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Deformable Anatomic Templates Embed Knowledge into Brain Images: Part 2. Validation Using Functional Magnetic Resonance Imaging of the Motor Hand

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Abstract

Objective—This study evaluated the concordance between the Deformable Anatomical Template (DAT)-identified origin of motor hand fibers and localization of the motor cortex of the hand (MCH) by functional magnetic resonance imaging (fMRI).

Methods—Preoperative fMRI during hand motor tasks was performed on 36 hemispheres in 26 patients with gliomas in or near eloquent areas. Reformatted volume-rendered surface images were labeled with the DAT's hand motor fibers and fMRI data. Five reviewers assessed the data for concordance.

Results—Available fMRI data were diagnostically usable in 92% (33 of 36 analyzed hemispheres), with DAT anatomic accuracy in the remaining cases. The DAT prediction and fMRI findings were concordant in all 9 normal hemispheres and in 20 of 24 (83%) glioma-bearing hemispheres. The 4 discordant cases resulted from substantial mass effect by large frontal tumors.

Conclusions—This study validated DAT's anatomical atlas and alignment process for the expected position of the MCH.

Keywords

Brain atlas; functional magnetic resonance imaging; brain mapping; mass effect; glial tumor

INTRODUCTION

The original motivation for the Deformable Anatomical Template (DAT) Project was to quickly enhance clinicians' knowledge of brain anatomy and its function. The resulting product has potential utility in preoperative planning as well as medical education. Details concerning the construction and display capabilities of the software were presented in the first article in this series (add reference, JCAT). In brief, the DAT workstation (Anatom-e Information Systems, Ltd., Houston, TX) is a 3-dimensional reference template of a normal

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Conflicts of Interest: L. Anne Hayman, Megan Groneman, John Pagani, and Mark Vabulas have ownership or are employed by Anatom-e Information Systems, Ltd., Houston, TX whose product is validated in this study. Dr. Hamilton had a small (<\$600) travel stipend paid as a fellow as part of a speaking engagement (8th Annual World Congress of the International Brain Mapping & Image Guided Therapy, San Francisco, 6/2011.) None of the other authors have a conflict of interest to report.

volunteer's brain with 1,185 segmented labeled structures which is overlaid on patients' brain magnetic resonance images with a linear fitting to the global cortical brain contours. The current article describes the first step of clinical validation, in which we tested the concordance between the DAT-identified origin of motor hand fibers and localization of the motor cortex of the hand (MCH) by functional magnetic resonance imaging (fMRI) during the performance of hand motor tasks.

The MCH is a unique cortical area because 1) neurosurgical stimulation has shown it has no important inter-individual variability or plasticity and 2) it cannot be surgically resected without producing a permanent neurological deficit.¹ During fMRI, the performance of motor tasks produces some of the most robust activations in normal patients, and these results compare well with findings from intraoperative electrophysiological methods, the gold standard for localization.²⁻⁷ Thus, fMRI of the MCH is a useful noninvasive starting point for validating the DAT. Additionally, the MCH and central sulcus has anatomical features that make it easily identifiable in most patients,^{8,9} which was useful when discrepancies arose between fMRI and DAT findings.

We chose to validate the localization of the MCH by the DAT in patients with gliomas so that we could also illustrate the clinical utility of the DAT in the presence of abnormalities. The peritumoral environment surrounding gliomas can diminish fMRI signals and make localization difficult.¹⁰ Additionally, gliomas in the motor cortex or corticospinal tract can result in partial motor deficits, making electrophysiological evaluation difficult despite the potential for clinical improvement with successful surgery.¹¹ Therefore, a supplementary technique that is time and cost effective would be useful in localization of eloquent brain areas.

MATERIALS AND METHODS

After we obtained institutional review board approval, preoperative fMRI during the performance of hand motor tasks with the affected hand (n=16) and/or both hands (n=10) was done in 26 patients with supratentorial gliomas in or near eloquent areas. This yielded a total of 36 hemispheres to analyze. The patients in this study represent a cohort of a larger group where intraoperative MRI and operative mapping techniques were used in combination with DAT for eloquent area gliomas, which will be reported in subsequent articles. This cohort was chosen because pre-operative imaging included hand motor fMRI.

All preoperative functional imaging data were obtained on 1.5 or 3.0 T GE MRI scanners (Excite HD or HDxt MR scanners; GE Healthcare, Waukesha, WI) using 8-channel phased-array head coils. fMRI was performed with an EPI based sequence (repetition time: 3000 ms, echo time: 50 ms at 1.5T or 28 ms at 3.0T, field of view: 26 cm, matrix: 128×128, section thickness: 6 mm). The motor task was 15-sec periods of rest alternating flexion-extension of the fingers in a block design paradigm. A 3D fast gradient-echo T1-weighted sequence (repetition time: ~6 ms, echo time: ~2 ms, flip angle: 20 degrees, field of view: 25 cm, matrix: 256×224, section thickness: 1.2 mm) was also performed in addition to the fMRI and clinically necessary imaging. Analysis of the fMRI data, including motion correction, thresholding of the fMRI results, and registration of fMRI results and high-resolution anatomic data, was performed by experienced MR physicists (E.F.J. and P.H.) using AFNI (National Institutes of Health, Bethesda, MD). The MR images were imported into the DAT program without scaling or warping. Next, the DAT was fitted by a trained operator (M.G., J.P. or M.V.) to the global cortical contours using linear scaling; this took approximately 5–15 minutes. To facilitate visual analysis in a surgically relevant format, fMRI obtained during the motor tasks were reformatted into volume-rendered surface views, with both the fMRI motor activation and hand motor fibers of the DAT displayed. Four

neuroradiologists (J.D.H., L.A.H., V.A.K., and A.J.K) and 1 neurosurgeon (S.S.P.) determined if the information about localization of the MCH and central sulcus provided by fMRI and by the DAT was concordant

Relevant demographic data were also gathered. Of the 26 patients (13 men and 13 women), all but 5 were white. Ages ranged from 24 to 71 years, with most patients in their 40s or 50s. The majority of patients ($n = 16$) had not had previous brain surgery. Glial tumor types consisted of 13 glioblastoma multiforme, 6 anaplastic astrocytomas, 2 astrocytomas, 2 anaplastic oligodendrogliomas, 2 oligodendrogliomas, and 1 anaplastic ependymoma, with several patients having superimposed treatment-related necrosis. The individual patient data is given in Table 1.

Most glial tumors ($n = 18$) were located predominantly in the frontal lobe, including specific regions of 1 in the cingulate gyrus, 5 in the frontal operculum/insula, 7 in the perirolandic region, and 1 diffuse involving the entire frontal lobe. The remaining 8 predominantly retrosylvian tumors most often involved predominantly the parietal rather than the occipital or temporal lobes. It should be noted that given the invasive nature of gliomas, many of these tumors spanned multiple lobes; this was particularly evident when accounting for non-enhancing T2-weighted abnormality.

Kappa statistics were used to ascertain interobserver variability. Fisher's exact test was used to assess the statistical significance of the demographic data in comparison to the concordance between fMRI and DAT (QuickCalcs, Graphpad Software: 2005, San Diego, CA).

RESULTS

Available fMRI data were of sufficient diagnostic quality to be used for localization in 24 of 26 patients with gliomas in or near eloquent areas. This was 33 of 36 (92%) for the hemispheres analyzed, with 9 diagnostic and 1 non-diagnostic fMRI of the normal, unaffected side. This number does not include patients outside this cohort in the larger study whose clinical deficits were such that no fMRI was ordered or attempted. The fMRI was non-diagnostic in two cases because of the patients' inability to cooperate. Our expert reviewers determined that the DAT was concordant with diagnostic bilateral hand motor fMRI tasks in all 9 normal hemispheres (Fig. 1A) and hand motor tasks in 20 of 24 (83%) glioma-bearing hemispheres (Fig. 1B–D). In the one normal and two glioma-bearing hemispheres of patients with non-diagnostic fMRIs, the large majority of the DAT fibers passed through the anatomic MCH. Thus a total of 10 normal hemispheres and 22 affected hemispheres without substantial mass effect were validated in this study. There was 100% agreement between the observers on the concordance between DAT, fMRI and anatomic landmarks.

All 4 discordant cases (Fig. 1E–L) had posterior displacement or thinning of the MCH because of a mass effect from large frontal tumors, with the DAT placing the fibers anteriorly in the prefrontal sulcus. In 3 cases (Figure 1E–G and 1I–K), which had undergone prior surgery the MCH was displaced half to one gyrus (6–10 mm) relative to the contralateral normal position of the central sulcus and the MCH. Tumors located in the frontal lobe, including the insula/operculum but not the perirolandic region, was significantly more likely to result in mass effect and subsequent discordance between the DAT and fMRI ($P = 0.02$). Patient gender, patient age, and tumor type were not significantly associated with the correspondence between fMRI and the DAT.

DISCUSSION

The DAT findings were concordant with fMRI and anatomical data for MCH localization in all normal hemispheres and in all glioma-bearing hemispheres that did not have MCH displacement due to a mass effect (i.e., 83% of all cases). The DAT is a complementary technique for localization and may be useful as an alternative technique when fMRI is unavailable or fails because of the glial peritumoral environment.¹⁰

The DAT has several potential advantages over functional imaging techniques in preoperative planning, including that 1) little training and no specialized staff are needed to use the software; 2) DAT can be overlaid on anatomical images so analysis is not precluded by hemorrhage, peritumoral environment, edema, or postoperative changes; and 3) DAT's utility does not require active patient participation.

In our opinion, an advantage of the DAT was its greater conspicuity with coherent easy to visualize DAT fibers localizing to the anatomical structure of interest, if no substantial mass effect was present. To illustrate this point, the four neuradiologists did a subjective analysis of the single slice volume rendered views. The percentage (by quintile) of DAT hand corticospinal tract white matter fibers terminating within the MCH anatomically (i.e., the hand knob) and the fMRI activation pixels which resided in the anatomic MCH or central sulcus was estimated. On DAT, an average of greater than 80% of the fibers passed through the anatomic MCH for normal and affected hemispheres, despite the 4 cases of substantial mass effect. However, diagnostic motor task fMRI showed only 40–60% of the pixels in the target location for normal hemispheres and glioma-bearing hemispheres, with the majority of remaining activity in the adjacent postcentral gyrus. Although this analysis is only “semi-quantitative”, the interobserver agreement for this technique of subjective estimations was very good for both the DAT and fMRI (weighted kappa of 94% and 96%, respectively).

The DAT and fMRI were consistent in most cases because, in our experience, most of the fMRI motor activity will be located near the central sulcus, often with a significant portion overlying the postcentral gyrus. This is likely due to the effects on oxygenation of the central vein superficially, which is less of an issue at sulcal depth. Thus, the expected targets for localization are slightly different by modality, with the DAT targeting the center of the precentral gyrus at the MCH (“hand knob”) while the fMRI often localizes the central sulcus just posterior to MCH. The DAT atlas appears to fit the MCH of adults robustly, despite previous studies that reported brain shape and volume variation by sex or age.^{12–14} In our study, there was not enough ethnic diversity to determine whether such differences^{13,15} are relevant to the global fitting.

In our experience and in the literature, gliomas are more likely to invade rather than substantially displace brain structures^{16–20}; therefore, the majority of patients with gliomas may be well suited to an atlas-based approach, unlike those with metastatic brain tumors. It is interesting to note that 3 of the 4 patients whose DAT prediction and fMRI findings were discordant had undergone prior brain tumor resection, with the mass effect resulting in substantial posterior displacement (up to 1 gyrus or ~10 mm) of the MCH on the affected side (Fig. 1E–G and 1I–K). However, the 1 patient with discordant findings who was surgically naïve (Fig. 1H and 1L) had thinning of the precentral gyrus because of the compression by mass effect, with only mild posterior displacement. Thus, even with very large tumors, the displacement is relatively small, on the order of a single gyrus (up to ~10 mm); and a more considerable displacement is not likely to be found in imaging performed non-emergently.

In all 4 cases in which the DAT showed motor fibers outside of the expected MCH region, this finding was due to substantial posterior mass effect; 4 of the 9 large frontal tumors had

such findings (Fig. 1E–L), but none of the 5 large parietal tumors did (Fig. 1D). The location of the tumor was thus significant in predicting discordant information. It is postulated that frontal tumors are more likely than temporal and parietal tumors to displace the central sulcus because of mechanical properties of the brain, with the posterior brain being able to decompress inferiorly more easily through the tentorial incisura than to move the central sulcus anteriorly. Additionally, if the tumor had substantial mass effect but did not directly involve the precentral gyrus with bulk tumor, the entire gyrus was pushed back, with the relative spatial position in the gyrus and central sulcus remaining intact as a transverse plane,⁹ rather than the MCH being displaced in the expected radial fashion with a portion of the precentral gyrus more posteriorly displaced than the rest.

The volume-rendered display of the normal position of the motor fibers by the DAT provided a context that contributed to interpretation by showing displacement of brain structures from their normal position shift that may be difficult to appreciate in another manner. Mass effect caused a problem for the DAT atlas in the minority of cases, and this could be improved by using visible clues of shift from any additional source of information (e.g., conventional MRI, diffusion tensor imaging, fMRI, surgical appearance, and intraoperative mapping). Using these clues, the atlas can be adjusted for a localized (rather than global) fitting of the peritumoral area, as needed for preoperative localization.

There are no established criteria for validation of an atlas. Construction and validation strategies for other atlases have varied and include using no validation (based on historical data research atlases^{21, 22}), using single-domain knowledge (e.g., using cadaver anatomy¹⁴), and using multiple subspecialty domains of knowledge.^{23, 1} Ultimately, however, for clinical utility, the atlas must be tested in multiple domains. Our study is the first to test the DAT for its positioning of the MCH and its global fitting against a functional imaging method, in order to establish the DAT's clinical utility as a supplemental technique to localize eloquent structures in glial tumor patients for preoperative planning. Other validation studies, such as using clinical deficits from lacunar infarctions or subsequent to brain tumor surgery, diffusion tensor imaging, and intraoperative electrophysiologic stimulation, are ongoing. This information can be used to further adjust the positioning of structures within the atlas for maximal clinical utility. As the global fitting method appears to be robust in cases without a significant mass effect, attempts to use the DAT as a supplement for localizing more variable or less visible structures, such as language or visual areas and white matter tracts, can now be assessed.

conclusion

This study validated the anatomical atlas and the alignment process used by the DAT to define the normal origin of the motor hand fibers in 10 normal and 22 glioma-bearing cerebral hemispheres that did not have substantial mass effect. In the 4 large frontal tumors with substantial mass effect, the DAT placed the fibers predominantly in the prefrontal sulcus.

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¹Nowinski WL, Chua BC, Yang GL, Qian GY. Three-dimensional interactive and stereotactic human brain atlas of white matter tracts. *Neuroinformatics* 2012;10:33–55.

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Figure 1.

Volume-rendered motor hand functional magnetic resonance imaging (fMRI) from 4 representative cases (A–D) and the 4 cases of discordance between the deformable anatomic template (DAT) and fMRI due to mass effect (E–H), with corresponding axial images (I–L). All volume-rendered surface views are positioned for uniformity regardless of the original image orientation (e.g., 1B was flipped horizontally). The fMRI activation during unilateral or bilateral hand motor tasks is shown in maximum-intensity white pixels. DAT localization of hand motor fibers is shown in red. Images have been overlaid with indicators of the central sulcus (interrupted green line), the center of the hand motor gyrus (gold line) based on anatomical landmarks, and the glial tumor location (shaded purple), which is superimposed on the cortical surface regardless of depth.

The top row (A–D) shows cases in which the DAT and fMRI placed motor hand fibers in or near the center of the motor gyrus. (A) A normal case that is representative of 9 normal hemispheres (Patient #24 in Table 1); (B) a predominantly insular glioblastoma multiforme (GBM) with edema and non-enhancing tumor extending to the perirolandic area (same patient as 1A) represents the 5 predominantly insular or opercular tumors; (C) a large, predominantly parietal GBM that is representative of the 8 retrosylvian cases in the parietal greater than temporal or occipital lobes (Patient #9 in Table 1); and (D) GBM-bearing expanded perirolandic glioma representing the 7 tumors in this area (Patient #10 in Table 1). The middle and lower rows show volume-rendered (E–H) and companion axial images (I–L) of 4 large frontal gliomas with mass effect, which caused the DAT to localize fibers

slightly anterior to the motor gyrus in the precentral sulcus (Patients # 1, 14, 13, and 7 respectively in Table 1). Blue horizontal lines are overlaid to show the position of the hand motor cortex on the normal side to demonstrate the mass effect, with $\frac{1}{2}$ to 1 gyrus (6–10 mm) of posterior displacement on the affected side (I–K) or thinning of the precentral gyrus (L). Three GBMs were operated on previously (E–G and I–K); 1 case of oligodendroglioma had not previously been resected (H and L). These 4 cases represent the minority of all frontal tumors (n = 18) and of large frontal tumors (n = 9).

Table 1

Individual patient demographic data including ethnicity, age, sex, if prior surgery was done, time from prior surgery (in months), tumor type, and location. If there was associated necrosis it is noted along with tumor type.

Patient #	Ethnicity	Age/Sex	Prior Surgery (in months)	Tumor Type, Necrosis present	Tumor Location
1	White	71/F	None	AA	Parietalandic
2	White	71/F	None	Oligo	Retrosylvian
3	White	29/F	None	GBM	Frontal
4	White	48/M	None	GBM	Retrosylvian
5	Spanish	45/M	None	GBM	Temporal Lobe & hippocampus
6	White	41/M	26	AO	Frontal
7	White	41/M	None	Oligo	Frontal
8	White	59/F	None	GBM	Temporal Operculum
9	White	56/M	None	GBM	Parietalandic
10	White	50/M	7	GBM, Necrosis	Retrosylvian
11	White	47/M	23	Astro	Parietalandic
12	White	35/F	55	GBM	Frontal operculum/insula
13	White	47/M	11	GBM, Necrosis	Frontal
14	White	54/M	10	GBM	Frontal operculum/insula
15	White	61/F	None	GBM	Frontal operculum/insula
16	White	69/M	None	GBM	Retrosylvian
17	Hispanic	70/F	None	AA	Retrosylvian
18	Greek	35/F	None	AA	Retrosylvian
19	White	24/F	None	GBM	Retrosylvian
20	Indian	45/F	None	AA	Frontal operculum/insula
21	White	37/F	120	AO	Retrosylvian
22	White	40/M	47	AA	Parietaland0069c
23	White	45/F	None	AA	Frontal (cingulate)
24	White	31/F	18	GBM	Parietalandic

Patient #	Ethnicity	Age/Sex	Prior Surgery (in months)	Tumor Type, Necrosis present	Tumor Location
25	Asian	38/M	18	AE	Retrosylvian
26	White	52/F	None	Astro	Frontal operculum/insula

Abbreviation index: M= male, F = female, Oligo= oligodendroglioma (WHO Grade 2), AO= anaplastic oligodendroglioma(WHO Grade 3), Astro= astrocytoma (WHO Grade 2), AA= anaplastic astrocytoma (WHO Grade 3), AE= anaplasticependymoma (WHO grade 3), and GBM= glioblastoma multiforme (WHO Grade 4).