Current Literature
In Clinical Science

A MAP of Seizure-Freedom in Patients with a Normal MRI Scan

Voxel-Based Morphometric Magnetic Resonance Imaging (MRI) Postprocessing in MRI-Negative Epilepsies.

Wang ZI, Jones SE, Jaisani Z, Najm IM, Prayson RA, Burgess RC, Krishnan B, Ristic A, Wong CH, Bingaman W, Gonzalez-Martinez JA, Alexopoulos AV. *Ann Neurol* 2015;77:1060–1075.

OBJECTIVE: In the presurgical workup of magnetic resonance imaging (MRI)-negative (MR– or "nonlesional") pharmacoresistant focal epilepsy (PFE) patients, discovering a previously undetected lesion can drastically change the evaluation and likely improve surgical outcome. Our study utilizes a voxel-based MRI postprocessing technique, implemented in a morphometric analysis program (MAP), to facilitate detection of subtle abnormalities in a consecutive cohort of MR– surgical candidates. METHODS: Included in this retrospective study was a consecutive cohort of 150 MR– surgical patients. MAP was performed on T1-weighted MRI, with comparison to a scanner-specific normal database. Review and analysis of MAP were performed blinded to patients' clinical information. The pertinence of MAP+ areas was confirmed by surgical outcome and pathology. RESULTS: MAP showed a 43% positive rate, sensitivity of 0.9, and specificity of 0.67. Overall, patients with the MAP+ region completely resected had the best seizure outcomes, followed by the MAP– patients, and patients who had no/partial resection of the MAP+ region had the worst outcome ($p < 0.001$). Subgroup analysis revealed that visually identified subtle findings are more likely correct if also MAP+. False-positive rate in 52 normal controls was 2%. Surgical pathology of the resected MAP+ areas contained mainly non–balloon-cell focal cortical dysplasia (FCD). Multiple MAP+ regions were present in 7% of patients. INTERPRETATION: MAP can be a practical and valuable tool to: (1) guide the search for subtle MRI abnormalities and (2) confirm visually identified questionable abnormalities in patients with PFE due to suspected FCD. A MAP+ region, when concordant with the patient's electroclinical presentation, should provide a legitimate target for surgical exploration.

Commentary

New techniques and technologies are continually being developed to improve the process of epilepsy surgery evaluation, though very few catch on widely. Let us count the reasons:

1. The technique in question may not be widely available or widely reproducible.

2. The relevant finding, even if highly predictive, may be present only in a small subset of surgical patients, making it only marginally useful for the overall population.

3. The appropriate gold standard by which to evaluate such a technique is long-term surgical outcome; as a consequence, it takes many years to accumulate and follow a large enough group of patients to demonstrate whether your technique works, and how well.

4. Because of #3, new techniques are often first tested in the only well-characterized form of focal epilepsy we have, which is medial temporal lobe epilepsy. Of course, this is precisely the type for which we already have good tests, which is why it is better characterized. Furthermore, it is the form of epilepsy for which we have less need of such new techniques, since surgical outcomes are quite good. In this setting, generalizability to more challenging cases becomes much less certain.

5. The marked variation in the individual characteristics of epilepsy surgery patients makes it very difficult to compare one group to another; there are likely to be innate differences between those who needed the test and those who did not, or between those in whom the test was positive and those in whom it was negative. The best way around this is randomization, which is also quite difficult due to the nature of the intervention.

6. A large amount of the surgical evaluation process is highly subjective; the necessary clinical intuition and savvy is some of what surgical epileptologists love about the work, but it also makes it difficult to make an objective assessment of the value of a new test.

7. If the test looks promising, its results might *themselves* impact the outcome of surgical evaluation; such a "self-fulfilling prophecy" can make it virtually impossible to determine if the test truly provides incrementally useful information.

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Reviewing this list helps to explain why there are, arguably, only two procedures that have been widely adopted by the epilepsy surgery community in the last 25 years: high-resolution MRI in the early 1990s, and functional MRI as a replacement for the WADA test in the last decade. So when something comes along that shows robust results in a challenging population, it's worth our attention.

Such is the case with the article from Wang et al. on the use of a Morphometric Analysis Program (MAP) in surgical evaluation for patients with nonlesional epilepsy. MAP consists of MRI postprocessing using sophisticated quantification and statistical techniques to look for marked deviations in the structure of individual cortical regions when compared to a database of normal subjects. The investigators' method focuses particularly on blurring of the grey-white junction, with abnormal gyration or grey matter formations and excessive cortical thickness being secondary algorithmic measures.

A key feature of this technique is that it can be performed retrospectively on MRI images that have already been obtained (assuming the proper sequences were done). This allowed the authors to study 150 patients who were considered to have no clear lesion on MRI and went on to have a resection. After MAP abnormalities were identified, a blinded radiologist took this information to review the original (standard epilepsy protocol) MRI scans to determine if they had a subtle abnormality in the same region; only then was the patient considered MAP positive (MAP+). A group of 52 normal controls was also evaluated using MAP in a similar blinded fashion, though only 1 (2%) had a MAP+ region.

The results are striking: of patients who were MAP+ and had that entire area included in the resection, 45 of 50 (95%) had an Engel Class Ia outcome (completely seizure- and aura-free) after 1 year. In the remaining 100 patients, only 49 (49%) had a similar outcome, which is typical for surgical outcomes in a nonlesional population. It made little difference whether one had a MAP+ area that was only partially resected, or whether MAP was negative. Interestingly, it also made no difference whether or not the MRI was performed on a 1.5 Tesla scanner or a 3 Tesla scanner; presumably, the "subtle" abnormalities seen are equally subtle, regardless of scanner strength. Furthermore, the authors looked back at the epilepsy surgery conference notes and divided the patients into those thought to be "subtly lesional" (i.e., the conferees thought they might see something, but couldn't be sure) and those who were "truly nonlesional" (e.g., the conferees saw nothing credible on the scan)—outcomes in MAP+ resected patients were just as good either way.

We can now go back to the aforementioned list and see why this study is of such value. Issue #2 (low incidence) is not relevant here, as the authors found 43% of their patients to be MAP+, which is more than enough to make a sizable impact. Issue #3 (gold standard) is achieved because the technique can be performed retrospectively, allowing for a large sample with postoperative follow-up. The authors have taken care of issue #4 (applicability) by studying the group in whom we need help: those with normal MRI scans. They have addressed issue #6 (subjectivity), at least in part, by looking at "subtly lesional" patients (which sounds wishy-washy, but is a realistic and important aspect of epilepsy surgery practice). Finally, issue #7 (self-fulfilling prophecy) is not applicable because of the retrospective nature of the study; in fact, this is one of the rare cases in which a retrospective design may actually be *better* than a prospective one!

Looking at the list also shows you which issues remain. One of them is #5 (inherent population differences). This is illustrated by the authors' finding that patients who were MAP+ had a better outcome overall than MAP– patients, regardless of whether the MAP+ area was resected. As they point out in their discussion, this may mean that MAP identifies a group of patients who have pathology that is simply more amenable to surgery altogether. This is particularly intriguing in light of the fact that while 56% of the MAP+ patients were found to have cortical dysplasias pathologically, another 30% had no real pathology identified. (Alas, the authors do not provide an outcome breakdown by pathology.) This issue does not imply that MAP is less useful, though it could have implications for how we use it.

The other remaining issue is #1 (availability/reproducibility). There does not seem to be any reason this technique cannot be performed in all epilepsy surgery centers, but it will take time to determine whether other centers have the same results that these investigators do. Hopefully other centers will be spurred by these results to try it, as it appears possibly poised to make a big impact on surgical outcomes in a challenging patient group.

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