presented. Subjects had to indicate whether the sentences were either semantically identical (eg, He entered the room when almost everybody was gone/Almost everybody was gone when he entered the room) or semantically different (eg, She writes him a letter/The letter to her has been written by him). The subjects responded by pressing hand-held buttons (cf verbal similarities [pairs], above).

(9) Mental Rotation (Figures). Two identical typographic symbols or simple line drawings of hand positions were presented on the screen (Figure 1 d). The stimulus on the left was always presented in a “normal,” upright position. The stimulus on the right side was presented in 1 of 3 orientations (120°, 180°, or 240°) and in either its “normal” orientation (ie, identical to the left stimulus) or as a mirror image of the left stimulus. Subjects had to decide whether the right figure was shown in its normal or backward form. The subjects responded by pressing hand-held buttons (cf verbal similarities [pairs], above).
Word Fluency. The subjects were required to produce as many words as possible (excluding proper names) beginning with a designated letter that was presented in the center of the screen. The letters N, A, K, and P were shown for 30 seconds each. The subjects were instructed to whisper the words to minimize acoustic interference with the TCD signal.

Visual Searching. The task consisted of finding a grid pattern (out of 24 similar designs) that matched the one in the center of the screen and is part of the Fepsy computer program for neurocognitive assessment. Subjects had to point to the identical grid with both index fingers simultaneously.

Computer Game. The task consisted of a commercially available computer game (Monster Truck Madness, version 1.00 TV 4, Microsoft). Subjects used a steering wheel and pedals to drive a car in a race circuit. Subjects were allowed a 2-minute drive regardless of speed or accuracy of the performance.

Three-Dimensional Puzzle. A commercially available 3D puzzle, illustrated in Figure 2, was used (Eureka bvba, 3D Puzzle). Subjects were allowed 2 minutes to try to free the ring from the game.

Tasks 1, 2, 4, 6, 8, and 10 are generally assumed to be processed predominantly by the left hemisphere and tasks 3, 5, 7, 9, 11, 12, and 13 by the right hemisphere.

Statistical Analysis
We calculated the average of all mean maximal BFVs over the last 60 seconds of the rest periods and the middle 60 seconds of the activation periods. We always used the immediately preceding rest period to determine the BFV change of the cognitive task under study. Because TCD cannot detect the difference between real asymmetries in BFV and differences caused by slightly different insonation angles, we calculated the relative increase from baseline to activation: \( \frac{(\text{BFV activation} - \text{BFV baseline})}{\text{BFV baseline}} \times 100 \). Data were analyzed by means of repeated-measures MANOVA. The quality of the task performance was expressed as the percentage of correct answers except for word fluency and syntactic sentence construction, in which the absolute number of words was taken into account.

Results
All tasks showed a bilateral increase in absolute BFV compared with their preceding rest phase (Table 1). Comparison of the relative changes indicated that the most marked increase occurred in the computer game task. The smallest BFV increase was observed in the syntactic sentence comparison task.

To evaluate the effect of lateralization, a repeated-measures MANOVA with side as within-subjects factor and gender (male/female), age (<30 years, <50 years, <65 years) and IQ (>1 SD below mean/mean ±1 SD/>1 SD above mean) as between-subjects factors was calculated. Relative changes were used as dependent variables. The MANOVA revealed a significant effect for side (Hotelling’s \( T^2_{13,61} = 15.09, P < 0.001 \)). Post hoc analyses with univariate F tests showed a significant lateralization for all tasks except visuospatial cube construction, verbal similarities (pairs), and mental rotation (alphanumeric) (Table 1). In decreasing...
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*Mean velocity values are given in cm/s (SD).
†Mean % change above baseline value (SD).
‡F value (df always 1, 77).
§Difference between left and right sides in % change.
order, syntactic sentence construction, word fluency, verbal similarities (list), reading, and syntactic sentence comparison showed a significant lateralization in favor of the left side. Again in decreasing order, the 3D puzzle, computer game, visuospatial design comparison, visual searching, and mental rotation (figures) showed a significant difference in favor of the right side.

We found no between-subjects effects for IQ or gender, although the effect of gender came close of reaching statistical significance, Hotelling $T^2_{1,126,5}=1.82, P=0.06$. Age appeared to be a significant between-subjects factor, Hotelling $T^2_{2,77,5}=2.27, P=0.002$. Post hoc univariate analyses of variance revealed that the differences between the 3 age groups were significant for syntactic sentence construction ($F_{2,77}=3.77, P=0.028$), visuospatial cube construction ($F_{2,77}=8.06, P=0.001$), verbal similarities (pairs) ($F_{2,77}=3.30, P=0.43$), mental rotation (alphanumeric) ($F_{2,77}=7.02, P=0.002$), syntactic sentence comparison ($F_{2,77}=1.58, P=0.06$), mental rotation (figures) ($F_{2,77}=3.71, P=0.029$), visual searching ($F_{2,77}=4.94, P=0.01$), and the computer game ($F_{2,77}=5.21, P=0.008$). Closer inspection of the data showed that the relative increase in BFV was always the highest in the eldest age subgroup ($\geq 50$ years). The age $\times$ side interaction effect was not significant. The mean BFV over the entire experiment (average of 13 rest and 13 task conditions of both hemispheres (pairs) ($F_{2,77}=1.36, P=0.22$), verbal similarities (pairs) ($F_{2,77}=3.30, P=0.43$), mental rotation (alphanumeric) ($F_{2,77}=7.02, P=0.002$), mental rotation (figures) ($F_{2,77}=3.71, P=0.029$), visual searching ($F_{2,77}=4.94, P=0.01$), and the computer game ($F_{2,77}=5.21, P=0.008$).

The quality of the task performance was generally high, with a mean of 78.4% (SD 21.8) correct answers for verbal similarities (list), 57.7% (SD 16.5) for design comparison, 66.5% (SD 27) for cube construction, 92.3% (SD 6.9) for verbal similarities (pairs), 92.4% (SD 8.2) for mental rotation (alphanumeric), 91% (SD 12) for sentence comparison, 90.2% (SD 9.5) for mental rotation (figures), and 93.4% (SD 8.5) for visual searching. During the sentence construction task an average of 38 words (SD 16) were correctly linked up, and during word fluency an average of 33 words (SD 9) were generated. We used Pearson correlations to evaluate the association between BFV change, IQ, and quality of performance. We used a significance level of 0.01 to take the multiple correlations into account. Because no objective score could be obtained for the computer game task and the 3D puzzle, these tasks were not included in the analysis of performance quality. No significant relationship was found between left and right BFV changes and quality of performance. IQ was significantly associated with quality of performance (except for visuospatial cube construction, mental rotation figures, and visual searching). No significant association was obtained between BFV change and IQ.

Discussion

In right-handed subjects, the prediction is that the left hemisphere is dominant for linguistic functions whereas the right hemisphere would be more involved in nonlinguistic or visuospatial functioning. In general, FTD research has confirmed a marked left-hemispheric lateralization for language functioning.

The strongest left-hemispheric BFV lateralization was elicited by a syntactic sentence construction task. A lesser, although still significant, left-sided asymmetry was found in another grammatical task that required the comparison of sentences. This finding is in agreement with the results on a similar syntactic sentence comparison task used by Rihs et al.

Significant left-hemispheric BFV lateralization of word fluency tasks in right-handed subjects has been reported repeatedly. Only Harders et al. failed to find a significant lateralization for this task. The fact that 34% of Harders’ subjects were left-handed may have obfuscated the outcome.

The significant left-sided lateralization of our verbal similarities (list) task is in agreement with the results on a similar task used by Hartje et al and Bulla-Hellwig et al who found a significant and close to significant left-hemispheric lateralization respectively. Our verbal similarities (pairs) task, however, failed to reach significance although a trend toward left-hemispheric lateralization was observed ($P=0.06$). This finding is in agreement with previous results on a similar (paired) synonym task, where a BFV shift to the left was observed that just failed significance from the lateralization observed during baseline.

The significant left-hemispheric lateralization of our reading aloud task is in line with the results of Droste et al and Rihs et al. Both studies found a tendency toward left-sided lateralization in relatively smaller samples of right-handed subjects ($n=28$ and $n=14$, respectively). Again, Harders et al failed to find any lateralization for this task in a larger ($N=70$), but mixed handedness group.

To summarize the research on verbal paradigms, it appeared that the magnitude of the left-sided lateralization was the greatest for linguistic tasks that required more active or creative processing of the verbal material, such as constructing a sentence with given words or retrieving words that begin with a designated letter. Tasks that merely required comparison of verbal stimuli (even if these stimuli were of a syntactic nature) or depended on well-learned automatic processing, such as reading, showed a lesser though still significant lateralization. If the semantic task became too simple, such as judging whether a pair of words were synonyms, the lateralization effect failed to reach significance.

The alleged right-hemispheric BFV lateralization for nonverbal visuospatial tasks is generally considered to be less straightforward. In our study, however, only 2 of 7 visuospatial tasks failed to show a significant right-hemispheric effect.

Lesion studies have provided conflicting evidence regarding hemispheric specialization for mental rotation. Positron emission tomography (PET) research with a task requiring mental rotation of alphanumeric stimuli found a regional cerebral blood flow increase in the right and left temporoparietal regions. These authors suggested that activation of the right posterosuperior parietal cortex and the bilateral posterior temporal cortex reflected the recognition of (transformed) visual patterns, whereas activation of the left inferior parietal lobe and the right head of the caudate nucleus reflected the mental rotation of the stimuli. A similar task in our study (mental rotation (alphanumeric)) showed a significant increase in BFV but no significant lateralization. These data suggest that both hemispheres are symmetrically
involved in this task. In contrast, our second mental rotation task, which used simple pictures or typographic symbols and required actual comparison with the “upright” stimulus (instead of comparison against a remembered stimulus), showed a significant right-hemispheric BFV asymmetry. Perhaps the stronger visuo-perceptual demand of this task was responsible for the significant right-hemispheric BFV shift. In other fTCD research, a similar task requiring the mental rotation and comparison of visual figures failed to find an asymmetry in MCA blood flow acceleration in a smaller right-handed sample, although a trend toward a right-hemispheric asymmetry was observed.6 In view of the current disagreement with regard to the hemispheric representation of the processes of mental rotation and visualization90–41 and in view of the low spatial resolution of fTCD data, mental rotation tasks appear not to be the method of choice for eliciting a robust right-hemispheric lateralization in BFV.

A second visuospatial task that failed to show the expected right-hemispheric lateralization was our cube construction task. Despite the fact that the task required the mental manipulation of a complex visual image, a significant right-hemispheric asymmetry was not obtained. Here, too, the fact that no significant lateralization could be induced may be interpreted in favor of a complex and bilateral hemispheric activation in the mental manipulation of visual stimuli.

The significant right-hemispheric asymmetry elicited by the visual searching task is in agreement with a similar task used by Hartje et al48 and Bulla-Hellwig et al.1 Both studies found a significant right-hemispheric MCA blood flow acceleration in what they defined as a typical example of a perceptual speed test. We also found a significant right-hemispheric effect in a design comparison task. Again, this is a task that requires visual attention and perceptual speed. Its significant right-hemispheric activation is in agreement with the hypothesis of a dominant right-hemispheric role in (at least visual) attention that has been illustrated in PET42 and TCD research.9

The most asymmetric right-sided BFV shift in our study was elicited by a computer game and a 3D puzzle. In contrast to the other visuospatial tasks that required a simple (bilateral) motor response, the motor manipulation of steering wheel and 3D puzzle were much less under experimental control and could have resulted in a predominant left-hemispheric motor cortex activation in right-handed subjects, thus masking an expected right-hemispheric acceleration for these visuomotor tasks. This was not the case, and both tasks showed a strong and highly lateralized right-hemispheric activation that was probably due to the visuospatial, visuomotor, and attentional demands of these tasks. Kelley et al7 used a computer game that just failed to find a right-hemispheric BFV shift (P<0.10). However, the study consisted of a smaller sample (n=21), including 5 ambidextrous subjects and 1 left-handed subject, and the game was played with a joystick held in the left hand and manipulated by the right hand. These methodological differences might explain the nonsignificant finding in this study. To our knowledge, 3D puzzles have never before been used in TCD research.

We conclude from these data that paradigms which combined visuospatial attention and visuomotor manipulation showed a strong bilateral BFV increase and elicited the most asymmetric right-hemispheric blood flow acceleration. Tasks that required the mental rotation of visual stimuli appeared to activate both hemispheres more symmetrically and reduce the lateralization effect that can be measured through TCD.

The decrease of CBF and absolute BFV with age has frequently been reported.3,4,7,43–46 This was also the case in our study, in which overall mean absolute BFV significantly decreased with increasing age. In contrast, all tasks elicited a higher percentage in BFV change from rest to mental activation in older people compared with younger. This age effect on relative BFV change was significant in 8 of the 13 tasks. Similar findings in 2 of 6 tasks have been reported elsewhere.3 The nonsignificant side×age interaction effect indicated that despite higher relative BFV reactivity, the effects of lateralization remained constant over the age groups. Interpretation of these findings remains to be determined.

Most previous studies failed to obtain (or report) data on the qualitative performance of their subjects, although a possible relationship with BFV has been hypothesized.15 One of the main reasons for not obtaining data on performance quality was that subjects were often not allowed to communicate their answers during the activation phase. Verbal or motor responses were believed to interfere with and mask lateralization effects or to influence the Doppler signal. Because we wanted to evaluate the relationship between performance quality and BFV and because we believed that communication of answers after the trial is of rather questionable reliability, we assessed our subjects’ responses during activation. In most tasks, subjects were instructed to give a bilateral motor response to avoid lateralized activation of one motor cortex. During the reading task subjects were instructed to read the words aloud, whereas during syntactic sentence construction and word fluency, subjects were instructed to whisper their answers. Reading aloud did not interfere with the visual Doppler spectrum and showed the expected left-hemispheric lateralization. A similar observation was made for the tasks in which the responses had to be whispered. This is in contrast with the belief that the production of speech sound (whether whispered or spoken aloud) might cloud potential lateralization effects15 because it involves larger bilateral areas of the brain.47 Although we managed to evaluate the actual performance quality for most tasks, no significant relationship was found between quality of performance and BFV change. In addition, no association was found between BFV change and IQ.

Our results demonstrate that bilateral TCD of the MCA is sufficiently sensitive to simultaneously compare the BFV response of the 2 hemispheres during various cognitive tasks. In general, our findings agree with present neuropsychological theories of hemispheric lateralization for cognitive functions and with the findings of fTCD research. Our data further suggest that left-hemispheric lateralization can best be elicited by linguistic tasks that require active or creative processing of the verbal material. Right-hemispheric lateralization appeared most readily in tasks that combined visual attention and visuomotor manipulation. Finally, we found no relationship between performance quality and BFV change, which implies that the sheer process of trying to solve a specific task...
activates specific brain regions regardless of whether the final response is correct or not. Further evaluation and refinements of tasks that show important hemispheric asymmetries in BFV are warranted. This research can contribute to our understanding of hemispheric specialization, it can serve as an inexpensive testing ground for new and promising cognitive paradigms, and it can be used, after further refinement of the experimental paradigms and validation against other techniques, as a noninvasive clinical tool to determine hemispheric dominance in the individual patient.

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References


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