

# fMRI Seems Reliable for Brain Tumor Mapping

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Contributing Writer

NEW ORLEANS — Functional MRI seems to be a reliable, safe, and effective technique to guide preoperative planning of brain tumor resection from eloquent cortex when used in conjunction with intraoperative stereotactic guidance, according to Kristin Houseknecht.

One benefit of using functional MRI (fMRI) preoperatively is that surgeons can

avoid extensive intraoperative maneuvers such as awake craniotomy and cortical mapping.

“Awake craniotomy has the advantage of allowing real-time evaluation of function. However, there are unique intraoperative risks associated with awake craniotomy, and it also requires a willing and compliant patient,” noted Ms. Houseknecht, who is a fourth-year medical student at the University of South Florida, Tampa.

In this large series gathered as a retrospective chart review, 209 patients were identified who had undergone fMRI and then resective craniotomy under general anesthesia for either primary or secondary brain tumor in eloquent cortex between July 2002 and December 2005.

Postoperatively, 53% were neurologically stable, 30% showed neurologic improvement, and 17% experienced a decline in neurologic function.

Of those who had postoperative im-

pairment, deficits were transient in about 30% and permanent in 13%.

Most patients in this group recovered rapidly and were discharged from the hospital within 2 days.

Tumors were located in the frontal (31%), parietal (20%), and temporal (11%) lobes, mostly within a single lobe.

Pathologically, 34% of tumors were glioblastoma, 12% grade 3 glioma, and 7% grade 2 glioma, and in a large number of patients, the brain tumors were secondary to cancer in other regions.

About half of the group had presented with motor deficits, 8% had speech deficits, and 11% had cognitive problems. fMRI paradigms were chosen according to the function of the eloquent cortex in proximity to the brain tumor.

A test of foot flexion and extension or finger tapping was used to evaluate motor

**ADVERSE REACTIONS**  
PLAVIX has been evaluated for safety in more than 42,000 patients, including over 9,000 patients treated for 1 year or more. The clinically important adverse events observed in CAPRIE, CURE, CLARITY and COMMIT are discussed below.

The overall tolerability of PLAVIX in CAPRIE was similar to that of aspirin regardless of age, gender and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions.

Hemorrhagic: In CAPRIE patients receiving PLAVIX, gastrointestinal hemorrhage occurred at a rate of 2.0%, and required hospitalization in 0.7%. In patients receiving aspirin, the corresponding rates were 2.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for PLAVIX compared to 0.5% for aspirin.

In CURE, PLAVIX use with aspirin was associated with an increase in bleeding compared to placebo with aspirin (see Table 5). There was an excess in major bleeding in patients receiving PLAVIX plus aspirin compared with placebo plus aspirin, primarily gastrointestinal and at puncture sites. The incidence of intracranial hemorrhage (0.1%), and fatal bleeding (0.2%), were the same in both groups.

The overall incidence of bleeding is described in Table 5 for patients receiving both PLAVIX and aspirin in CURE.

Table 5: CURE Incidence of bleeding complications (% patients)

| Event  | PLAVIX (+ aspirin)* (n=6259) | Placebo (+ aspirin)* (n=6303) | P-value |
|--|------------------------------|-------------------------------|---------|
| Major bleeding †                                     | 3.7 ‡                        | 2.7 §                         | 0.001   |
| Life-threatening bleeding                            | 2.2                          | 1.8                           | 0.13    |
| Fatal  | 0.2                          | 0.2                           |         |
| ‡ 5 g/dL hemoglobin drop                             | 0.9                          | 0.9                           |         |
| Requiring surgical intervention                      | 0.7                          | 0.7                           |         |
| Hemorrhagic strokes                                  | 0.1                          | 0.1                           |         |
| Requiring intropes                                   | 0.5                          | 0.5                           |         |
| Requiring transfusion (≥ 2 units)                    | 1.2                          | 1.0                           |         |
| Other major bleeding                                 | 1.6                          | 1.0                           | 0.005   |
| Significantly disabling                              | 0.4                          | 0.3                           |         |
| Intraocular bleeding with significant loss of vision | 0.05                         | 0.03                          |         |
| Requiring 2-3 units of blood                         | 1.3                          | 0.9                           |         |
| Minor bleeding ††                                    | 5.1                          | 2.4                           | <0.001  |

\* Other standard therapies were used as appropriate.  
† Life threatening and other major bleeding.  
‡ Major bleeding event rate for PLAVIX + aspirin was dose-dependent on aspirin: <100 mg=2.6%; 100-200 mg= 3.5%; >200 mg=4.9%.  
§ Major bleeding event rates for PLAVIX + aspirin by age were: <65 years = 2.5%, ≥65 to <75 years = 4.1%, ≥75 years 5.9%  
¶ Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin: <100 mg=2.0%; 100-200 mg= 2.3%; >200 mg=4.0%.  
|| Major bleeding event rates for placebo + aspirin by age were: <65 years = 2.1%, ≥65 to <75 years = 3.1%, ≥75 years 3.6%.  
†† Led to interruption of study medication.

Ninety-two percent (92%) of the patients in the CURE study received heparin/LMWH, and the rate of bleeding in these patients was similar to the overall results.

There was no excess in major bleeds within seven days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (event rate 4.4% PLAVIX + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for PLAVIX + aspirin, and 6.3% for placebo + aspirin.

In CLARITY, the incidence of major bleeding (defined as intracranial bleeding or bleeding associated with a fall in hemoglobin > 5 g/dL) was similar between groups (1.3% versus 1.1% in the PLAVIX + aspirin and in the placebo + aspirin groups, respectively). This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytic or heparin therapy. The incidence of fatal bleeding (0.8% versus 0.6% in the PLAVIX + aspirin and in the placebo + aspirin groups, respectively) and intracranial hemorrhage (0.5% versus 0.7%, respectively) was low and similar in both groups.

The overall rate of noncerebral major bleeding or cerebral bleeding in COMMIT was low and similar in both groups as shown in Table 6 below.

Table 6: Number (%) of Patients with Bleeding Events in COMMIT

| Type of Bleeding                          | PLAVIX (+ aspirin) (N=2295) | Placebo (+ aspirin) (N=2291) | P-value |
|---|-----------------------------|------------------------------|---------|
| Major* noncerebral or cerebral bleeding** | 134 (0.6%)                  | 125 (0.5%)                   | 0.59    |
| Major noncerebral                         | 82 (0.4%)                   | 73 (0.3%)                    | 0.48    |
| Fatal                                     | 36 (0.2%)                   | 37 (0.2%)                    | 0.90    |
| Hemorrhagic stroke                        | 55 (0.2%)                   | 56 (0.2%)                    | 0.91    |
| Fatal                                     | 39 (0.2%)                   | 41 (0.2%)                    | 0.81    |
| Other noncerebral bleeding (non-major)    | 831 (3.6%)                  | 721 (3.1%)                   | 0.005   |
| Any noncerebral bleeding                  | 896 (3.9%)                  | 777 (3.4%)                   | 0.004   |

\* Major bleeds are cerebral bleeds or non-cerebral bleeds thought to have caused death or that required transfusion.  
\*\* The relative rate of major noncerebral or cerebral bleeding was independent of age. Event rates for PLAVIX + aspirin by age were: <60 years = 0.3%, ≥60 to <70 years = 0.7%, ≥70 years 0.8%. Event rates for placebo + aspirin by age were: <60 years = 0.4%, ≥60 to <70 years = 0.6%, ≥70 years 0.7%.  
Adverse events occurring in ≥2.5% of patients on PLAVIX in the CAPRIE controlled clinical trial are shown below regardless of relationship to PLAVIX. The median duration of therapy was 20 months, with a maximum of 3 years.

Table 7: Adverse Events Occurring in ≥2.5% of PLAVIX Patients in CAPRIE

| Body System/Event  | % Incidence (% Discontinuation) |                  |
|--|---------------------------------|------------------|
|  | PLAVIX (n=9599)                 | Aspirin (n=9586) |
| <b>Body as a Whole – general disorders</b>               |                                 |                  |
| Chest Pain   | 8.3 (0.2)                       | 8.3 (0.3)        |
| Accidental/Inflicted Injury                              | 7.9 (0.1)                       | 7.3 (0.1)        |
| Influenza-like symptoms                                  | 7.5 (<0.1)                      | 7.0 (<0.1)       |
| Pain   | 6.4 (0.1)                       | 6.3 (0.1)        |
| Fatigue  | 3.3 (0.1)                       | 3.4 (0.1)        |
| <b>Cardiovascular disorders, general</b>                 |                                 |                  |
| Edema  | 4.1 (<0.1)                      | 4.5 (<0.1)       |
| Hypertension   | 4.3 (<0.1)                      | 5.1 (<0.1)       |
| <b>Central &amp; peripheral nervous system disorders</b> |                                 |                  |
| Headache   | 7.6 (0.3)                       | 7.2 (0.2)        |
| Dizziness  | 6.2 (0.2)                       | 6.7 (0.3)        |
| <b>Gastrointestinal system disorders</b>                 |                                 |                  |
| Any event  | 27.1 (3.2)                      | 29.8 (4.0)       |
| Abdominal pain   | 5.6 (0.7)                       | 7.1 (1.0)        |
| Dyspepsia  | 5.2 (0.6)                       | 6.1 (0.7)        |
| Diarrhea   | 4.5 (0.4)                       | 3.4 (0.3)        |
| Nausea   | 3.4 (0.5)                       | 3.8 (0.4)        |
| <b>Metabolic &amp; nutritional disorders</b>             |                                 |                  |
| Hypercholesterolemia                                     | 4.0 (0)                         | 4.4 (<0.1)       |
| <b>Musculo-skeletal system disorders</b>                 |                                 |                  |
| Arthralgia   | 6.3 (0.1)                       | 6.2 (0.1)        |
| Back Pain  | 5.8 (0.1)                       | 5.3 (<0.1)       |
| <b>Platelet, bleeding, &amp; clotting disorders</b>      |                                 |                  |
| Purpura/bruise   | 5.3 (0.3)                       | 3.7 (0.1)        |
| Epistaxis  | 2.9 (0.2)                       | 2.5 (0.1)        |
| <b>Psychiatric disorders</b>                             |                                 |                  |
| Depression   | 3.6 (0.1)                       | 3.9 (0.2)        |
| <b>Respiratory system disorders</b>                      |                                 |                  |
| Upper resp tract infection                               | 8.7 (<0.1)                      | 8.3 (<0.1)       |
| Dyspnea  | 4.5 (0.1)                       | 4.7 (0.1)        |
| Rhinitis   | 4.2 (0.1)                       | 4.2 (<0.1)       |
| Bronchitis   | 3.7 (0.1)                       | 3.7 (0.1)        |
| Coughing   | 3.1 (<0.1)                      | 2.7 (<0.1)       |
| <b>Skin &amp; appendage disorders</b>                    |                                 |                  |
| Any event  | 15.8 (1.5)                      | 13.1 (0.8)       |
| Rash   | 4.2 (0.5)                       | 3.5 (0.2)        |
| Pruritus   | 3.3 (0.3)                       | 1.6 (0.1)        |
| <b>Urinary system disorders</b>                          |                                 |                  |
| Urinary tract infection                                  | 3.1 (0)                         | 3.5 (0.1)        |

**PLAVIX®**  
clopidogrel bisulfate tablets  
Rx only

**INDICATIONS AND USAGE**  
PLAVIX (clopidogrel bisulfate) is indicated for the reduction of atherothrombotic events as follows:  
• **Recent MI, Recent Stroke or Established Peripheral Arterial Disease**  
For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, PLAVIX has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.  
• **Acute Coronary Syndrome**  
-For patients with non-ST-segment elevation acute coronary syndrome (unstable anginal/non-Q-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG, PLAVIX has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.  
-For patients with ST-segment elevation acute myocardial infarction, PLAVIX has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke. This benefit is not known to pertain to patients who receive primary angioplasty.

**CONTRAINDICATIONS**  
The use of PLAVIX is contraindicated in the following conditions:  
• Hypersensitivity to the drug substance or any component of the product.  
• Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

**WARNINGS**  
• **Thrombotic thrombocytopenic purpura (TTP):**  
TTP has been reported rarely following use of PLAVIX, sometimes after a short exposure (<2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. (See **ADVERSE REACTIONS**.)

**PRECAUTIONS**  
General  
PLAVIX prolongs the bleeding time and therefore should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly gastrointestinal and intracranial). If a patient is to undergo elective surgery and an antiplatelet effect is not desired, PLAVIX should be discontinued 5 days prior to surgery. Due to the risk of bleeding and undesirable hematological effects, blood cell count determination and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment (see **ADVERSE REACTIONS**). In patients with recent TIA or stroke who are at high risk of recurrent ischemic events, the combination of aspirin and PLAVIX has not been shown to be more effective than PLAVIX alone, but the combination has been shown to increase major bleeding.

GI Bleeding: In CAPRIE, PLAVIX was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. In CURE, the incidence of major gastrointestinal bleeding was 1.3% vs. 0.7% (PLAVIX + aspirin vs. placebo + aspirin, respectively). PLAVIX should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients taking PLAVIX.

Use in Hepatically Impaired Patients: Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. PLAVIX should be used with caution in this population.

Use in Renally Impaired Patients: Experience is limited in patients with severe renal impairment. PLAVIX should be used with caution in this population.

**Information for Patients**  
Patients should be told that it may take them longer than usual to stop bleeding, that they may bruise and/or bleed more easily when they take PLAVIX or PLAVIX combined with aspirin, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking PLAVIX and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken.

**Drug Interactions**  
Study of specific drug interactions yielded the following results:  
Aspirin: Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by PLAVIX. PLAVIX potentiated the effect of aspirin on collagen-induced platelet aggregation. PLAVIX and aspirin have been administered together for up to one year.

Heparin: In a study in healthy volunteers, PLAVIX did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on inhibition of platelet aggregation induced by PLAVIX.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs): In healthy volunteers receiving naproxen, concomitant administration of PLAVIX was associated with increased occult gastrointestinal blood loss. NSAIDs and PLAVIX should be coadministered with caution.

Warfarin: Because of the increased risk of bleeding, the concomitant administration of warfarin with PLAVIX should be undertaken with caution. (See **PRECAUTIONS-General**.)

Other Concomitant Therapy: No clinically significant pharmacodynamic interactions were observed when PLAVIX was coadministered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of PLAVIX was also not significantly influenced by the coadministration of phenobarbital, cimetidine or estrogen.

The pharmacokinetics of digoxin or theophylline were not modified by the coadministration of PLAVIX (clopidogrel bisulfate).

At high concentrations in vitro, clopidogrel inhibits P-gp (2C9). Accordingly, PLAVIX may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, rosirox, fluvastatin, and many non-steroidal anti-inflammatory agents, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with PLAVIX.

In addition to the above specific interaction studies, patients entered into clinical trials with PLAVIX received a variety of concomitant medications including diuretics, beta-blockers, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, anti-diabetic agents (including insulin), thrombolytics, heparins (unfractionated and LMWH), GPIIb/IIIa antagonists, anti-epileptic agents and hormone replacement therapy without evidence of clinically significant adverse interactions.

There are no data on the concomitant use of oral anticoagulants, non study oral antiplatelet drugs and chronic NSAIDs with clopidogrel.

**Drug/Laboratory Test Interactions**  
None known.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**  
There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg.

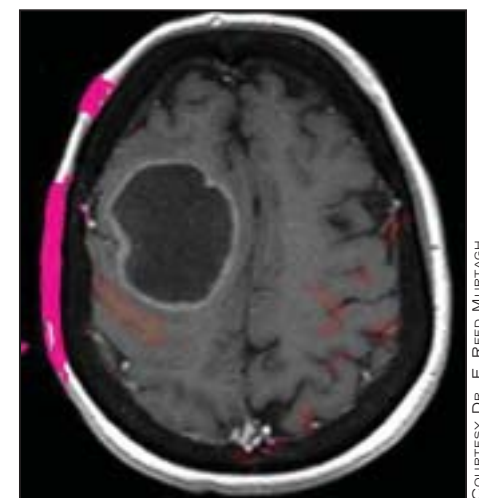
Clopidogrel was not genotoxic in four *in vitro* tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one *in vivo* test (micronucleus test by oral route in mice). Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m<sup>2</sup> basis).

**Pregnancy**  
Pregnancy Category B. Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day (respectively, 65 and 78 times the recommended daily human dose on a mg/m<sup>2</sup> basis), revealed no evidence of impaired fertility or fetotoxicity during clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, PLAVIX should be used during pregnancy only if clearly needed.

**Nursing Mothers**  
Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.

**Pediatric Use**  
Safety and effectiveness in the pediatric population have not been established.

**Geriatric Use**  
Of the total number of subjects in the CAPRIE, CURE and CLARITY controlled clinical studies, approximately 50% of patients treated with PLAVIX were 65 years of age and older, and 15% were 75 years and older. In COMMIT, approximately 58% of the patients treated with PLAVIX were 60 years and older, 26% of whom were 70 years and older. The observed risk of thrombotic events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Figures 3 and 6 for the CURE and COMMIT trials, respectively (see **CLINICAL STUDIES**). The observed risk of bleeding events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Tables 5 and 6 for the CURE and COMMIT trials, respectively (see **ADVERSE REACTIONS**).



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Right motor strip (red shading) activated when the patient moved her left hand; at 1 month post resection of lesion, the patient was neurologically stable.

cortex and a number counting paradigm was employed to test the speech cortex.

“The majority of patients were able to satisfactorily complete the fMRI paradigms,” Ms. Houseknecht said.

Intraoperative somatosensory evoked potential monitoring was used to confirm sensory and motor cortex in some patients.

“Currently most tumors in eloquent cortex are referred to tertiary or quaternary referral centers because traditionally these cases are treated with an awake craniotomy to minimize postoperative neurologic deficits,” according to Dr. Nicolas Arredondo, a neurosurgery chief resident at the University of South Florida and one of the coinvestigators of the study.

“These preliminary data suggest that with preoperative fMRI and meticulous surgical technique, comparable outcomes may be possible in some cases without all of the resources that are required to successfully perform an awake craniotomy,” he commented.

Since the close of the enrollment date for this study, several hundred more patients with brain tumors have undergone fMRI, Ms. Houseknecht said at the American Society of Neuroradiology annual meeting.

“These results are just the tip of the iceberg,” he said.



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