The first objective of the study was to determine whether functional magnetic resonance imaging (fMRI) signal was correlated with motor performance at different stages of poststroke recovery. The second objective was to assess the existence of prognostic factors for recovery in early functional MR images. Eight right-handed patients with pure motor deficit secondary to a first lacunar infarct localized on the pyramidal tract were included. This study concerned moderately impaired patients and recovery of handgrip strength and finger-tapping speed. The fMRI task was a calibrated flexion-extension movement. Ten healthy subjects served as a control group. The intensity of the activation in the "classical" motor network (ipsilesional S1M1, ipsilesional ventral premotor cortex [BA 6], contralesional cerebellum) 20 days after stroke was indicative of the performance (positive correlation). The cluster in M1 was posterior and circumscribed to BA 4p. No area was associated with bad performance (negative correlation). No correlation was found 4 and 12 months after stroke. Prognosis factors were evidenced. The higher early the activation in the ipsilesional M1 (BA 4p), S1, and insula, the better the recovery 1 year after stroke. Although the lesions partly deafferented the primary motor cortex, patients who activated the posterior primary motor cortex early had a better recovery of hand function. This suggests that there is benefit in increasing ipsilesional M1 activity shortly after stroke as a rehabilitative approach in mildly impaired patients.

**Keywords:** fMRI, longitudinal study, motor recovery, prognosis, stroke

**Introduction**

The quality and speed of functional recovery after stroke is unforeseeable. The recovery of impaired behavioral functions is accompanied by brain reorganization, and identifying neurophysiological processes will lead to more suitable treatments. Neuroimaging techniques developed in the last decade have driven the hope of better understanding the mechanisms and the substrates of recovery and perhaps predicting recovery. Unfortunately, correlations between imaging data and clinical status have been difficult to evidence.

Crafton et al. (2003) demonstrated the contribution of functional magnetic resonance imaging (fMRI) compared with simple anatomical description of the injury volume and demonstrated that a "functional" map of the injury was more strongly correlated to behavioral outcome than the total infarct volume. The best recovery for paresis or aphasia seems to be achieved if the primary areas that are normally responsible for these functions regain functional activity (Calautti and Baron 2003; Fuji and Nakada 2003; Ward, Newton, et al. 2006). The current idea is that activations in the contralesional hemisphere or secondary sensorimotor areas are maybe maladaptive or at least less efficient than those in the healthy hemisphere (Fuji and Nakada 2003; Ward, Newton, et al. 2006).

For motor function, Loubinoux et al. (2003) demonstrated that best performance was associated with the activation of the "initial" sensorimotor network 5–6 weeks after stroke. Fuji and Nakada (2003) demonstrated 2 recovery processes in 46 patients with hemiparesis after thalamic, putaminal, or striato-capsular lesions. One process characterized by a reorganization of the ipsilesional SIM1 (primary sensorimotor cortex) was associated with successful recovery within 1 month. The other process involved the contralesional pathway and was correlated with slow recovery. Calautti, Leroy, Guincestre, Marie, and Baron (2001) demonstrated a shift toward the unaffected hemisphere that was inversely correlated to recovery over a few months in 5 patients with pyramidal tract lesions. More precisely, poor performance of the task has been demonstrated to be correlated with a bilateral activation of the primary sensorimotor cortex during the task (Weder et al. 1994). A follow-up study on 8 patients with first-ever corticospinal tract lacunes showed that the ratio of contralateral to ipsilateral sensorimotor activity increased significantly over time as the paretic hand regained function (Marshall et al. 2000). Finally, Small et al. (2002) found a correlation between the extent of activation and the amount of recovery in the contralesional cerebellum.

However, counterexamples of the latter hypothesis can be found. A shift of activation to homologous areas in the right hemisphere was correlated with improvement of aphasia (Thulborn et al. 1999). Interestingly, the role of the premotor cortex (PMC) in the contralesional hemisphere was clarified in a transcranial magnetic stimulation (TMS) study showing that its functional recruitment was greatest in the more impaired patients and represented a functionally relevant, adaptive response to the associated brain injury (Johansen-Berg, Rushworth, et al. 2002).

Therapeutic interventions may help to decide whether recruitment of the ipsilesional and/or the contralesional hemisphere would be efficient. Motor or language training as well as pharmacological treatments improved function in association with an overactivation or an enlargement of primary and secondary areas in the lesioned side (Liepert et al. 1998, 2000; Nelless et al. 2001; Pariente et al. 2001; Carey et al. 2002; Johansen-Berg, Dawes, et al. 2002; Leger et al. 2002; Tardy et al. 2006). However, rehabilitation-induced improvements associated with contralesional hemisphere targeting have been shown (Schaechter et al. 2002; Dechaumont et al. 2004; Kimberley et al. 2004).
Finally, fMR images seem to have a predictive value because early recruitment of the supplementary motor area and ipsilateral inferior BA 40 have been shown to positively correlate with better motor recovery (Loubinoux et al. 2003); whereas activation of the prefrontal cortex and parietal cortex in the contralateral hemisphere predicted a slower and worse recovery. Thus, instead of reasoning in terms of hemisphere, one should now consider each area by itself because each one may play a particular role in recovery. Such prognosis factors were evidenced with activations generated by a passive movement and for a group of patients suffering from a subcortical infarct involving the pyramidal tract and with a wide range of deficits (plegic to well-recovered patients). Thus, we wanted to know if correlations and prognosis factors could be found in a population of patients suffering from mild/moderate hand impairment and with activations coming from simple voluntary movements. We first described the longitudinal changes following a subcortical stroke in such patients compared with healthy subjects and mainly demonstrated that the deafferented primary motor cortex was less activated in patients just after the stroke and regained activity thereafter (Tombari et al. 2004). Beyond abnormalities, the aim of the present study was to explore which activation was crucial to recovery.

Patients and Methods

The study was performed with the approval of our local institutional human studies committees. All subjects gave written informed consent to the study.

Patients

Eight highly selected patients with pure motor hemiparesis (3 women and 5 men; mean age 62 ± 11 years; range 43-75 years) were prospectively included. All were right-handed according to the Edinburgh Handedness Inventory. Inclusion criteria were as follows: 1) age between 40 and 80 years, 2) pure motor hemiparesis secondary to a first acute subcortical infarct localized on the pyramidal tract (confirmation and location of stroke by MRI), and 3) patient able to perform a flexion-extension of the fingers of the affected hand. Exclusion criteria were as follows: 1) other major diseases, 2) sensory loss or cortical symptoms, 3) aphasia or neglect, 4) contraindication to MRI, 4) alcoholism or drug addiction, and 5) language or cognitive deficits sufficient to impair cooperation in the study. A description of the patients is provided in Table 1. Their lesions can be seen in Figure 1. Transcranial Doppler with particular examination of the carotid and vertebrobasilar arteries showed that none of the patients had critical stenosis of any arteries and of the right hand for the controls, with maximal opening (180°) position at each session. The kinematics did not vary across sessions. During "rest," subjects were told to relax (hand neither extended nor flexed) and not to think about finger movements with hypertension and 1 from diabetes mellitus.

All patients underwent daily standard rehabilitation according to Bobath's procedure during the first 2 or 3 weeks after stroke. A first fMRI session (E1) was performed 20 ± 9 days after stroke. The second and third fMRI sessions (E2 and E3) were performed 4 months and 12 months after stroke. At each time, patients underwent a complete neurological examination using validated neurological scales (NIH stroke scale, Motricity Index, Barthel Index, Trunk Control Test, Asworth Scale, and Somatosensory Scale) (Tombari et al. 2004).

Behaviors Evaluation of Recovery

Patients were asked to execute 3 different motor tasks: 9-peg hole test, grip strength (dynamometer), and finger-tapping test with both hands (the paretic hand and the healthy hand), 3 consecutive times each, at random, within 15 min.

The hand dynamometer test used an instrument that measured grip force in kilograms. The subject was allowed to position his/her arm as he/she liked, except that he/she could not bring the instrument or his/her arm into contact with his/her body. The elbow could be flexed or extended, as long as the subject felt that maximum force was obtained. The subject had to exert the strongest grip possible. In fact, the position was similar from one session to another.

The finger-tapping test consisted in tapping on a computer mouse with the index finger as many times as possible within 10 s and this test was performed 3 consecutive times.

The 9-peg hole test measured finger-hand coordination in terms of the time it took a subject to place 9 pegs in a 5 × 5-in. board and then to remove them. The pegs were placed in a container next to the board on the same side as the hand being tested. The subject was told to pick up the pegs one at a time, using one hand only, and to put them in the holes until all 9 were filled, and then to remove all the pegs, one at a time. The holes could be filled in any order.

Data were normalized with the mean value obtained for the healthy hand and averaged. They were further correlated with fMR images.

Healthy Subjects

Ten healthy right-handed subjects (7 women and 3 men; mean age 49 ± 7 years; range 41-63 years) with no history of neurological or psychiatric disease were recruited. Three fMRI examinations (E1, E2, and E3) were performed at intervals of 5 h and 2 months.

Task Paradigm

During each fMRI examination, one run was recorded. Subjects were instructed to keep their eyes closed. Their arms were restrained to prevent any movement of the shoulder, arm, or elbow. The paradigm consisted of eight 30-s epochs alternating between rest and activation, resulting in an acquisition time of 4 min. During "activation," the subjects performed an active 1-Hz auditory-cued motor task consisting of a flexion-extension of the fingers of the affected hand for the patients and of the right hand for the controls, with maximal opening (180°) if possible. The subjects opened all the digits and thumb from a fist to the neutral (180°) position at each session. The kinematics did not vary across sessions. During "rest," subjects were told to relax (hand neither extended nor flexed) and not to think about finger movements with

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age</th>
<th>Sex</th>
<th>Lesion</th>
<th>FT (mean)</th>
<th>Dynamometer (mean)</th>
</tr>
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<td></td>
<td></td>
<td></td>
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<td>Session</td>
<td>Session</td>
</tr>
<tr>
<td>1</td>
<td>64</td>
<td>M</td>
<td>Corona radiata</td>
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</tr>
<tr>
<td>2</td>
<td>43</td>
<td>F</td>
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<td>Left</td>
<td>40.8</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>M</td>
<td>Corona radiata</td>
<td>Left</td>
<td>32.6</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>M</td>
<td>Corona radiata</td>
<td>Right</td>
<td>24.6</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>F</td>
<td>Internal capsule-corona radiata-insula-basal ganglia</td>
<td>Right</td>
<td>2.6</td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>M</td>
<td>Brain stem</td>
<td>Left</td>
<td>28.0</td>
</tr>
<tr>
<td>7</td>
<td>71</td>
<td>F</td>
<td>Posterior limb of the internal capsule</td>
<td>Right</td>
<td>20.0</td>
</tr>
<tr>
<td>8</td>
<td>54</td>
<td>M</td>
<td>Internal capsule (posterior limb)—corona radiata-thalamus—lenticular nucleus</td>
<td>Left</td>
<td>22.0</td>
</tr>
</tbody>
</table>

FT, finger tapping.
their hand in the neutral position. All subjects were seen to comply with the task and the auditory pacing.

Data Acquisition and fMR Image Postprocessing

MRI was performed on a 1.5-T scanner (Siemens Vision, Erlangen) equipped for echo-planar imaging (EPI). Blood oxygen level-dependent (BOLD) imaging was performed using a $T_2^*$-weighted single-shot EPI sequence (time echo 60 ms, 90° flip angle, $64 \times 64$ field of view, $3.125 \text{ mm}$ in-plane resolution, 5 mm slice thickness). Sixteen slices (12 supratentorial + 4 centered on the cerebellum) were acquired every 3 s (Tombari et al. 2004).

Three patients had a right-hemispheric lesion, so their scans were flipped about the $y$ axis. Thus, all patients had the infarct on the “left” side of the brain. All images were realigned, coregistered, and resized into the space defined by the atlas of Talairach, and finally smoothed with a Gaussian kernel of full width at half maximum 7–10 mm.

Statistical Analyses of fMR Images

Cerebral Motor Activation (Main Contrasts)
The main effect of moving was assessed for each subject and each session (fixed-effect analysis). Data analysis was performed by modeling the voluntary and rest conditions as reference waveforms (boxcar functions). All images were inspected for evidence of misregistration (e.g., edge effects, rims of activity along the cortical surface, and absence of activity). Using image analysis and general linear model statistics (SPM99, random-effect module), single-subject contrasts were then moved into a second-level analysis (1-sample $t$-test) to create group maps ($P < 0.05$, extent threshold = 20 voxels) separately for both groups at each time point. Only changes in the activated areas obtained on group maps were considered for the following statistics (significant activated areas of the 1-sample $t$-test analysis specified as a mask with statistical parametric mapping software).

Correlation Analyses

We wanted to determine the relationship between individual BOLD response and motor function. We applied the same methodology as in our previous paper (Loubinoux et al. 2003) and, at each session E1, E2, and E3, performed a second-level correlation analysis at each time point separately using the simple regression model in SPM99: the individual beta parameters were correlated with the individual finger-tapping test performance taken as covariate of interest (random-effect model, regression analysis, $P < 0.025$; extent threshold = 20 voxels; masked with E1, E2, or E3 motor activation). Similarly, we correlated individual beta images at E1 (20 days after stroke) with performance at 1 year (E3) to find early prognosis factors. The same procedure was applied for the handgrip performance.

Results

Behavioral Study
Two patients could not perform the 9-peg hole test at E1. Individual data are given for the grip strength and finger-tapping test (Fig. 2, Table 1). The distribution of performance was similar for both tests. At E1, the level of performance ranged from low to high, giving a wide distribution. This gradient was still present at E2 and E3.

fMRI Motor Activation
The “classical” sensorimotor network was activated for the patient and the healthy subject groups despite differences in intensity (Fig. 3) (see Tombari et al. 2004 for details). No mirror movements were observed by visual inspection during fMRI scanning.
Correlation between fMRI Motor Activation and Motor Performance

At E1, among all activated areas (Fig. 3), the ipsilesional M1 (BA 4p) deep in the central sulcus, S1, ventral PMC (BA 6, ventral limb of the precentral sulcus between $z = 20$ and 35 mm), and the contralesional anterior cerebellum showed a positive correlation between intensity of activation and level of performance (Fig. 4). Negative correlations were not found. Similar maps were found with both hand dynamometer and finger-tapping performance.

Prognosis Factors

Correlation analyses of the fMRI individual activations at E1 with the motor performance at E3 revealed clusters in the ipsilesional M1 (BA 4p), S1, and the insula (positive correlation) (Fig. 5). Negative correlations were not found. To summarize, the higher the activation in the ipsilesional BA 4p, S1, and insula 20 days after stroke, the better the recovery 1 year later.

Figure 2. Individual motor performance at E1, E2, and E3 for the handgrip strength and the finger-tapping test.

Figure 3. Areas activated during the active movement task of the paretic hand at E1. Images of −20, 5, 40, and 45 mm under and above the anterior-posterior commissural plane are shown. Activations are overlaid on a healthy brain. The lesioned side is on the left of the image (radiological convention).
This work deals with recovery of hand function in patients who were homogeneous in terms of location of the lesion (on the cortico-spinal tract). They were moderately impaired a few weeks after stroke (finger tapping possible but their levels of deficit varied). In cases of capsular lesions, despite an appearance of normality in coarse movements, substantial deficits in the control of fine independent finger movement persisted. We demonstrated, through a positive correlation, that the level of activation in the classical cerebral hand network approximately 20 days after stroke was indicative of the hand performance level. Furthermore, we brought out prognosis factors indicative of the quality of the outcome. The higher the early activation in the ipsilesional BA 4p, S1, and insula, the better the recovery 1 year later. It was demonstrated that the hand had a representa-

tion in BA 4p, an area that seems more dedicated to somato-sensory guided movement than area 4a (Geyer et al. 1996). Thus, although the lesion partly deafferented the primary motor cortex, patients who could activate the posterior primary motor cortex early had a better recovery.

**Correlation Study**

**Positive Correlations**

The positive correlation found, 20 days after stroke, between the hand motor status and the fMRI activation in a part of the classical motor network involving the ipsilesional S1M1, ventral PMC, and the contralesional cerebellum means that no activation in these areas was associated with low performance and activation close to normal was associated with normal
It seems as if the partly deafferented S1M1 is able to ''reconnect'' itself, probably after 1) temporary and partial deafferentation or by 2) unmasking of existing but functionally inactive excitatory connections consecutive to decreased intra-cortical inhibition (Jacobs and Donoghue 1991), 3) change in neuronal membrane excitability, 4) increased efficacy of existing synapses, and/or 5) synaptic proliferation and axonal sprouting from surviving neurons confined to a range of a few millimeters, a small-scale plasticity that would operate rapidly.

Our results are consistent with previous neuroimaging studies that suggest a primary role for the ipsilesional S1M1 in recovery (Marshall et al. 2000; Fujii and Nakada 2003; Loubinoux et al. 2003; Ward, Newton, et al. 2006). In a previous study, we found a positive correlation between BA 4p activation generated by a passive task and hand motor status around 39 days after stroke (Loubinoux et al. 2003). At first sight, our results seem contradictory to those of Ward et al. (2003a) who found overactivation and negative correlation in the first month after stroke for M1 (BA 4a and 4p), whereas we found hypoactivation in BA 4a (Tombari et al. 2004). However, the present study included patients who were more impaired than those of Ward’s study since, for example, 2 of our patients could not perform the 9-peg hole test. Also, the tasks were different (grip strength compared with flexion-extension movement), which may be more relevant. Exerting a force that must be carefully adjusted to a percentage of maximal contraction may increase the difficulty and lead to overactivations in the most impaired patients and thus negative correlations between activations and motor performance (Ward et al. 2003a). Meanwhile, performing smooth movements at a slow pace is quite easy and may reveal hypoactivations in the deafferented M1 BA 4a (Tombari et al. 2004), which do not correlate with the level of deficit, and positive correlations with motor performance in a recruited part of M1, BA 4p, which would correspond to a functionally relevant recruitment. Moreover, in a recent study, the same authors, this time using the passive flexion-extension movement, found a positive correlation in BA 4p (Ward, Brown, et al. 2006) consistent with our present and previous results (Loubinoux et al. 2003).

The prominent role of the PMC in functional reorganization during recovery of lost function has been demonstrated in both humans and animals. The dorsal and ventral premotor areas accommodate corticospinal neurons (Dum and Strick 1991; He et al. 1993; Darian-Smith et al. 1999), giving rise to a cortical-reticulospinal route that is bilaterally organized (Liu and Rouiller 1999). In experimental S1M1 lesions in adult monkeys, transient inactivation (with the gamma-aminobutyric acid agonist muscinol) of dorsal and ventral PMCs of the damaged hemisphere suppressed the recovered manual dexterity of the affected hand (Liu and Rouiller 1999).

Small et al. (2002) found that the degree of motor recovery appeared to be related to brain activation in the contralesional cerebellum but not in the injured M1, with which this region has extensive connections. We found a correlation in both regions. There may be 2 explanations for this discrepancy: the way the data were processed (volume of activation for Small et al. or intensity of activation for the present study) and the heterogeneity of the patients’ lesions in Small’s study (3 cortical and 9 subcortical lesions), compared with only subcortical lesions in our study. Indeed, reorganization differs between cortical and subcortical stroke (Marshall et al. 2000; Calautti and Baron 2003). No Correlation

Patients recruited the primary motor cortex ipsilateral to the moving hand at E1. This cortex is not activated in healthy subjects (Tombari et al. 2004). It was not found in the correlation analyses. It follows that nothing was found about the efficacy of this recruited cortex in the present study. Its activation may be associated with good performance in some patients and bad performance in others. We personally deduce from our data that we cannot conclude today on the efficacy of the contralesional M1, which might depend on the individual or on lesion location.

Correlation analyses might evidence common processes among patients. However, individual strategies, even efficacious ones, cannot be revealed by such an approach.

Figure 5. (A) Areas where the intensity of activation 20 days after stroke (E1) correlates with finger-tapping motor performance at E3 (1 year after stroke). Activations are overlaid on a healthy brain. The lesioned side is on the left of the image (radiological convention). (B) Corresponding plots of the positive correlations between the individual β values and finger-tapping performance. The β values of the 10 healthy subjects at E1 are also given for the same coordinates.
No correlations were found 4 and 12 months after stroke. Again, our data differ from those of Ward et al. (2003b). We propose that the discrepancy arises from the different tasks used by each group as explained in Positive Correlations. To perform correlation analyses that are predictors of recovery, one must be careful to choose a task that is not heavily weighted by factors other than recovery—such as difficulty, effort, or attention. Our data are in accordance with those of Weder et al. (1994), who found it difficult to prove an unequivocal correlation in patients with subcortical infarcts and marked recovery of hand function seen 3-8 months after stroke. The absence of correlation may indicate that patients had established individual strategies at that time (Weiller et al. 1993). However, it is impossible to know whether these strategies are associated with good performance and whether they represent a well-adapted functional reorganization or maladaptive processes. Finally, our results are in accordance with the pattern of the curve of fMRI activation in stroke patients as summarized by Rijntjes et al. (2006). An early phase corresponds to a loss of signal and function, a second phase to an upregulation of the motor network (overactivations), and a chronic phase to a consolidation and “normalization” of activation. The very changing pattern of the activation in the intermediate part of the curve, which may occur more or less early among individuals depending on the timing of recovery, is in accordance with our results: positive correlations in the early phase and no correlation at 4 and 12 months.

Prognosis Factors

A normalized activation of the ipsilesional S1M1 approximately 20 days after stroke was predictive of a nearly normal performance in terms of finger-tapping speed or grip strength, 1 year after stroke. It has been shown that the degree of Wallerian degeneration can be detected as early as 2-3 weeks after stroke and may be useful to predict motor outcome in stroke patients (Watanabe et al. 2001). Our results also suggest a putative role of the insula in motor recovery. In the macaque, 3.5% of the corticospinal projections arise from the insular cortex. Parallel pathways mediating manual dexterity exist (Disbrow et al. 2000). Recruitment of the insular cortex has been previously described and was thought to represent a relay node of an accessory motor system in a compensatory mechanism (Chollet et al. 1991; Weiller et al. 1992; Dettmers et al. 1997; Calautti, Leroy, Guincestre, Baron 2001). Dettmers et al. (1997) demonstrated the involvement of the insula and showed a change from force-independent to force-correlated activations in these areas underlying their critical role in the reorganization processes. Redistribution of activity within the framework of a preexisting, modality-specific, parallel-acting network including bilateral, multiple primary task- or secondary task-related areas rather than any more radical substitution of function may constitute the dominant principle underlying recovery (Dettmers et al. 1997; Weiller et al. 1999).

In conclusion, most of the areas evidenced in the present correlation analyses (ipsilesional S1M1, ventral PMC, insula, and contralesional cerebellum) had hardly ever been pointed out before as indicators or predictors of recovery. This stresses the fact that groups of patients must be homogeneous in terms of location of the lesion even among purely subcortical lesions. Of course, before fMRI can be used to provide surrogate markers of recovery, such results must be confirmed in larger groups of patients and other types of lesion. From a rehabilitation point of view, if patients who are able to activate the ipsilesional primary motor cortex early experience a better recovery, this highlights the importance of establishing suitable rehabilitation procedures in the early phase of poststroke recovery. Additional experiments (TMS, transcranial direct current stimulation) will be needed to determine the exact role of the M1 (BA 4p) activation, which can have an inhibitory or excitatory role on hand function. Meta-analyses have shown that rehabilitation is more efficient in the early phase (<6 months) than the chronic phase (Ottenbacher and Jannell 1993; Kwakkel et al. 2004). However, rehabilitation studies in the postacute phase are sparse, and nothing is known about which interventions are beneficial, although it would be pertinent to take advantage of the enhanced brain plasticity, notably in this phase. The present study approaches the underlying mechanisms of recovery and suggests a benefit in enhancing the activation of ipsilesional M1 (BA 4p) early. This is consistent with pharmacological studies where one dose of mono-aminergic drug, either fluoxetine or methylphenidate, was able to transiently enhance activation and improve motor performance (Pariente et al. 2001; Tardy et al. 2006).

Notes

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