Functional lesional neurosurgery for tremor - a systematic review and meta-analysis

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ABSTRACT

Background: This work evaluates the consistency, effect size and incidence of persistent side effects of lesional neurosurgical interventions in the treatment of tremor due to Parkinson`s disease (PD), Essential Tremor (ET), Multiple Sclerosis (MS) and midbrain lesions.

Methods: Systematic review and meta-analysis according to PRISMA-P guidelines. Random effects meta-analysis of standardized mean difference based on a peer-reviewed protocol (PROSPERO no. CRD42016048049).

Results: From 1249 abstracts screened, 86 peer-reviewed studies reporting 102 cohorts homogeneous for tremor aetiology, surgical target and technique were included.

Effect on PD tremor was better when targeted at the ventral intermediate nucleus (V.im.) by radiofrequency ablation (RF) (Hedge`s g: -4.15;) over V.im. by Gamma knife (GK) (-2.2), subthalamic nucleus (STN) by RF (-1.12) and globus pallidus internus (GPi) by RF (-0.89). For ET MRI-guided focused ultrasound (MRIgFUS) ablation of the cerebellothalamic tract (CTT) (-2.35) and V.im. (-2.08) showed similar mean tremor reductions to V.im. ablation by RF (-2.42) or GK (-2.13). In MS V.im. ablation by GK (-1.96) and RF (-1.63) were similarly effective.

Mean rates of persistent side effects after unilateral lesions in PD were 12.8% (RF V.im.), 13.6% (RF STN), 9.2% (RF GPi), 0.7% (GK V.im.) and 7.0% (MRIgFUS V.im.). For ET, rates were 9.3% (RF V.im.), 1.8% (GK V.im.), 18.7% (MRIgFUS V.im.) and 0.0% (MRIgFUS CTT), for MS 37.7% (RF V.im.) and for rubral tremor 30.3% (RF V.im.).

Conclusion: This meta-analysis quantifies safety, consistency and efficacy of lesional neurosurgical interventions for tremor by target, technique and aetiology.

Key words: tremor, thalamotomy, subthalamotomy, pallidotomy

INTRODUCTION

Tremor due to Essential Tremor (ET), Parkinson´s diseae (PD), dystonic tremor, multiple sclerosis (MS) and lesions to the midbrain or cerebellar structures (rubral tremor) frequently shows limited response to oral medication [1-3]. According to current pathophysiological understanding tremor is most likely the result of abnormal central oscillatory activity within a network involving motor cortex, thalamus, globus pallidus and cerebellum[4-6]. Since the 1940ies, therapeutic lesional surgical interventions have aimed at various anatomical structures within this network with variable success[7-10]. The historical development of lesional neurosurgery over the past 8 decades was markedly influenced by the technology available for target location, identification, and lesioning[11]. Accordingly, the advent of in principle reversible deep brain stimulation (DBS) technology[12] by and large replaced irreversible lesional approaches in academic centres for the past 25 years. Although only a single randomized controlled trial on a heterogeneous patient population compared lesional and stimulation approaches head-to-head[13], efficacy was deemed similar between both techniques, while the side effect risk was found to be higher with thalamotomy than DBS[14,15].
Nevertheless, lesional interventions were performed world-wide[16] and appreciated in terms of efficacy[17]. Since the introduction of Gamma Knife (GK)[18], incisionless functional neurosurgery, i.e. lesion placement through the intact skull, became a possibility[9]. Recently, the addition of MRI-guided high-intensity focused ultrasound (MRIgFUS)[19] has again stimulated interest in this field [20,21], as it offers an incisionless approach to create an intracerebral lesion under direct imaging-control in a step-wise manner[22-25]. First data comparing surgical interventions by DBS, GK and MRIgFUS indicate better functional disability improvement with MRIgFUS over DBS and GK, while incisionless approaches show better cost-effectiveness [26]. One could therefore say that these technological advances lead to a renaissance of lesional functional neurosurgery.

A wealth of studies on lesional tremor treatment has been published over time but has never been formally compiled, summarized and assessed in order to estimate consistency of treatment effects or persisting side effects after lesional interventions. In order to guide the renewed interest in lesional neurosurgical interventions for tremor, we summarize the efficacy and safety of lesional interventions by a systematic review and meta-analysis of the existing literature. In particular we aimed to answer the following questions:
- What is the evidence for efficacy of lesional neurosurgical interventions on tremor severity in tremor due to PD, ET, MS and midbrain / rubral origin by different lesioning techniques and targets?

- What is the prevalence rate of *persistent* side effects after unilateral lesional interventions for different lesioning techniques and targets?

Different thalamic nomenclature systems have been used and cited for the same structures[27]. Throughout the following we use Hassler´s ventral intermediate nucleus (V.im.) analogous to Walker´ s VIM and the ventral lateral posterior nucleus (VLp) by Jones. Hassler´ s ventralis oralis anterior nucleus (V.oa.) corresponds to Jones´ ventral lateral anterior nucleus (VLa), while the ventralis oralis posterior nucleus (V.op.) is considered a transition zone between VLa and VLp.

Subthalamic structures, containing the radiatio prelemniscalis (Ra.prl), including the cerebellothalamic tract (CTT) and the nucleus of the caudal zona incerta (cZI) as well as the pallidothalamic tract containing ansa lenticularis and the fasciculus lenticularis, are referred to as the posterior subthalamic area (PSA)[11].

METHODS

This work was conducted according to the recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement[28]. The review protocol has been registered in the International Prospective Register of Systematic reviews (PROSPERO no. CRD4201604804), peer-reviewed and published[29].

Study design and selection criteria

This study assessed the intervention effect by comparing pre- and post-interventional tremor severity. Cohorts reporting a minimum of five patients of or above the age of 18 with a tremor diagnosis of confirmed aetiology, subjected to uni- or bilateral lesional functional neurosurgery in a central neuroanatomical structure (thalamus, pallidum, subthalamic nucleus, alternative subcortical targets) by means of an intracerebral lesion, either by incisional (placement of a stylette, leukotome, cryosurgery or radiofrequency (RF) probe after skull opening) or incisionless (MRIgFUS, GK) means. Cases reporting results from mixed aetiologies (subjects of different aetiologies grouped together) or mixed interventions (different techniques, different anatomical targets or more than one target grouped together), as well as non-lesional approaches including DBS, were excluded (see Table 1).

Table 1. In- and Exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	- Adult patients (>18yrs.) with a tremor diagnosis of confirmed aetiology - uni- or bilateral lesional functional neurosurgical intervention in a central neuroanatomical structure - by incisional (placement of a stylette, leukotome, cryosurgery or radiofrequency probe after skull opening) or incisionless (transcranially focused ultrasound (MRI-guided focused ultrasound (MRIgFUS)), radiation energy (Gamma Knife (GK)) means	- cases subjected to lesional functional neurosurgery in more than one anatomical structure at the same time - or stimulation techniques (deep brain stimulation)
Study design	- randomized controlled trials (RCTs), Meta-Analysis, case-control, prospective and retrospective case series - a minimum of five subjects included per cohort (indication / treatment) - minimum follow-up of 2 months after the intervention	- studies reporting results from mixed aetiologies or mixed intervention (different anatomical targets or techniques)
Efficacy Outcome	- reporting tremor outcome on a validated tremor scale	
Safety Outcome	- side effects after unilateral only interventions	- cohorts including bilateral interventions
Type of publication	- Peer-reviewed articles without language restriction	- Letters, abstracts and editorials
Time-frame	January 1990 – February 2017	Before January 1990

Data from peer-reviewed randomized controlled trials (RCTs), Meta-Analyses, case-control, prospective and retrospective case series were included in the analysis, while letters, abstracts and editorials were not. Due to limitations of earlier reports pertaining to established diagnostic criteria, use of validated clinical assessment tools and target verification[7], we restricted the inclusion to publications/studies from January 1990 onwards. As sometimes more than one group of patients homogeneous for aetiology, technique and target is reported per publication/study, we refer to these homogeneous groups as cohorts throughout this work.

For the efficacy analysis, cohorts reporting upper limb tremor outcome contralateral to the intervention using validated tremor scales were included. PD cohorts reporting tremor in the ON state only as well as cohorts excluding tremor-dominant PD cases were not included in the analysis (see Figure 1).

For the safety assessment, all cohorts reporting persistent side effects after unilateral only interventions were included - mean and standard deviation (SD) of the incidence of all persistent side effects was calculated per group.

Search strategy

Searches of Medline and the Cochrane databases were conducted without restrictions of publication language. The search terms “tremor*” AND “lesion*”, “neurosurg*”, “thalamotomy”, “subthalamotomy”, “pallidotomy” were used - additional publications were identified from the reference lists of selected papers. Identified abstracts were screened and selected based on reporting human clinical outcome data by one investigator (SRS) – screening for in depth review was performed independently by two investigators (SRS & GK) and discrepancies were resolved before further analysis. Data was then extracted by using a standardized data collection tool.

Statistical Analysis

Primary outcome measure was the change in upper limb tremor severity from baseline to follow-up. To minimize selection/reporting bias if more than one follow-up time-point was reported, the time-point with the largest number of patients retained was included in the analysis. The standardized mean difference (Hedges` g) was used to calculate the effect size of the treatment effect, as this transforms original data to a uniform scale and allows to combine data measured with different scales or scale-items[30] to account for reporting heterogeneity in the primary data. Pooled participant data from studies reporting pre- and post-interventional tremor scores (mean ± SD) were included in a random-effects meta-analysis using the Meta-Essentials workbook4 toolbox[31] and displayed in Forest plots.

Heterogeneity of subgroups was calculated using the I^2 statistic with an I^2 >50% assumed to represent substantial heterogeneity. Follow-up duration in months was imputed as a moderator and computed by univariate, weighted regression using a random effects model[31] to control for an effect of follow-up duration on the effect size.

Homogeneous cohorts (same tremor aetiology, intervention target and technique) were grouped together for subgroup-analysis if they consisted of a minimum of n=2. A formal assessment of publication bias is useful in the presence of a sufficient number (>10) of homogeneous data sets but can be misleading in small and heterogeneous ones[32]. Our pre-set cut-off for formal bias assessment was if subgroups with more than 10 studies included were shown to have no substantial level of heterogeneity (I^2 < 50%). A narrative evaluation is provided for all other cases. After testing for normality, safety data was analysed using non-parametric Kruskal-Wallis test and Dunn`s multiple comparison test where appropriate using GraphPad PRISM 6 (La Jolla, CA/USA).

Quality assessment

Studies included in this meta-analysis were assessed according to standardized tools established for the grading of cohort studies (Newcastle Ottawa-Scale [33]), and randomized controlled trials (Jadad-Scale [34]).

RESULTS

The database searches (final on January 14th 2017) identified 1249 abstracts, from which 127 studies were selected for screening (see Figure 1). After exclusion of studies not fulfilling in-/exclusion criteria (see Table 1), 86 studies reporting 102 cohorts were reviewed in depth (extracted data are summarized in Supplementary Table 1). According to our standardized quality assessment, the scientific quality of studies included was variable – detailed results are given in supplementary tables 1 and 2.

The efficacy meta-analysis (Figure 2) is based on data from 1255 patients (46 cohorts), the majority of which suffered from PD (64.2%) and ET (32.8%), with MS (2.5%) and rubral tremor cases (0.4%) being much less frequently reported. The rate of reported persistent side effects after unilateral lesional interventions (Figure 3) is based on data from 1415 subjects reported in 59 cohorts. Again, patients with PD (71.2%) were more frequent than with ET (19.3%), MS (6.4%) and rubral tremor (3.0%).

We have identified studies reporting outcome after interventions in the following categories – subgroup analysis was done if ≥ 2 studies reported outcome of the same aetiology and target: 1) PD tremor: RF ablation ventral intermedial (V.im.) nucleus, RF ablation Globus pallidus internus (GPi), RF ablation subthalamic nucleus (STN), Leukotome

ablation GPi, GK ablation V.im.; 2) ET tremor: RF ablation V.im., GK ablation V.im., MRIgFUS ablation V.im., MRIgFUS ablation CTT; 3) MS tremor: RF ablation V.im., GK ablation V.im.; 4) Rubral tremor: RF ablation V.im.. The selected publications used the following standardized and validated clinical scales for tremor quantification: United Parkinson´s disease rating scale, part III (UPDRS III)[35], clinical rating scale for tremor (CRST[36,37]), Washington Hights-Inwood genetic study of essential tremor (Whiget) scale[38] and Bain Findley tremor scale[39].

Parkinson´s disease tremor

We identified 17 retrospective, 10 prospective (1 controlled[40]) and one RCT[41] cohorts that fulfilled criteria for efficacy analysis – overall 31.4% of cases were assessed prospectively. The majority of PD cases received treatment using RF ablation (n=677), followed by GK (n=129) (Figure 2A). Anatomically, the majority were treated at the GPi (n=367), with V.im. (n=304) and STN (n=135) following. Effect on tremor was strongest in the RF V.im. group (Hedge`s g: -4.15, 95% CI: -5.13 to -3.17) with substantial heterogeneity (I^2=0.77), followed by GK V.im. (-2.20, -3.62 to -0.78, I^2=0.94), RF STN (-1.12, -1.4 to -0.84; I^2=0.38) and RF GPi (-0.89, -1.16 to -0.61, I^2=0.68). Across cohorts, duration of follow-up did not have a significant influence on effect size (slope -0.01, p=0.61).

For the safety analysis 35 cohorts fulfilled inclusion criteria, with the majority of patients being subjected to RF pallidotomy (Figure 3A). The rates of reported persistent side effects after unilateral lesions were 12.8±19.0% for RF V.im. (n=198), 13.6±8.2% for RF STN (n=150), 9.2±15.9% for RF pallidum (n=514), 0.7±1.2% for GK V.im. (n=126) and 7.0±9.9% for MRIgFUS V.im. (n=20) lesions - this side effect rate (χ^2=6.022, p=0.20) as well as the duration of follow-up (χ^2=1.005, p=0.91) was not significantly different between groups. One RCT reporting leucotomy lesions in the GPi for PD (n=9) reported no persistent side effects[42].

Essential Tremor

For the efficacy analysis 6 retrospective and 7 prospective cohorts fulfilled inclusion criteria – overall 64.3% of cases were assessed prospectively. Lesions were placed at the V.im. using GK (n=254), MRIgFUS (n=79) and RF (n=25), as well as the CTT using MRIgFUS (n=27) (Figure 2B). Mean effect on tremor was similar between groups: MRIgFUS ablation of the cerebellothalamic tract (CTT) (-2.35; -2.51/-2.19) and V.im. (-2.08; -2.77/-1.39) showed similar mean tremor reductions to V.im. ablation by RF (-2.42; -5.26/0.43) or GK (-2.13; -3.78/-0.48). Across cohorts, duration of follow-up did not have a significant influence on treatment effect size (slope -0.02, p=0.28).

For the safety analysis 13 cohorts (n=273) were identified (Figure 3B). The rate of reported persistent side effects after

unilateral lesions were 9.3±8.6% for RF V.im. (n=32), 1.8±3.0% for GK V.im. (n=153), 18.7±16.2% for MRIgFUS V.im. (n=82) and 0.0±0.0% for MRIgFUS CTT (n=6) – this was not significantly different between groups (χ^2=4.49, p=0.21). Follow-up duration between studies differed on a group level (χ^2=7.46, p=0.02), but not on multiple comparisons (RF V.im. vs. GK V.im. p=0.07, RF V.im. vs. MRIgFUS V.im. p=0.51, RF V.im. vs. MRIgFUS CTT p>0.99, GK V.im. vs. MRIgFUS V.im. p>0.99, GK V.im. vs. MRIgFUS CTT p=0.69, MRIgFUS V.im. vs. MRIgFUS CTT p>0.99).

MS tremor

Four retrospective cohorts reporting 32 subjects were included in the efficacy meta-analysis. Tremor reduction after RF V.im. (-1.63, -2.56 to -0.70, I^2=0.14) and GK V.im. ablation (-1.96, -3.12 to -0.81, I^2=0.32) were similar (Figure 2C). Across cohorts, duration of follow-up did not have a significant influence on effect size (slope -0.13, p=0.59).

For the safety analysis six retrospective cohorts of RF V.im. ablation were included (Figure 3C) reporting a persistent side effect rate after unilateral lesions of 37.7±23.9% (n=85) – the only GK V.im. study reported no persistent side effects (n=6) [43].

Rubral tremor

The effect size in one retrospective RF V.im. cohort for rubral tremor fulfilling inclusion criteria was -4.03 (95% CI -7.68 to -0.38; n=5). For the safety analysis four cohorts were identified (Fig. 3C), reporting a persistent side effect rate of 30.3±10.9% (n=43).

Dystonic Tremor

There was no publication on lesional neurosurgery for dystonic tremor found that fulfilled inclusion criteria for this analysis – the therapeutic evidence for this entity, mainly based on small trials and case series, has been reviewed elsewhere[44].

DISCUSSION

This systematic review summarizes and assesses the efficacy of lesional functional neurosurgical interventions for tremor published since 1990 in a systematic manner. Applying a stringent set of inclusion and exclusion criteria it

summarizes the available evidence to support the efficacy for each different intervention target and technique. As such it presents the current state of the field and allows comparison between different intervention techniques and anatomical targets according to tremor aetiology.

Efficacy of lesioning for tremor

Across all tremor aetiologies, the large majority of patients have been treated at the V.im. target and with all but one of the GK studies[45] showing significant improvement, our data confirm the efficacy of this target. In this regard, the PD subgroup analysis is of particular interest, as it confirms the previous perception from decades of functional neurosurgery on the superiority of the V.im. target for tremor suppression. We acknowledge that our analysis does not take other major motor symptoms of PD such as bradykinesia, rigidity and dyskinesia, nor non-motor symptoms into account. As it was, however, designed to quantify treatment efficacy for tremor across aetiologies this is deemed acceptable. We would however expect a selection bias against tremor-dominant cases in the RF GPi group beyond the studies that explicitly mentioned their exclusion[46] or preference of akinetic-rigid cases[47-49], as pallidotomies are historically considered to be less effective for tremor reduction than thalamotomies. Nevertheless, pallidotomies form the largest group (n=514) of PD patients with the highest rate of prospectively sampled data in this analysis. By and large they show a stronger effect size in larger[50-52] than smaller samples[53,54], confirming that pallidotomies have a significant effect on tremor. The significant superiority of RF V.im. over both RF GPi and RF STN ablation for PD tremor reduction (95% CI intervals non-overlapping) nevertheless confirms the superiority of the thalamic target for tremor reduction in PD and corroborates the importance of this structure in the involved tremor-network.

Thalamic V.im. target

Essential Tremor

We were surprised to find only very few data on RF V.im. lesioning in ET published during the time period studied, resulting in the large 95% confidence interval crossing the midline (Figure 2A). However, given only two studies were included in this subgroup, each showing a significant effect individually, we consider this observation a statistical artefact common to subgroup analyses with a low n. The GK thalamotomy group showed the highest degree of heterogeneity and included both studies reporting the highest[55] and lowest effect size[45] in this work. In part this might reflect the variability of radiation effect on tissue, which still cannot be predicted for individual cases[56]. Given

that much larger pro-[57] and retrospective[58] studies reported a smaller effect size, the efficacy reported in Kondziolka et al.[55] seems very optimistic. Interestingly, heterogeneity of results was lowest amongst MRIgFUS studies, in particular targeting the CTT (I^2=0.00), which is surprising given the small number of cases and cohorts. Although a direct comparison between MRIgFUS V.im. vs. CTT is inappropriate given the current number of available cases, it nevertheless indicates at least similar efficacy. Overall the combined effect size for V.im. lesions in ET indicates a robust effect on tremor reduction and corroborates decades of thalamotomy experience. Long-term follow-up studies report a robust reduction of tremor severity after a mean 59 months using RF[59] and a mean 36-40 months[55,57] using GK V.im. ablation. The longest follow-up of a lesional tremor study has been reported for targeting of the ZI + V.oa./V.op./Ra.prl at 8.5 years of follow-up[60], although this study of combined targets is not included in the efficacy meta-analysis.

Our analysis revealed different rates of persistent side effects of unilateral lesional treatment at the V.im. target according to surgical technique: while overall the rate recorded was highest for MRIgFUS V.im. lesions (18.7%), severe effects such as hemiparesis were reported in 9.3% after RF V.im., 1.8% after GK V.im. and 1.2% after MRIgFUS V.im. ablation, while paraesthesia accounted for 60% of persistent side effects after MRIgFUS V.im. treatment. Importantly, the rate of prospectively monitored patients was much higher in MRIgFUS V.im. (100%) than in RF V.im. (28%) or GK V.im. (12%) studies, possibly introducing recall bias in the latter. Taking these mean values as a benchmark illustrates how the dysarthria rate after unilateral V.im. lesions (RF: 0%, n=32; GK: 1.3%, n=153; Figure 3B) drastically increases with simultaneous, bilateral treatment (RF: 66%, n=3 [61]).

Parkinson´s disease tremor

It is difficult to explain the much larger effects size of RF V.im. (Hedge`s g -4.15) over GK V.im. (-2.20) lesioning in PD, especially as the effect size of V.im. lesions in ET (-2.34) is similar to the latter. Unfortunately, primary data do not allow to compare baseline tremor severities between studies and groups, making it difficult to ascertain the reason for this difference. It is a possibility that electrophysiological target verification, used in all of RF V.im. PD cases but in only a fraction of RF V.im. ET and none of the GK V.im. PD cases included, may have contributed to this difference. Still, the relative consistent outcome in the well sized RF V.im. group supports the validity of this finding.

Unilateral lesioning using RF ablation appeared to cause similar rates of persistent side effects between 9.2-13.6% if aiming at the V.im. (mainly hemiparesis, dysarthria, gait disturbance), STN (mainly hemiballism, dyskinesia) and the pallidum (mainly hemiparesis, dysarthria, anopsia), while incisionless interventions and in particular GK caused

somewhat less frequent side effects. Comparing the mean incidence rate of persistent dysarthria & dysphagia after pallidal unilateral (2.5%, n=515, Figure 3A) and bilateral (11%, n=28 [62]; 43%, n=7 [63]), as well as RF V.im. thalamic unilateral (1.5%, n=198, Figure 3A) and bilateral (11%, n=9[64]; 50%, n=2[59]) quantifies the dramatically increased risk with bilateral treatment.

MS tremor

MS tremor differs from the above-mentioned aetiologies as its phenotype depends on the lesion location. Our data indicate a robust positive effect of V.im. lesional surgery (Figure 2C). However, efficacy seems much more short-lived than in other aetiologies and the mean tremor-free interval after V.im. ablation or stimulation has been reported to be as short as 3 months only[65]. Two retrospective, controlled studies suggest that thalamotomy might be superior to thalamic stimulation on longer follow-up [66,67].

Furthermore, our analysis suggests persistent side effects of unilateral lesional interventions in up to 40% of cases. In interpreting both the modest results and higher rate of side effects, the advanced disease stages of MS patients subjected to surgery have to be taken into account[43,68,69]. Caution should therefore be exercised in patients presenting with tremor and ataxia, as thalamotomy might improve tremor but aggravate ataxia, compromising limb dysfunction[13,70] and even worsening quality of life[70] or manual skills[43]. The limited number of reported cases of MS relapses after GK treatment do not allow to conclude that irradiation has a causal relationship with demyelinating events, although MS patients have a higher susceptibility for demyelinating events after whole brain irradiation[43]. Overall, lesional therapy for tremor appears to be a therapeutic option in only a limited, highly selected subset of MS tremor patients, particularly with low disease activity and little ataxia.

Rubral tremor

Injury to the cerebellum, midbrain or thalamus containing the afferent cerebellar fibres to the thalamus are causal in the generation of midbrain/rubral tremor[71]. Our analysis confirms the paucity of data on lesional treatment for this entity, for which historically the majority of patients have been treated at the V.im. target[72]. In the past, authors repeatedly pointed out that spontaneous improvement of tremor may occur within 12 months of the initial injury, which therefore should have lapsed before planning an intervention[73,74]. This and the 30% incidence rate of persistent side-effects shown in our analysis preclude lesional treatment to highly selected cases. There is only sparse evidence to support

lesional treatment of symptomatic tremors due to Wilson`s disease, PKAN and other rare aetiologies[75].

Subthalamic nucleus target

Among the targets employed for PD tremor, the high level of consistency of tremor improvement after RF STN ablation studies (I^2=0.38) points at a very reliable and predictable, although not very strong effect of this target. Although theoretically elegant, STN lesioning has never been widely practised in the field, mainly due to the risk of causing hemiballism and -dyskinesia. Our side effect analysis (n= 140, figure 3A) suggests a mean rate of 9.3% of persistent hemiballism/-dyskinesia after unilateral lesional STN treatment in PD. This increases with bilateral treatment up to 20% (n=5[76]). While some argue the risk for surgery-induced dyskinesia to be smaller if a STN lesion involves also dorsally located pallidofugal fibres in the ZI[46,77,78], others reported dyskinesia to be associated with larger lesion size[79-81]. In general, the effect on tremor after STN lesions has been described to decrease over time[79-81]. Some authors also suggested that a predominant improvement of tremor might actually be due to lesion encroachment on the adjacent ZI and even V.im.[82], as confirmed on post-mortem analysis[78].

Certainly, the STN proper as a neurosurgical target is limited to PD only and although the effect on bradykinesia and rigidity are appreciated, our analysis confirms its effect on tremor to be less powerful than that of thalamic targets.

Incisionless approaches

Incisionless approaches using GK or MRIgFUS for functional neurosurgery appeal due to their apparent non-invasiveness. Indeed, they clearly circumvent the risks associated with open brain surgery or implantation of devices but their technique-inherent advantages and disadvantages should be weighed carefully. Furthermore, at least for MRIgFUS, the evidence base for its efficacy and safety is promising but still limited.

In ET our analysis shows that the efficacy of GK and MRIgFUS ablation of thalamic/PSA targets is comparable to established RF V.im. ablation. Interestingly, both the number of cases (n=358 vs. n=25) as well as the percentage of prospective cases (74% vs. 0%) was much higher among incisionless treated patients, pointing that the latter has possibly by en large replaced RF ablation for ET at least in academic centres. Within the group of incisionless interventions, the effect size was found to be much more heterogeneous with GK V.im. (I^2=0.92) than MRIgFUS V.im. (I^2=0.51) or MRIgFUS CTT (I^2=0.00) ablation, although the prior is based on a larger number of and higher rate of

prospectively assessed patients. This indicates a technique-inherent heterogeneity related to GK.

Persistent mild contralateral paresis, hypaesthesia, dysarthria and dysphagia have been reported after GK lesioning, but overall this technique caused the lowest rate of persistent side effects both in PD and ET, although this is also based on cohorts with the lowest rate of prospective follow-up. The unexpected enlargement of lesions documented up to 14 months after treatment even with moderate doses of 140Gy[45] argues for adherence to follow-up durations long enough to cover the evolution of potential side effects – therefore, we suggest that follow-up in GK trials should be at least 14 months. Given the natural evolution of GK lesions with time, 6 months follow-up[83] seems insufficient.

Although so far data of only 126 tremor patients have been published in series of MRIgFUS ablation[23-25,84-87], the majority of them have been treated in prospective trials. Comparison of treatment effect sizes, so far only possible for ET, shows similar efficacy for MRIgFUS and RF ablation. MRIgFUS V.im. lesions however entail a comparably high rate of persistent side effects, although this in the majority of cases refers to paraesthesia only (see Figure 3B). The only randomized sham-controlled, multicentre, blind-assessed trial of MRIgFUS V.im. ablation[84] reported persistent paraesthesia in 14%, gait disturbance in 9%, contralateral paresis in 2%, dysmetria in 4% and disequilibrium in 2% of cases 12 months after the intervention. In comparison, the side effect rate of MRIgFUS CTT treatment, even when including three cases of staged bilateral treatment, is lower[25,85] and does not include paraesthesia. This can be seen as early indication that the larger anatomical distance of the CTT to eloquent structures might translate into a lower side effect rate.

So far the limited number of patients and short follow-up published for V.im. MRIgFUS interventions in PD[86,87] await replication. The use of conventional thalamotomy to treat PD in the 21st century is in our opinion however limited to exceptional cases, in which tremor is the predominant symptom.

Posterior subthalamic area target

Mundinger's subthalamotomy appeals to investigators today again. Initially intended to minimize the lesion size necessary to create sufficient effect and increase the anatomical safety margin to eloquent structures near by, over the years considerable evidence accumulated in the DBS literature to suggest that stimulation within the PSA (cZI and Ra.prl) might be superior over V.im. stimulation in ET[88-92] and PD[93]. In the past, neurosurgeons had adapted the idea of targeting this area, as it contains the CTT, containing the connecting fibre tracts between cerebellum and thalamus. In the PSA these fibres are at their highest anatomical density and at a larger Euclidian distance to vulnerable structures such as sensory thalamic nuclei or the internal capsule, providing a rationale to target them at this location.

Our analysis provides first evidence that lesioning of the CTT[25,85] compared to V.im.[23,24,84] using the same MRIgFUS technique might be of equal effect size and possibly at a smaller rate of persistent side effects. Of course, this will have to be confirmed by additional, well-designed studies. Nevertheless, the observation of no paraesthesia occurrence after CTT lesioning can be seen as confirmation of the use of a larger Euclidian safety margin in particular to thalamic sensory nuclei. Importantly, this indicates a target- and not technique-specific side effect profile for MRIgFUS interventions. Further exploration of this target seems appropriate and needed.

Methodological considerations

When interpreting the results of this meta-analysis, several factors call for consideration. Although applying a rigid set of in- and exclusion criteria to ensure data homogeneity, validity and reliability, inconsistencies in the included primary data necessitate discussion.

The heterogeneity of targeting and operating technique, inevitably slightly different from one surgical team to another, introduces variability, for which it is impossible to control for. In particular, this applies to targeting accuracy, which of course is one of the most important parameters in functional neurosurgery, which however in most instances is not verified independently. Furthermore, retrospective studies are known to introduce potential recall bias. As indicated in Figures 2 and 3 the proportion of pro- and retrospectively assessed cases differed considerably between tremor aetiologies, techniques and surgical targets. Although the degree of variability introduced by this is difficult to quantify, results in groups with a higher degree of prospective cases may be viewed as more reliable.

Particular attention should also be paid to the fact that primary tremor data was heterogeneous in its use of rating scales, items and compound item sums. Ideally, all studies included would have used the same scale and item, with comparable baseline tremor severity between all study cohorts. As the primary data available was not structured in this way (see Supplementary Table 1) our analysis after data normalization to Hedges` g cannot differentiate between “resting”, “kinetic” or “postural” tremor components or their combination, but reports the change in overall tremor severity. We posit that inherent to aetiology this naturally would pertain more to postural and kinetic aspects in ET and more to rest tremor in PD etc. Furthermore, the analysis does not allow for comparison between baseline tremor severity to match for different disease severity, which is impossible given the primary data available. This method however allows for comparison of the effect size in accordance to empiric findings that tremor scales are not linear but logarithmic measures of tremor severity[94].

As another potential weakness, follow-up time-points were not homogeneous between cohorts. Although therefore the

mean follow-up between cohorts included in the meta-analysis may differ, our analysis with follow-up as a nuisance factor did not provide evidence that this significantly influenced the effect size in any category studied. This should not be interpreted as evidence that the effect size of the discussed interventions does not change over time, which cannot be conclusively answered from the data available.

Using the heterogeneity index I^2 as a measure of consistency, summing up all of the above discussed potential causes of heterogeneity, our meta-analysis results for MRIgFUS CTT for ET (I^2 =0.00), V.im. ablation using RF (I^2 =0.14) and GK for rubral tremor (I^2 =0.32) and RF STN for PD tremor (I^2 =0.38) showed the most consistent results.

In addition to the above, this work highlights systematic shortcomings in the functional neurosurgery literature. For example it is impossible to calculate the rate of tremor recurrence, as this is mentioned and quantified in only a fraction of publications. The scarcity of RCTs in our primary data is another important point. Furthermore, the quantification of quality of life and functional impairment, established in many other fields of movement disorder research, is barely reported on in the functional neurosurgical literature. Only prospective, blind-assessed, controlled trials with adequately designed follow-up will answer these important questions.

CONCLUSION

Results of this meta-analysis confirm the prime role of thalamotomies in lesional surgery for various tremor aetiologies. Theoretical advantages and promising clinical data with regards to safety and efficacy of incisionless procedures currently build up momentum to reappraise lesional interventions as treatment strategies for tremor disorders. This analysis provides evidence in ET to suggest that in particular the rate of persistent side effects is target- and not technique-specific. The exciting technical possibilities of GK and especially MRIgFUS therefore should be geared not only to close the gaps in the existing literature highlighted but also to further advance our knowledge base for treatment decisions. Nevertheless, this systematic review also shows how limited the evidence base is in particular for MRIgFUS ablation so far. It therefore highlights the need for adequately designed prospective trials to support the existing data on safety and efficacy not only for established targets such as V.im., but also of recently rediscovered targets within the PSA. Before that, the indiscriminate application of incisionless interventions to novel indications could potentially harm the further development of this fascinating technique.

This work is not able to answer the ultimate question in how far the treatment of tremor in the future should rely on stimulation or lesional techniques but it aims to provide the basis for future studies to answer this question. Most likely, tremor aetiology and the target used will influence this decision in addition to available resources and patient preference. Ultimately, however, only head-to-head comparison of DBS and MRIgFUS will be able to answer this question. Similarly, it remains to be seen in how far incisionless technology might be able to reduce the so far inacceptable high side effect rates of bilateral lesional treatment.

Figure legends:

Figure 1: PRISMA Flow chart of study selection.

Figure 2: Forest plot of data on treatment for Parkinson`s disease tremor (A), Essential Tremor (B) and Multiple Sclerosis tremor (C) included in the meta-analysis. The effect size (Hedge`s g) including 95% CI is shown for each individual study, as well as for subgroups of homogeneous indication and intervention. Combined effect sizes were calculated for Essential Tremor and MS tremor, as all lesions aimed at the V.im., whereas in Parkinson`s disease this was omitted due to target heterogeneity. The solid vertical line at zero indicates no effect, a negative effect size indicates improvement of tremor, whereas a positive effect size indicates tremor worsening. References for the studies are provided in the appendix.

Figure 3: Rate of reported persistent side effects after unilateral lesional functional neurosurgical interventions for Parkinson`s disease tremor (A), Essential Tremor (B) and MS/Rubral tremor (C). Mean percentages (± standard deviation) of persistent side effects were calculated per target/technique and compared using non-parametric statistics. Additional information on the percentage of subjects assessed prospectively as well as the nature of side effects per group are given in the table below (* indicates statistically different at group level but not on multiple testing).

Table 1: In- and exclusion criteria.

Supplementary files:

Suppl_Table 1: Characteristics and details of studies included in the systematic review and meta-analysis, reporting tremor severity using validated (A) or non-validated tremor scales (B). Studies reporting tremor scale data. References for the studies are provided in the appendix. ∗ data included in efficacy meta-analysis; † data included in safety analysis of reported persistent side effect after unilateral lesioning; ‡ number of subjects with complete efficacy data (of number of subjects subjected to intervention); data on bilateral interventions in *italics*; n.r. not reported; - data from same cohort but different time point; retro – retrospective; pro – prospective; ? – not given;

Suppl_Table 2: Jadad quality assessment of randomized controlled trials included in this meta-analysis.

Suppl_Table 3: Newcastle Ottawa quality assessment of cohort studies included in this meta-analysis.

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