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Assessing the clinical outcome of Vim radiosurgery with voxel-based morphometry: visual areas are linked with tremor arrest!

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Abstract

Introduction: Radiosurgery (RS) is an alternative to open standard stereotactic procedures (deep-brain stimulation or radiofrequency thalamotomy) for drug-resistant essential tremor (ET), aiming at same target (ventro-intermediate nucleus, Vim). We investigated Vim RS outcome using voxel-based morphometry, by evaluating interaction between clinical response and time.

Methods: Thirty-eight patients with right-sided ET benefited from left unilateral Vim RS. Targeting was performed using 130 Gy and single 4-mm collimator. Neurological and neuroimaging assessment was completed at baseline and 1 year. Clinical responders were considered those with at least 50% improvement in tremor score on treated hand (TSTH).

Results: Interaction between clinical response and time showed left temporal pole and occipital cortex (Brodmann area 19, including V4, V5 and parahippocampal place area) as statistically significant. A decrease in grey matter density (GMD) 1 year after Vim RS correlated with higher TSTH improvement (Spearmann= 0.01) for both anatomical areas. Higher baseline GMD within left temporal pole correlated with better TSTH improvement (Spearmann= 0.004).

Conclusions: Statistically significant structural changes in relationship to clinical response after Vim RS are present in remote areas, advocating a distant neurobiological effect. The former regions are mainly involved in locomotor monitoring towards local and distant environment, suggesting requirement to recruit in targeting specific visuomotor networks.

Key words: tremor, ventro-intermediate nucleus, voxel-based morphometry, Gamma Knife surgery, radiosurgery

INTRODUCTION

Essential tremor (ET) is gradually progressive movement disorder, characterized mainly by kinetic and postural tremor, affecting head, forearms and hands[17]. Recent clinical and neuroimaging studies have suggested cerebellar involvement and mediation of tremor by cerebello-thalamo-cortical (CTC) loop, but including also multiple other anatomical regions within the basal ganglia (basal ganglia loop) and cortex[5, 6].

Pharmacological treatment is in a vast majority of cases unsatisfactory. Drug-resistant ET can benefit from standard deep brain stimulation (DBS) or radiofrequeny thermocoagulation or alternatively from minimally invasive radiosurgery (RS) and high-focused ultrasound (HIFU), aiming at the same target (ventro-intermediate nucleus, Vim)[3, 12, 14, 30]. Radiosurgical targeting is indirect and clinical effect installs progressively, over mean period of months, up to one year[30], unlike open surgery, with immediate tremor stop. It has been previously hypothesized that, beside a lesionning effect, Vim RS might have a neuromodulatory one[24].

Neuroimaging procedures have given new insight onto the pathophysiology of tremor [27]. Computational approaches for analyzing high-resolution structural MRI provide a powerful and non-invasive tool for characterizing individual and/or group differences in brain anatomy[1]. With regard to structural changes, voxel-based morphometry (VBM) has been used both at 1.5 and 3 Tesla (T), including in ET, with large spectrum of controversial findings[2, 4, 7-10, 16, 21, 23]. In fact, VBM assesses subtle regional differences, between subjects, in white or gray matter (GM), by a well-established and robust methodology[1].

In the present study, we used VBM to investigate whether Vim RS induces structural gray matter density (GMD) transformations one year after the intervention, in relationship with clinical effect. We hypothesize that changes in remote areas relate to clinical response after Vim RS, beside the targeted site (e.g. left thalamus).

METHODS

Subjects

We analyze 38 patients (mean age 71.8 years, range 52-80) with severe refractory right-dominant in right-handed ET, treated with unilateral left Vim RS, between April 2012 and March 2015. All were part of a research (including neuroimaging) protocol, aiming at the understanding of Vim RS radiobiology. All had given informed written consent. The study

was approved by local ethics committee (in compliance with the national legislation and the Declaration of Helsinki).

Tremor definition and inclusion criteria

Essential tremor has been defined according to Elble et al.[11]. Parkinson's disease cases were excluded, as well as those patients with previous stroke or epilepsy etc, susceptible to induce structural changes. The indication for Vim RS rather than DBS were medical co-morbidities drug-resistance, advanced age or patient's refusal.

Gamma Knife thalamtomy

All Vim RS procedures were all performed by same neurosurgeon (JR). After application of the Leksell® coordinate G Frame (Elekta AB, Stockholm, Sweden), under local anesthesia[30], all underwent both stereotactic CT and MRI. Indirect targeting was performed in all cases using Guiot's diagram, placed 2.5 mm above the AC-PC line, 11 mm lateral to the wall of the third ventricle, and at a mean of 7.3 mm in front of the PC (3.9-9.9; SD: 1.33). A unique 4-mm isocenter was used, and a maximal prescription dose of 130 Gy.

Clinical evaluation and outcome measures after Vim radiosurgery

The same neurologist (TW) performed all clinical assessment, at baseline and 1 year after Vim RS. Tremor score on the treated hand (TSTH) was assessed according to the Fahn-Tolosa-Marin Tremor Rating Scale [28]. It has been previously advocated that medication diminishes TSTH by approximately 50%[19] in around 50% of cases. In this sense, to be at least as effective as medication, clinical responders (R) were considered those with at least 50% amelioration of TSTH 1 year after Vim RS, to take into account the delayed clinical effect[30]. At the time of the study, no patient was under medication.

MRI acquisition and evaluation after GKT

All imaging was obtained on a 3-T magnetic resonance imaging (MRI) scanner, SIEMENS Skyra TrioTim Scanner (Munich, Germany), with 32 channels receive array head coil. The acquisition protocol included for all cases a high-resolution, contrast-enhanced, T1-weighted (T1w), TR/TE=2300/2.03, inversion time 900 ms, isotropic voxel of 1mm^3, 192 slices. Images artefacted by movement were excluded.

Data processing and analysis

Statistical Parametric Mapping (SPM12) (Department of Neurology, London), performed with MATLAB 2014a, 2014 (MathWorks, Boston, MA, USA) was utilized for preprocessing and analyzing of the MRI data.

The anatomical MR images were normalized to the Montreal Neurological Institute (MNI) atlas, with voxel-size of 2 × 2 × 2 mm. The normalization procedure allows the warped images to fit into a standard template brain. Furthermore, this establishes a voxel-to-voxel correspondence, between brains of different individuals. It will enable to drive group statistics and to report the results in a standard coordinate system (e.g. MNI, which is based upon data from many individuals and is fully 3D, with data at every voxel).

They were further segmented in GM, white matter and cerebro-spinal fluid. Furthermore, they were spatially smoothed using a 8-mm full-width-at-half-maximum (FWHM) Gaussian Kernel in SPM12, to blur individual variations in gyral anatomy and to increase the signal-to-noise ratio. The smoothing procedure enables the subsequent voxel-by-voxel analysis comparable to a region of interest approach, as the voxel will contain the average concentration of gray matter from around the voxel (where the voxel is characterized by the form of the smoothing kernel). The former is so often referred as to GMD. In a structural MRI of the brain, the intensity of each volumetric pixel, or voxel, relates to the density of the gray matter in that region. The VBM technique is so comparing brain structure on a voxel-by-voxel basis. After the classical preprocessing steps, the intensity values of the voxels are compared, to identify localized differences in GMD.

The between groups SPM (T) GM maps were obtained using an analysis of variance (ANOVA) full factorial model, at a height threshold (voxel-level significance) of $p<0.05$, corrected for multiple comparisons for the cluster (FWE, family-wise error method). Secondarily, if no change was initially found using FWE correction, with a less constraint voxel-threshold of $p<0.005$, only corrected for the cluster volume to avoid type II errors as recommended [15]. Age, gender and the type of tremor were used as nuisance variables. Was evaluated the interaction between clinical response and time, mainly between R versus non-responders (NR) patients, with the different time frame (baseline versus 1 year after Vim RS), so as to identify the eventual structural changes in GMD. The primary aim was to find differences between groups (R versus NR) in interaction with the time point (before and after Vim RS).

The SPM analysis was done by medical staff (CT, EG) not involved in the indication for treatment, Vim RS procedure or follow-up evaluation. Gray matter density was further extracted from statistically significant regions. For correlation between GMD and TSTH

improvement, STATA version 11 (STATA Corp LLC, College Stations, TX, USA) was used, and p values evaluated with Spearman correlation coefficient.

RESULTS

Thirty-one (81.6%) patients were R and 7 (18.4%) NR. Overall improvement in TSTH was 62.1% (mean 62.6%, standard deviation 32.3; range 0-100%) and in R subgroup was 75.2%. No difference in clinical characteristics was found between R and NR (age, gender, tremor severity before Vim RS; p>0.05). No side effect was found 1 year after Vim RS.

Changes in GMD between R and NR*, during time (group factor X time, figure 1)*

Changes in GMD between R and NR with time showed left temporal pole (Brodmann area, BA 38), and a larger cluster [kc= 135 (left occipital) > kc=124 (left temporal), indicating the number of voxels in each cluster] within the left occipital area. The former included beside the left occipital lobe (BA 19), the V4, V5, and parahippocampal place area (PPA). Figure 1 (1.1 and 1.2,) displays the boxplots with the overall value and the median for baseline and 1 year, for R and NR, by the individual cluster.

Interestingly, GMD was lower at baseline in the NR group for both regions and at 1 year had a median value similar to the R groups (which presented a slight decrease in GMD).

The table at the bottom of the figure shows the respective p values at the cluster and peak level (for a detailed explanation please see the figure legend).

Furthermore, higher GMD decrease between 1 year and baseline correlated with better TSTH improvement (Spearmann= 0.01 for clusters 1 and 2, respectively; figure 1, 1.3 and 1.4). For cluster 1 (left temporal pole), higher baseline GMD predicted better improvement (Spearmann= 0.004; figure 1, 1.5).

The GMD increase at 1 year after Vim RS was fairly similar for both clusters in NR, while it tended to zero in R (figure 1, 1.6).

DISCUSSION

To the best of our knowledge, we performed the first VBM analysis after Vim RS for drug-resistant ET. We report changes in GMD between R and NR with time within left temporal pole (BA 38) and a larger cluster including left occipital lobe (BA 19, V4, V5, and PPA), as statistically significant. Grey matter density was lower at baseline in the NR group for both regions and at 1 year had a median value similar to R groups (which presented a slight decrease in GMD). Higher GMD decrease between 1 year and baseline correlated with

better TSTH improvement, for both anatomical regions. For left temporal pole, higher baseline GMD predicted better TSTH improvement.

VBM methodology has been previously used in ET (at 1.5 and 3 T), with studies reporting inconsistent results[2, 4, 7-9, 16, 23], while showing no change, atrophy or volume increase in different regions. In the present study, it was beyond our purpose to analyze a healthy control group, as we were interested in how brain structurally adapts to Vim RS, in relationship to clinical response.

The involvement of left temporal pole and occipital BA 19 is a very interesting and novel finding, suggesting a distant effect of Vim RS. Left temporal pole is mainly involved in complex functions, including visual (« what and where » visual pathways distinction), emotional (visual processing of emotional images, emotional attachment), processing phonological properties of written words, sign language or complex auditory processing[20]. The visual cluster actually extends beyond the BA 19, and includes parts of V4 and V5 and the PPA (posterior subdivision). Visual area V4 is part of extrastriate visual cortex[25] and is tuned for orientation, spatial frequency and color, but also long-term plasticity, stimulus salience, and is gated by signals coming from frontal-eye-fields (FEF)[31]. The former connections would be of special interest in patients with ET: in a crowded visual scene, all factors that could help distinguishing the target include color, shape and eye movements.

Vim RS is classically performed with the aim of inducing a small area of necrosis after several months, up to one year after the procedure[24]. By the expected radiobiological effect, it mimics a histologically destructive one, compared to that produced by thermocoagulation[26]. However, Ohye[22] was the first to advocate that necrotic lesion solely was not sufficient to produce tremor alleviation. Moreover, he advocated that the magnitude of the lesion induced by Vim RS was too small to account for the benefic clinical effect. The proposed «cocade theory», advocates for 4 distinct zones that might appear after Vim RS, including necrotic, subnecrotic, neuromodulatory and no effect[24].

The advantages of the VBM analysis are related to an unbiased and objective procedure, fully automated, not based on regions of interest and which is more exploratory. Furthermore, it depicts differences and/or changes (in our study) at a global and local scale. The limitations of our study are mainly related to those of the VBM method (preprocessing steps, statistical challenges etc), but also to the studied population of patients, the former including the limited sample size or the absence of a blinded-neurological assessment.

With regards to the main reasons for incomplete tremor alleviation, our experience and/or our hypothesis are : the size of the lesion (small size classically associated with more

failures[29]), an eventual different phenotype of ET[18] (more resistant to Vim RS?), eventual adaptive changes (including structural, as depicted by VBM?), which makes the "reset" of the « tremor network » more difficult, and eventually the targeting, although we used a uniform and well-established methodology.

The role of visual association areas is reported for the first time as statistically significant and thus relevant in tremor improvement after Vim RS. How the “tremor network” (cerebello-thalamo-cortical pacemaker) modulates these structural changes in remote areas remains unknown. The anatomical connections between the primary motor cortex and visual areas might be of relevance, as previously advocated[13], for sensory guidance of movements.

Conclusion

Responders present changes in areas involved in motion, mainly locomotor monitoring towards the local and distant environment, suggesting the requirement to recruit in the targeting specific visuomotor networks.

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Conflict of Interest: All authors certify that they have no affiliations, with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval: The study was approved by local ethics committee of Timone University Hospital, Marseille, France.

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Figure 1: The main effect of time point, interacting with clinical response;

Upper part: 1.1 and 1.2, global overview of GMD at baseline and 1 year for left temporal pole and visual association area, depending on clinical response (<=50% TSTH improvement, versus >50% TSTH improvement); the boxplots reveal the range of values for GMD, as well as the median for each one of them; it is of interest that for both clusters (temporal and occipital), for a TSTH improvement <=50%, the baseline values are lower as compared with

the ones for TSTH improvement >50%; at 1 year, the NR patients achieve a median value comparable to that of R at baseline, while the former remain stable; 1.3 (for the left temporal cluster) and 1.4 (for the left occipital cluster), correlations between TSTH improvement and differences in GMD (Spearmann= 0.01 for both clusters); 1.5, correlation between baseline GMD within the left temporal cluster and TSTH improvement (Spearmann= 0.004); 1.6, illustration of GMD increase (for the NR) and respectively no change (for R), as structural differences between R and NR during time, before and after Vim RS, presented by clusters (1=left temporal and 2=left occipital, with a sagittal illustration for each one of them);

Lower part, table with the main SPM results: it corresponds to the statistically significant results at cluster-level and peak-level, respectively; the overall p value is 0.049; for cluster and peak level, are reported p family-wise error correction (FEW), false-discovery rate (FDR), Kc= size of the cluster, meaning the number of the included voxels in each one fo them, and p unc= uncorrected p value, as opposed to the previous (FEW and FDR); the uncorrected p values show statistical significance (<0.05); for the peak-level, the MNI signifies Montreal Neurological Institute, which is the common space where the brains have been analyzed, so as to be able to compare them;

Lower part: and an artistic draw, illustrating the main functions for these statistically significant clusters.

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