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

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

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Abstract

Introduction: The recent introduction of incision-less lesional neurosurgery using Gamma knife and MRI-guided focused ultrasound has revived interest in lesional treatment options for tremor disorders. Preliminary literature researches reveal that the consistency of treatment effects after lesional neurosurgery for tremor has not formally been assessed yet. Similarly, the efficacy of different targets for lesional treatment and incidence of persistent side effects of lesional neurosurgical interventions has not been comprehensively assessed. This work therefore aims to describe a suitable process how to review the existing literature on efficacy and persistent side effects of lesional neurosurgical treatment for tremor due to Parkinson`s disease (PD), Essential Tremor (ET), Multiple Sclerosis (MS) and midbrain / rubral tremor.

Methods and Analysis: We will search electronic databases (Medline, Cochrane) and reference lists of included articles for studies reporting lesional interventions for tremor in cohorts homogeneous for tremor aetiology and intervention (technique and target). We will include cohorts with a minimum number of five subjects and follow-up of two months. One investigator will perform the initial literature search and two investigators will then independently decide which references to include for final efficacy and safety analysis. After settling of disagreement, data will be extracted from articles using a standardized template. We will perform a random-effect meta-analysis calculating standardized mean differences (Hedge`s g) for comparison in Forest plots and subgroup analysis after assessment of heterogeneity using I^2 statistics.

Ethics and Dissemination: This study will summarize the available evidence on the efficacy of lesional interventions for the most frequent tremor disorders, as well as for the incidence rate of persisting side effects after unilateral lesional treatment. This data will be useful to guide future work on incision-less lesional interventions for tremor.

Systematic review registration: This study has been registered with the PROSPERO database (no. CRD42016048049).

Keywords: Tremor, Lesional neurosurgery, Thalamotomy, Subthalamotomy, Pallidotomy, Radiofrequency ablation, Focused ultrasound, Gamma knife

Strengths and Limitations of this study:

- Protocol for first formal, systematic review and meta-analysis of lesional functional neurosurgery for tremor
- Comprehensive comparison of consistency and efficacy of lesional targets in most prevalent tremor aetiologies
- First meta-analysis of persistent side effect prevalence after lesional neurosurgical treatment
- Protocol to establish safety and efficacy benchmarks for emerging incision-less lesional functional neurosurgery approaches
- Frequent retrospective nature and potential reporting bias of primary source data will be addressed

Main text

INTRODUCTION:

Tremor is defined as an involuntary, oscillating sinusoidal movement of a body part and is a frequent symptom in Parkinson`s disease (PD), Essential Tremor (ET), but also in Multiple Sclerosis (MS) or after midbrain lesions. ET is one of the most common movement disorders affecting up to 4.6% of the population ≥ 65 years [1]. While most patients do well with first line oral medication like betablockers or Primidone, at least 50% of them do not tolerate this long term [2], leaving 10% severely disabled by their tremor, loosing dexterity to a great extent [3]. Similarly in PD, tremor is one of the most challenging symptoms to treat with oral medication [4] and this group of severely incapacitated patients depends on advanced therapeutic options [5].

Although it`s phenomenology considerably differs between the above mentioned aetiologies, our current understanding points at a common abnormal central oscillatory activity within a network involving motor cortex, thalamus, globus pallidum and cerebellum [6-8]. Accordingly, lesional surgical interventions within parts of this network using functional neurosurgery have been utilized successfully since the 1940ies [9]. Over time, interventions at various anatomical structures within this network have been studied [9-12] and it is now generally accepted that thalamotomy, influencing afferent cerebellar signalling, provides the highest level of tremor symptom relief.

During the past two decades lesional interventions, although performed world-wide [13], were largely superseded in the academic setting by stimulation technology [14], which contributed dramatically to our understanding of tremor pathoaetiology [15-18]. Since the introduction of Gamma Knife (GK), incision-less functional neurosurgery, i.e. lesion placement through the intact skull, is a possibility [12] and the recent addition of MRI-guided high-intensity focused ultrasound (MRIgFUS) [19-22] has again stimulated interest in this field [23,24].

A preliminary literature search performed in June 2016 suggests a wealth of studies on this topic, although the majority of published reports are of small or medium size. Obvious heterogeneity in study design, data collection, documentation and presentation limit the accessibility of this data and complicate it`s interpretation. So far, there are no reliable estimates on the consistency of treatment effects after lesional interventions for tremor. Similarly, the prevalence of persisting side effects after such interventions has not been compared in a comprehensive way. We therefore aim to summarize the available data on lesional functional surgery for tremor disorders to allow

comparisons between aetiologies, treatment targets and techniques. The limitations of earlier reports with regards to established and recognized diagnostic criteria, use of validated clinical assessment tools and electrophysiological or imaging-based target verification [10] led us to restrict the literature search to a publication date from 1990 onwards.

We specifically aim to answer the following questions:

What is the efficacy of lesional neurosurgical interventions on tremor severity in tremor due to PD, ET, MS and midbrain/rubral origin for different lesioning techniques and targets according to published, peer-reviewed studies?

What is the prevalence rate of persistent side effects after unilateral lesional interventions for different lesioning technique and target according to published, peer-reviewed studies?

This will not only allow to objectively assess the safety and efficacy of existing lesional tremor treatment approaches but also to compare novel, incision-less lesional interventions with this benchmark.

METHODS AND ANALYSIS:

Protocol

The methods for this systematic review have been developed according to the recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement [25]. This systematic review protocol has been registered in the International Prospective Register of Systematic reviews (PROSPERO) on September 20th 2016: CRD42016048049. A PRISMA-P file is attached (see Additional file 1).

Eligibility criteria

Cohorts reporting a minimum of five patients of or above the age of 18 years 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 incision-less (MRIgFUS, GK) means. Cases that received lesional functional neurosurgery in

more than one anatomical structure at the same time or non-lesional approaches including deep brain stimulation (DBS) will be excluded.

Outcome Measures:

As we expect only limited amount of data from controlled trials to be found, this protocol aims to assess intervention effects by comparing pre- and post-interventional states. Primary outcome measure will be the change in upper limb tremor severity from baseline to follow-up time points, as reported on a validated tremor rating scale (United Parkinson´s disease rating scale, part III (UPDRS III), clinical rating scale for tremor (CRST [26,27]), Whiget tremor scale etc.). Results from controlled trials comparing lesional interventions to alternative interventions, such as e.g. best medical treatment or deep brain stimulation will be included and discussed in a narrative way as far as meaningful for comparison to lesional interventions. As we expect the literature to be heterogeneous in terms of follow-up duration and applied tremor rating scales we aim to primarily summarize the outcome as standardized mean difference (Hedge`s g) [28] irrespective of follow-up duration. To limit bias we will chose the follow-up time-point with the largest number of patients retained in the analysis. Homogeneous cohorts (same tremor aetiology, intervention target and technique) will be grouped together for subgroup-analysis if they consist of a minimum of n=2.

Secondary outcome measure will be the frequency of reported persistent side-effects after unilateral lesions per indication and intervention group, calculated as % of cases per group. In addition, we aim to calculate the mean rate of dysarthria and gait difficulties reported for unilateral vs. bilateral procedures. Homogeneous cohorts (tremor aetiology, intervention target and technique) will be grouped together for analysis if they consist of a minimum of n=2.

Study design:

The choice of inclusion/exclusion criteria reflects that we expect very few randomized trials in this field. Inclusion: Randomized controlled trials (RCTs), Meta-Analysis, case-control, prospective and retrospective case series. Exclusion: Studies reporting results from mixed aetiologies (subjects of different aetiologies grouped together) or mixed interventions (different anatomical targets grouped together). We will include peer-reviewed articles without language restriction. Letters, abstracts and editorials will not be included (see Table 1).

Information sources and search strategy:

A full search of MEDLINE and Cochrane (ovid) database will be performed limited to time of publication (between January 1990 and September 2016), using “tremor*” AND “lesion*”, “neurosurg*”, “thalamotomy”,

"subthalamotomy", "pallidotomy" as search terms. Contact with authors will be made if needed.

183 Table 1. Planned 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 incision-less (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

Data collection:

Primary database searches will be performed by one researcher who will compile a list of non-duplicate studies according to in- and exclusion criteria. In addition to the primary searches we will identify relevant studies from the reference lists of primary search results. From this list, two researchers will independently compile a definitive list of studies to be included in the safety and efficacy analysis – before analysis, lists will be compared and discrepancies settled. Data will be extracted from original sources by use of a standardized template. As we aim to cover publications from the past 26 years, which might cover interventions dating back to >35 years we deem it unrealistic to compile data on individual participant basis, unless given in publications.

Data Items:

1. Publication details: title, authors, publication year
2. Design: pro- retrospective, randomization, blind-assessment, controlled;
3. Clinical details: cohort size, anatomical target, treatment technique, uni- or bilateral intervention, guidance/targeting technique, tremor scale and item used, pre- and postinterventional tremor score (mean ± standard deviation), follow-up duration, art / number and severity of transient and persistent side-effects reported;

Quality assessment according to Jadad [29] and Newcastle Ottawa scale[30];

Bias assessment:

If several follow-up time points are reported per cohort, the time-point with the largest number of subjects retained will be chosen to minimize selection/reporting bias. We will assess the quality of RCTs (Jadad scale [29]) and non-randomized trials (Newcastle-Ottawa Scale [30]) by means of standardized assessment tools and will discuss the limitations of the data synthesis in terms of study and data quality. In addition to that, in the discussion of results - depending on the overall quality of data – we will discuss potential shortcomings of our source data, as retrospective analyses with incomplete follow-up tend to introduce bias.

A formal assessment of publication bias however only makes sense in the presence of a sufficient number (>10) of homogeneous data sets [31]. As we expect the data compiled in this analysis to be of limited homogeneity we do not plan to formally calculate bias assessments such as by means of Funnel plots, as this can result in misleading results in small and heterogeneous data sets [31]. This shall only be calculated in case subgroups with more than 10 studies included are shown to have no substantial level of heterogeneity ($I^2 < 50\%$).

Data synthesis and statistics:

Aggregate data on pre-/post-interventional tremor severity will be extracted from publications or calculated from them in the form of mean ± standard deviation for outcome variables per indication/intervention group per publication. Data for continuous outcome measures will be used to calculate standardized mean difference (Hedge`s g) values including 95% confidence intervals [28] and to compute Forest plots using the Meta-Essentials workbook4 toolbox [32]. Based on study heterogeneity we will use a random-effects meta-analysis for quantitative comparison. Heterogeneity between studies will be assessed using I^2 statistics, with an I^2 >50% regarded as an indicator of substantial heterogeneity.

As we will analyse data from different tremor aetiologies and interventions, we will undertake subgroup analyses by the following subgroups: PD tremor: RF ablation ventral intermedial (V.im.) nucleus, RF ablation Globus pallidus internus (GPi), RF ablation subthalamic nucleus (STN), GK ablation V.im.; ET tremor: RF ablation V.im., GK ablation V.im., MRIgFUS ablation V.im. MS tremor: RF ablation V.im., GK ablation V.im. Formal subgroup analysis will be done in case of groups of a minimum of 2 studies per study intervention, target and aetiology.

We will provide a narrative synthesis of results structured by aetiological category and intervention type and also discuss the influence of study design and follow-up, taking GRADE guidelines into consideration [33].

ETHICS AND DISSEMINATION:

The aim of this systematic review and meta-analysis is to summarize the data on consistency and efficacy of lesional functional neurosurgical interventions for the treatment of tremor disorders. The recent development of incision-less lesional functional neurosurgery techniques warrants this careful reassessment of the existing literature to guide future research into lesional interventions. Ethically, we consider it an obligation to summarize this data in a systematic manner to optimize treatment outcome for future patients. It will provide the basis to compare the efficacy of lesional interventions across anatomical targets, tremor aetiologies and lesional techniques. Furthermore, the calculation of prevalence rates of persistent side-effects after unilateral lesional interventions will allow for safety comparisons of established, incisional lesioning techniques and novel incision-less procedures, such as MRIgFUS and Gamma knife. This will allow a more unbiased evaluation of the effects of bilateral interventions of the past and possible future.

We are committed to publish the results of this study in a peer-reviewed journal to distribute the outcome of this work. To maximise data transparency, we aim to include the data extracted from published sources in our final

publication in the form of a table. This protocol, as well as it`s registration and publication with the PROSPERO database (no. CRD42016048049) documents our continuing efforts of transparent research.

List of abbreviations:

Clinical rating scale for tremor (CRST), deep brain stimulation (DBS), Essential Tremor (ET), Gamma knife (GK), Globus pallidus internus (GPi), MRI-guided high-intensity focused ultrasound (MRIgFUS) Parkinson`s disease (PD), Multiple Sclerosis (MS), Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P), Randomized controlled trials (RCTs), subthalamic nucleus (STN), United Parkinson´s disease rating scale, part III (UPDRS III), ventral intermedial (V.im.) nucleus,

Declarations:

Ethics approval: not applicable

Data sharing statement: not applicable – research protocol only

Competing interest: The authors declare that they have no competing interests.

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Author`s contribution: SRS initialized and conceptualised the research plan for the proposed systematic review and wrote the first manuscript draft. KB provided critical input on the proposed methodology and statistical analysis and reviewed the manuscript for important intellectual content. JKK and JWC reviewed the methodology and reviewed the manuscript for important intellectual content. GK supervised the project and corrected the manuscript for important intellectual content. All authors approved of the final version of the manuscript.

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Supplement to "Functional lesional neurosurgery for tremor - a protocol for a systematic review and meta-analysis" Schreglmann et al.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title page
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2 and 4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 8
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Page 8
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3, 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4
METHODS			
Eligibility	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years	Page 4-6

criteria		considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 5, 6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 5, 6
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 6, 7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 6, 7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 6, 7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 6, 7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Abstract

Introduction: The recent introduction of incision-less lesional neurosurgery using Gamma knife and MRI-guided focused ultrasound has revived interest in lesional treatment options for tremor disorders. Preliminary literature researches reveal that the consistency of treatment effects after lesional neurosurgery for tremor has not formally been assessed yet. Similarly, the efficacy of different targets for lesional treatment and incidence of persistent side effects of lesional neurosurgical interventions has not been comprehensively assessed. This work therefore aims to describe a suitable process how to review the existing literature on efficacy and persistent side effects of lesional neurosurgical treatment for tremor due to Parkinson`s disease (PD), Essential Tremor (ET), Multiple Sclerosis (MS) and midbrain / rubral tremor.

Methods and Analysis: We will search electronic databases (Medline, Cochrane) and reference lists of included articles for studies reporting lesional interventions for tremor in cohorts homogeneous for tremor aetiology and intervention (technique and target). We will include cohorts with a minimum number of five subjects and follow-up of two months. One investigator will perform the initial literature search and two investigators will then independently decide which references to include for final efficacy and safety analysis. After settling of disagreement, data will be extracted from articles using a standardized template. We will perform a random-effect meta-analysis calculating standardized mean differences (Hedge`s g) for comparison in Forest plots and subgroup analysis after assessment of heterogeneity using I^2 statistics.

Ethics and Dissemination: This study will summarize the available evidence on the efficacy of lesional interventions for the most frequent tremor disorders, as well as for the incidence rate of persisting side effects after unilateral lesional treatment. This data will be useful to guide future work on incision-less lesional interventions for tremor.

Systematic review registration: This study has been registered with the PROSPERO database (no. CRD42016048049).

Keywords: Tremor, Lesional neurosurgery, Thalamotomy, Subthalamotomy, Pallidotomy, Radiofrequency ablation, Focused ultrasound, Gamma knife

Strengths and Limitations of this study:

- Protocol for first formal, systematic review and meta-analysis of lesional functional neurosurgery for tremor
- Comprehensive comparison of consistency and efficacy of lesional targets in most prevalent tremor aetiologies
- First meta-analysis of persistent side effect prevalence after lesional neurosurgical treatment
- Protocol to establish safety and efficacy benchmarks for emerging incision-less lesional functional neurosurgery approaches
- Frequent retrospective nature and potential reporting bias of primary source data will be addressed

Main text

INTRODUCTION:

Tremor is defined as an involuntary, oscillating sinusoidal movement of a body part and is a frequent symptom in Parkinson`s disease (PD), Essential Tremor (ET), but also in Multiple Sclerosis (MS) or after midbrain lesions. ET is one of the most common movement disorders affecting up to 4.6% of the population ≥ 65 years [1]. While most patients do well with first line oral medication like betablockers or Primidone, at least 50% of them do not tolerate this long term [2], leaving 10% severely disabled by their tremor, losing dexterity to a great extent [3]. Similarly in PD, tremor is one of the most challenging symptoms to treat with oral medication [4] and this group of severely incapacitated patients depends on advanced therapeutic options [5].

Although its` phenomenology considerably differs between the above mentioned aetiologies, our current understanding points at a common abnormal central oscillatory activity within a network involving motor cortex, thalamus, globus pallidum and cerebellum [6-8]. Accordingly, lesional surgical interventions within parts of this network using functional neurosurgery have been utilized successfully since the 1940ies [9]. Over time, interventions at various anatomical structures within this network have been studied [9-12] and it is now generally accepted that thalamotomy, influencing afferent cerebellar signalling, provides the highest level of tremor symptom relief.

During the past two decades lesional interventions, although performed world-wide [13], were largely superseded in the academic setting by stimulation technology [14], which contributed dramatically to our understanding of tremor pathoaetiology [15-18]. Since the introduction of Gamma Knife (GK), incision-less functional neurosurgery, i.e. lesion placement through the intact skull, is a possibility [12] and the recent addition of MRI-guided high-intensity focused ultrasound (MRIgFUS) [19-22] has again stimulated interest in this field [23,24].

A preliminary literature search performed in June 2016 suggests a wealth of studies on this topic, although the majority of published reports are of small or medium size. Obvious heterogeneity in study design, data collection, documentation and presentation limit the accessibility of this data and complicate it`s interpretation. So far, there are no reliable estimates on the consistency of treatment effects after lesional interventions for tremor. Similarly, the prevalence of persisting side effects after such interventions has not been compared in a comprehensive way. We therefore aim to summarize the available data on lesional functional surgery for tremor disorders to allow comparisons between aetiologies, treatment targets and techniques. The limitations of earlier reports with

regards to established and recognized diagnostic criteria, use of validated clinical assessment tools and electrophysiological or imaging-based target verification [10] led us to restrict the literature search to a publication date from 1990 onwards.

We specifically aim to answer the following questions:

What is the efficacy of lesional neurosurgical interventions on tremor severity in tremor due to PD, ET, MS and midbrain/rubral origin for different lesioning techniques and targets according to published, peer-reviewed studies?

What is the prevalence rate of persistent side effects after unilateral lesional interventions for different lesioning technique and target according to published, peer-reviewed studies?

This will not only allow to objectively assess the safety and efficacy of existing lesional tremor treatment approaches but also to compare novel, incision-less lesional interventions with this benchmark.

METHODS AND ANALYSIS:

Protocol

The methods for this systematic review have been developed according to the recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement [25]. This systematic review protocol has been registered in the International Prospective Register of Systematic reviews (PROSPERO) on September 20th 2016: CRD42016048049. A PRISMA-P file is attached (see Additional file 1).

Eligibility criteria

Cohorts reporting a minimum of five patients of or above the age of 18 years 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 incision-less (MRIgFUS, GK) means. Cases that received lesional functional neurosurgery in more than one anatomical structure at the same time or non-lesional approaches including deep brain stimulation

(DBS) will be excluded.

Outcome Measures:

As we expect only limited amount of data from controlled trials to be found, this protocol aims to assess intervention effects by comparing pre- and post-interventional states. Primary outcome measure will be the change in upper limb tremor severity from baseline to follow-up time points, as reported on a validated tremor rating scale (United Parkinson´s disease rating scale, part III (UPDRS III), clinical rating scale for tremor (CRST [26,27]), Whiget tremor scale etc.). Results from controlled trials comparing lesional interventions to alternative interventions, such as e.g. best medical treatment or deep brain stimulation will be included and discussed in a narrative way as far as meaningful for comparison to lesional interventions. As we expect the literature to be heterogeneous in terms of follow-up duration and applied tremor rating scales we aim to primarily summarize the outcome as standardized mean difference (Hedge`s g) [28] irrespective of follow-up duration. To limit bias we will choose the follow-up time-point with the largest number of patients retained in the analysis. Homogeneous cohorts (same tremor aetiology, intervention target and technique) will be grouped together for subgroup-analysis if they consist of a minimum of n=2.

Secondary outcome measure will be the frequency of reported persistent side-effects after unilateral lesions per indication and intervention group, calculated as % of cases per group. In addition, we aim to calculate the mean rate of dysarthria and gait difficulties reported for unilateral vs. bilateral procedures. Homogeneous cohorts (tremor aetiology, intervention target and technique) will be grouped together for analysis if they consist of a minimum of n=2.

Study design:

The choice of inclusion/exclusion criteria reflects that we expect very few randomized trials in this field. Inclusion: Randomized controlled trials (RCTs), Meta-Analysis, case-control, prospective and retrospective case series. Exclusion: Studies reporting results from mixed aetiologies (subjects of different aetiologies grouped together) or mixed interventions (different anatomical targets grouped together). We will include peer-reviewed articles without language restriction. Letters, abstracts and editorials will not be included (see Table 1).

Information sources and search strategy:

A full search of MEDLINE and Cochrane (ovid) database will be performed limited to time of publication (between January 1990 and February 2017), using “tremor*” AND “lesion*”, “neurosurg*”, “thalamotomy”, “subthalamotomy”, “pallidotomy” as search terms. Contact with authors will be made if needed.

Search Strategy:

Item	Search Term	Boolean operator
Tremor	("tremor*"[All Fields] OR "tremor*" [MeSH Terms], "shaking" [All Fields] OR "shaking" [MeSH Terms])	AND
Lesion	("lesion*"[All Fields] OR "lesion*" [MeSH Terms], "thalamotomy" [All Fields] OR "thalamotomy" [MeSH Terms], "subthalamotomy" [All Fields] OR "subthalamotomy" [MeSH Terms], "pallidotomy" [All Fields] OR "pallidotomy" [MeSH Terms],	AND
neurosurgery	("neurosurg*"[All Fields] OR "neurosurg*" [MeSH Terms])	AND
Time-period	Between 1st January 1990 and 1st February 2017	

186 Table 1. Planned 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 incision-less (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

Data collection:

Primary database searches will be performed by one researcher who will compile a list of non-duplicate studies according to in- and exclusion criteria. In addition to the primary searches we will identify relevant studies from the reference lists of primary search results. From this list, two researchers will independently compile a definitive list of studies to be included in the safety and efficacy analysis – before analysis, lists will be compared and discrepancies settled. Data will be extracted from original sources by use of a standardized template. As we aim to cover publications from the past 26 years, which might cover interventions dating back to >35 years we deem it unrealistic to compile data on individual participant basis, unless given in publications.

Data Items:

1. Publication details: title, authors, publication year
2. Design: pro- retrospective, randomization, blind-assessment, controlled;
3. Clinical details: cohort size, anatomical target, treatment technique, uni- or bilateral intervention, guidance/targeting technique, tremor scale and item used, pre- and postinterventional tremor score (mean ± standard deviation), follow-up duration, art / number and severity of transient and persistent side-effects reported;

Quality assessment according to Jadad [29] and Newcastle Ottawa scale[30];

Bias assessment:

If several follow-up time points are reported per cohort, the time-point with the largest number of subjects retained will be chosen to minimize selection/reporting bias. We will assess the quality of RCTs (Jadad scale [29]) and non-randomized trials (Newcastle-Ottawa Scale [30]) by means of standardized assessment tools and will discuss the limitations of the data synthesis in terms of study and data quality. In addition to that, in the discussion of results - depending on the overall quality of data – we will discuss potential shortcomings of our source data, as retrospective analyses with incomplete follow-up tend to introduce bias.

A formal assessment of publication bias however only makes sense in the presence of a sufficient number (>10) of homogeneous data sets [31]. As we expect the data compiled in this analysis to be of limited homogeneity we do not plan to formally calculate bias assessments such as by means of Funnel plots, as this can result in misleading results in small and heterogeneous data sets [31]. This shall only be calculated in case subgroups with more than 10 studies included are shown to have no substantial level of heterogeneity ($I^2 < 50\%$).

Data synthesis and statistics:

Aggregate data on pre-/post-interventional tremor severity will be extracted from publications or calculated from them in the form of mean ± standard deviation for outcome variables per indication/intervention group per publication. Data for continuous outcome measures will be used to calculate standardized mean difference (Hedge`s g) values including 95% confidence intervals [28] and to compute Forest plots using the Meta-Essentials workbook4 toolbox [32]. Based on study heterogeneity we will use a random-effects meta-analysis for quantitative comparison. Heterogeneity between studies will be assessed using I^2 statistics, with an I^2 >50% regarded as an indicator of substantial heterogeneity.

As we will analyse data from different tremor aetiologies and interventions, we will undertake subgroup analyses by the following subgroups: PD tremor: RF ablation ventral intermedial (V.im.) nucleus, RF ablation Globus pallidus internus (GPi), RF ablation subthalamic nucleus (STN), GK ablation V.im.; ET tremor: RF ablation V.im., GK ablation V.im., MRIgFUS ablation V.im. MS tremor: RF ablation V.im., GK ablation V.im. Formal subgroup analysis will be done in case of groups of a minimum of 2 studies per study intervention, target and aetiology. We have not planned to restrict this meta-analysis to particular targeting modalities in order not to fragment results, although we are aware that older modalities, such as ventrculography or CT-based approaches, are not used anymore at least in the western hemisphere academic setting.

We will provide a narrative synthesis of results structured by aetiological category and intervention type and also discuss the influence of study design and follow-up, taking GRADE guidelines into consideration [33]. We will also discuss tremor recurrence in the narrative section of this review, as we expect only limited data on this in the bulk of reports.

ETHICS AND DISSEMINATION:

The aim of this systematic review and meta-analysis is to summarize the data on consistency and efficacy of lesional functional neurosurgical interventions for the treatment of tremor disorders. The recent development of incision-less lesional functional neurosurgery techniques warrants this careful reassessment of the existing literature to guide future research into lesional interventions. Ethically, we consider it an obligation to summarize this data in a systematic manner to optimize treatment outcome for future patients. It will provide the basis to compare the efficacy of lesional interventions across anatomical targets, tremor aetiologies and lesional techniques. Furthermore, the calculation of prevalence rates of persistent side-effects after unilateral lesional interventions will allow for safety comparisons of established, incisional lesioning techniques and novel

incision-less procedures, such as MRIgFUS and Gamma knife. This will allow a more unbiased evaluation of the effects of bilateral interventions of the past and possible future.

We are committed to publish the results of this study in a peer-reviewed journal to distribute the outcome of this work. To maximise data transparency, we aim to include the data extracted from published sources in our final publication in the form of a table. This protocol, as well as it`s registration and publication with the PROSPERO database (no. CRD42016048049) documents our continuing efforts of transparent research.

List of abbreviations:

Clinical rating scale for tremor (CRST), deep brain stimulation (DBS), Essential Tremor (ET), Gamma knife (GK), Globus pallidus internus (GPi), MRI-guided high-intensity focused ultrasound (MRIgFUS) Parkinson`s disease (PD), Multiple Sclerosis (MS), Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P), Randomized controlled trials (RCTs), subthalamic nucleus (STN), United Parkinson´s disease rating scale, part III (UPDRS III), ventral intermedial (V.im.) nucleus,

Declarations:

Ethics approval: not applicable

Data sharing statement: not applicable – research protocol only

Competing interest: The authors declare that they have no competing interests.

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Author`s contribution: SRS initialized and conceptualised the research plan for the proposed systematic review and wrote the first manuscript draft. KB provided critical input on the proposed methodology and statistical analysis and reviewed the manuscript for important intellectual content. JKK and JWC reviewed the methodology and reviewed the manuscript for important intellectual content. GK supervised the project and corrected the manuscript for important intellectual content. All authors approved of the final version of the manuscript.

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Supplement to "Functional lesional neurosurgery for tremor - a protocol for a systematic review and meta-analysis" Schreglmann et al.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title page
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2 and 4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 8
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Page 8
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3, 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4
METHODS			
Eligibility	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years	Page 4-6

criteria		considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 5, 6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 5, 6
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 6, 7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 6, 7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 6, 7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 6, 7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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