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

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3 1 **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

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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

94

95 **Main text**

96

97 **INTRODUCTION:**

98 Tremor is defined as an involuntary, oscillating sinusoidal movement of a body part and is a frequent symptom
99 in Parkinson's disease (PD), Essential Tremor (ET), but also in Multiple Sclerosis (MS) or after midbrain
100 lesions. ET is one of the most common movement disorders affecting up to 4.6% of the population ≥ 65 years
101 [1]. While most patients do well with first line oral medication like betablockers or Primidone, at least 50% of
102 them do not tolerate this long term [2], leaving 10% severely disabled by their tremor, losing dexterity to a
103 great extent [3]. Similarly in PD, tremor is one of the most challenging symptoms to treat with oral medication
104 [4] and this group of severely incapacitated patients depends on advanced therapeutic options [5].

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

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113 superseded in the academic setting by stimulation technology [14], which contributed dramatically to our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

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

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3 124 comparisons between aetiologies, treatment targets and techniques. The limitations of earlier reports with
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5 125 regards to established and recognized diagnostic criteria, use of validated clinical assessment tools and
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7 126 electrophysiological or imaging-based target verification [10] led us to restrict the literature search to a
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9 127 publication date from 1990 onwards.

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11 128 We specifically aim to answer the following questions:

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14 129 What is the efficacy of lesional neurosurgical interventions on tremor severity in tremor due to PD, ET, MS and
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16 130 midbrain/rubral origin for different lesioning techniques and targets according to published, peer-reviewed
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18 131 studies?

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21 132 What is the prevalence rate of persistent side effects after unilateral lesional interventions for different lesioning
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23 133 technique and target according to published, peer-reviewed studies?

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25 134 This will not only allow to objectively assess the safety and efficacy of existing lesional tremor treatment
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27 135 approaches but also to compare novel, incision-less lesional interventions with this benchmark.

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33 137 **METHODS AND ANALYSIS:**

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36 139 **Protocol**

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38 140 The methods for this systematic review have been developed according to the recommendations from the
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40 141 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement
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42 142 [25]. This systematic review protocol has been registered in the International Prospective Register of Systematic
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44 143 reviews (PROSPERO) on September 20th 2016: CRD42016048049. A PRISMA-P file is attached (see
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46 144 Additional file 1).

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48 145 Eligibility criteria

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51 146 Cohorts reporting a minimum of five patients of or above the age of 18 years with a tremor diagnosis of
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53 147 confirmed aetiology, subjected to uni- or bilateral lesional functional neurosurgery in a central neuroanatomical
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55 148 structure (thalamus, pallidum, subthalamic nucleus, alternative subcortical targets) by means of an intracerebral
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57 149 lesion, either by incisional (placement of a stylette, leukotome, cryosurgery or radiofrequency (RF) probe after
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59 150 skull opening) or incision-less (MRIGFUS, GK) means. Cases that received lesional functional neurosurgery in
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3 151 more than one anatomical structure at the same time or non-lesional approaches including deep brain stimulation
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5 152 (DBS) will be excluded.
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7 153 Outcome Measures:

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9 154 As we expect only limited amount of data from controlled trials to be found, this protocol aims to assess
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11 155 intervention effects by comparing pre- and post-interventional states. Primary outcome measure will be the
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13 156 change in upper limb tremor severity from baseline to follow-up time points, as reported on a validated tremor
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15 157 rating scale (United Parkinson's disease rating scale, part III (UPDRS III), clinical rating scale for tremor (CRST
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17 158 [26,27]), Whiget tremor scale etc.). Results from controlled trials comparing lesional interventions to alternative
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19 159 interventions, such as e.g. best medical treatment or deep brain stimulation will be included and discussed in a
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21 160 narrative way as far as meaningful for comparison to lesional interventions. As we expect the literature to be
22
23 161 heterogeneous in terms of follow-up duration and applied tremor rating scales we aim to primarily summarize
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25 162 the outcome as standardized mean difference (Hedge's g) [28] irrespective of follow-up duration. To limit bias
26
27 163 we will chose the follow-up time-point with the largest number of patients retained in the analysis.
28
29 164 Homogeneous cohorts (same tremor aetiology, intervention target and technique) will be grouped together for
30
31 165 subgroup-analysis if they consist of a minimum of n=2.

32 166 Secondary outcome measure will be the frequency of reported persistent side-effects after unilateral lesions per
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34 167 indication and intervention group, calculated as % of cases per group. In addition, we aim to calculate the mean
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36 168 rate of dysarthria and gait difficulties reported for unilateral vs. bilateral procedures. Homogeneous cohorts
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38 169 (tremor aetiology, intervention target and technique) will be grouped together for analysis if they consist of a
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40 170 minimum of n=2.

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42 172 Study design:

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44 173 The choice of inclusion/exclusion criteria reflects that we expect very few randomized trials in this field.
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46 174 Inclusion: Randomized controlled trials (RCTs), Meta-Analysis, case-control, prospective and retrospective case
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48 175 series. Exclusion: Studies reporting results from mixed aetiologies (subjects of different aetiologies grouped
49
50 176 together) or mixed interventions (different anatomical targets grouped together). We will include peer-reviewed
51
52 177 articles without language restriction. Letters, abstracts and editorials will not be included (see Table 1).
53

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55 179 Information sources and search strategy:

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57 180 A full search of MEDLINE and Cochrane (ovid) database will be performed limited to time of publication
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59 181 (between January 1990 and September 2016), using "tremor*" AND "lesion*", "neurosurg*", "thalamotomy",
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182 “subthalamotomy”, “pallidotomy” as search terms. Contact with authors will be made if needed.

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183 Table 1. Planned In- and Exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	<ul style="list-style-type: none"> - 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 	<ul style="list-style-type: none"> - cases subjected to lesional functional neurosurgery in more than one anatomical structure at the same time - or stimulation techniques (deep brain stimulation)
Study design	<ul style="list-style-type: none"> - 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 	<ul style="list-style-type: none"> - studies reporting results from mixed aetiologies or mixed intervention (different anatomical targets or techniques)
Efficacy Outcome	<ul style="list-style-type: none"> - reporting tremor outcome on a validated tremor scale 	
Safety Outcome	<ul style="list-style-type: none"> - side effects after unilateral only interventions 	<ul style="list-style-type: none"> - cohorts including bilateral interventions
Type of publication	<ul style="list-style-type: none"> - Peer-reviewed articles without language restriction 	<ul style="list-style-type: none"> - Letters, abstracts and editorials

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3 184 Data collection:

4 185 Primary database searches will be performed by one researcher who will compile a list of non-duplicate studies
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6 186 according to in- and exclusion criteria. In addition to the primary searches we will identify relevant studies from
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8 187 the reference lists of primary search results. From this list, two researchers will independently compile a
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10 188 definitive list of studies to be included in the safety and efficacy analysis – before analysis, lists will be
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12 189 compared and discrepancies settled. Data will be extracted from original sources by use of a standardized
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14 190 template. As we aim to cover publications from the past 26 years, which might cover interventions dating back
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16 191 to >35 years we deem it unrealistic to compile data on individual participant basis, unless given in publications.
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19 193 Data Items:

- 20 194
- 21 195 1. Publication details: title, authors, publication year
 - 22 196 2. Design: pro- retrospective, randomization, blind-assessment, controlled;
 - 23 197 3. Clinical details: cohort size, anatomical target, treatment technique, uni- or bilateral intervention,
24 198 guidance/targeting technique, tremor scale and item used, pre- and postinterventional tremor score
25 199 (mean \pm standard deviation), follow-up duration, art / number and severity of transient and persistent
26 200 side-effects reported;

27 201 Quality assessment according to Jadad [29] and Newcastle Ottawa scale[30];

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29 203 Bias assessment:

30 204 If several follow-up time points are reported per cohort, the time-point with the largest number of subjects
31 205 retained will be chosen to minimize selection/reporting bias. We will assess the quality of RCTs (Jadad scale
32 206 [29]) and non-randomized trials (Newcastle-Ottawa Scale [30]) by means of standardized assessment tools and
33 207 will discuss the limitations of the data synthesis in terms of study and data quality. In addition to that, in the
34 208 discussion of results - depending on the overall quality of data – we will discuss potential shortcomings of our
35 209 source data, as retrospective analyses with incomplete follow-up tend to introduce bias.

36 210 A formal assessment of publication bias however only makes sense in the presence of a sufficient number (>10)
37 211 of homogeneous data sets [31]. As we expect the data compiled in this analysis to be of limited homogeneity we
38 212 do not plan to formally calculate bias assessments such as by means of Funnel plots, as this can result in
39 213 misleading results in small and heterogeneous data sets [31]. This shall only be calculated in case subgroups with
40 214 more than 10 studies included are shown to have no substantial level of heterogeneity ($I^2 < 50\%$).

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3 215 Data synthesis and statistics:
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5 216 Aggregate data on pre-/post-interventional tremor severity will be extracted from publications or calculated from
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7 217 them in the form of mean \pm standard deviation for outcome variables per indication/intervention group per
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9 218 publication. Data for continuous outcome measures will be used to calculate standardized mean difference
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11 219 (Hedge's g) values including 95% confidence intervals [28] and to compute Forest plots using the Meta-
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13 220 Essentials workbook4 toolbox [32]. Based on study heterogeneity we will use a random-effects meta-analysis for
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15 221 quantitative comparison. Heterogeneity between studies will be assessed using I^2 statistics, with an $I^2 >50\%$
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17 222 regarded as an indicator of substantial heterogeneity.

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19 223 As we will analyse data from different tremor aetiologies and interventions, we will undertake subgroup analyses
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21 224 by the following subgroups: PD tremor: RF ablation ventral intermedial (V.im.) nucleus, RF ablation Globus
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23 225 pallidus internus (GPi), RF ablation subthalamic nucleus (STN), GK ablation V.im.; ET tremor: RF ablation
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25 226 V.im., GK ablation V.im., MRIGFUS ablation V.im. MS tremor: RF ablation V.im., GK ablation V.im. Formal
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27 227 subgroup analysis will be done in case of groups of a minimum of 2 studies per study intervention, target and
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29 228 aetiology.

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31 229 We will provide a narrative synthesis of results structured by aetiological category and intervention type and also
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33 230 discuss the influence of study design and follow-up, taking GRADE guidelines into consideration [33].
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234 **ETHICS AND DISSEMINATION:**

38
39 234 The aim of this systematic review and meta-analysis is to summarize the data on consistency and efficacy of
40
41 235 lesional functional neurosurgical interventions for the treatment of tremor disorders. The recent development of
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43 236 incision-less lesional functional neurosurgery techniques warrants this careful reassessment of the existing
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45 237 literature to guide future research into lesional interventions. Ethically, we consider it an obligation to
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47 238 summarize this data in a systematic manner to optimize treatment outcome for future patients. It will provide the
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49 239 basis to compare the efficacy of lesional interventions across anatomical targets, tremor aetiologies and lesional
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51 240 techniques. Furthermore, the calculation of prevalence rates of persistent side-effects after unilateral lesional
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53 241 interventions will allow for safety comparisons of established, incisional lesioning techniques and novel
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55 242 incision-less procedures, such as MRIGFUS and Gamma knife. This will allow a more unbiased evaluation of the
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57 243 effects of bilateral interventions of the past and possible future.

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59 244 We are committed to publish the results of this study in a peer-reviewed journal to distribute the outcome of this
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245 work. To maximise data transparency, we aim to include the data extracted from published sources in our final

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3 246 publication in the form of a table. This protocol, as well as its registration and publication with the PROSPERO
4 247 database (no. CRD42016048049) documents our continuing efforts of transparent research.

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10 250 **List of abbreviations:**

11 251 Clinical rating scale for tremor (CRST), deep brain stimulation (DBS), Essential Tremor (ET), Gamma knife
12 252 (GK), Globus pallidus internus (GPI), MRI-guided high-intensity focused ultrasound (MRIgFUS) Parkinson's
13 253 disease (PD), Multiple Sclerosis (MS), Preferred Reporting Items for Systematic Review and Meta-Analysis
14 254 Protocols (PRISMA-P), Randomized controlled trials (RCTs), subthalamic nucleus (STN), United Parkinson's
15 255 disease rating scale, part III (UPDRS III), ventral intermedial (V.im.) nucleus,

16 256

17 257 **Declarations:**

18 258 Ethics approval: not applicable

19 259

20 260 Data sharing statement: not applicable – research protocol only

21 261

22 262 Competing interest: The authors declare that they have no competing interests.

23 263

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26 266

27 267 Author's contribution: SRS initialized and conceptualised the research plan for the proposed systematic
28 268 review and wrote the first manuscript draft. KB provided critical input on the proposed methodology and
29 269 statistical analysis and reviewed the manuscript for important intellectual content. JKK and JWC reviewed the
30 270 methodology and reviewed the manuscript for important intellectual content. GK supervised the project and
31 271 corrected the manuscript for important intellectual content. All authors approved of the final version of the
32 272 manuscript.

33 273

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56 357

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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BMJ Open

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

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Manuscripts

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3 1 **Functional lesional neurosurgery for tremor – a protocol for a systematic review and meta-analysis**
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3 32 **Abstract**

4 33 **Introduction:** The recent introduction of incision-less lesional neurosurgery using Gamma knife and MRI-
5
6 34 guided focused ultrasound has revived interest in lesional treatment options for tremor disorders. Preliminary
7
8 35 literature researches reveal that the consistency of treatment effects after lesional neurosurgery for tremor has not
9
10 36 formally been assessed yet. Similarly, the efficacy of different targets for lesional treatment and incidence of
11
12 37 persistent side effects of lesional neurosurgical interventions has not been comprehensively assessed. This work
13
14 38 therefore aims to describe a suitable process how to review the existing literature on efficacy and persistent side
15
16 39 effects of lesional neurosurgical treatment for tremor due to Parkinson's disease (PD), Essential Tremor (ET),
17
18 40 Multiple Sclerosis (MS) and midbrain / rubral tremor.

19 41 **Methods and Analysis:** We will search electronic databases (Medline, Cochrane) and reference lists of included
20
21 42 articles for studies reporting lesional interventions for tremor in cohorts homogeneous for tremor aetiology and
22
23 43 intervention (technique and target). We will include cohorts with a minimum number of five subjects and follow-
24
25 44 up of two months. One investigator will perform the initial literature search and two investigators will then
26
27 45 independently decide which references to include for final efficacy and safety analysis. After settling of
28
29 46 disagreement, data will be extracted from articles using a standardized template. We will perform a random-
30
31 47 effect meta-analysis calculating standardized mean differences (Hedge's g) for comparison in Forest plots and
32
33 48 subgroup analysis after assessment of heterogeneity using I^2 statistics.

34 49 **Ethics and Dissemination:** This study will summarize the available evidence on the efficacy of lesional
35
36 50 interventions for the most frequent tremor disorders, as well as for the incidence rate of persisting side effects
37
38 51 after unilateral lesional treatment. This data will be useful to guide future work on incision-less lesional
39
40 52 interventions for tremor.

41 53 **Systematic review registration:** This study has been registered with the PROSPERO database (no.
42
43 54 CRD42016048049).
44
45 55

46
47 56 **Keywords:** Tremor, Lesional neurosurgery, Thalamotomy, Subthalamotomy, Pallidotomy, Radiofrequency
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49 57 ablation, Focused ultrasound, Gamma knife
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3 63 Strengths and Limitations of this study:

- 4 64 • Protocol for first formal, systematic review and meta-analysis of lesional functional neurosurgery for
5 tremor
6 65
7
8 66 • Comprehensive comparison of consistency and efficacy of lesional targets in most prevalent tremor
9 aetiologies
10 67
11
12 68 • First meta-analysis of persistent side effect prevalence after lesional neurosurgical treatment
13
14 69 • Protocol to establish safety and efficacy benchmarks for emerging incision-less lesional functional
15 neurosurgery approaches
16 70
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18 71 • Frequent retrospective nature and potential reporting bias of primary source data will be addressed
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2
3 94 **Main text**
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5 95

6 96 **INTRODUCTION:**
7

8 97 Tremor is defined as an involuntary, oscillating sinusoidal movement of a body part and is a frequent symptom
9
10 98 in Parkinson's disease (PD), Essential Tremor (ET), but also in Multiple Sclerosis (MS) or after midbrain
11
12 99 lesions. ET is one of the most common movement disorders affecting up to 4.6% of the population ≥ 65 years
13
14 100 [1]. While most patients do well with first line oral medication like betablockers or Primidone, at least 50% of
15
16 101 them do not tolerate this long term [2], leaving 10% severely disabled by their tremor, losing dexterity to a great
17
18 102 extent [3]. Similarly in PD, tremor is one of the most challenging symptoms to treat with oral medication [4] and
19
20 103 this group of severely incapacitated patients depends on advanced therapeutic options [5].

21 104 Although its` phenomenology considerably differs between the above mentioned aetiologies, our current
22
23 105 understanding points at a common abnormal central oscillatory activity within a network involving motor cortex,
24
25 106 thalamus, globus pallidum and cerebellum [6-8]. Accordingly, lesional surgical interventions within parts of this
26
27 107 network using functional neurosurgery have been utilized successfully since the 1940ies [9]. Over time,
28
29 108 interventions at various anatomical structures within this network have been studied [9-12] and it is now
30
31 109 generally accepted that thalamotomy, influencing afferent cerebellar signalling, provides the highest level of
32
33 110 tremor symptom relief.
34

35 111 During the past two decades lesional interventions, although performed world-wide [13], were largely
36
37 112 superseded in the academic setting by stimulation technology [14], which contributed dramatically to our
38
39 113 understanding of tremor pathoaetiology [15-18]. Since the introduction of Gamma Knife (GK), incision-less
40
41 114 functional neurosurgery, i.e. lesion placement through the intact skull, is a possibility [12] and the recent
42
43 115 addition of MRI-guided high-intensity focused ultrasound (MRIGFUS) [19-22] has again stimulated interest in
44
45 116 this field [23,24].
46

47 117 A preliminary literature search performed in June 2016 suggests a wealth of studies on this topic, although the
48
49 118 majority of published reports are of small or medium size. Obvious heterogeneity in study design, data collection,
50
51 119 documentation and presentation limit the accessibility of this data and complicate its` interpretation. So far, there
52
53 120 are no reliable estimates on the consistency of treatment effects after lesional interventions for tremor. Similarly,
54
55 121 the prevalence of persisting side effects after such interventions has not been compared in a comprehensive way.
56
57 122 We therefore aim to summarize the available data on lesional functional surgery for tremor disorders to allow
58
59 123 comparisons between aetiologies, treatment targets and techniques. The limitations of earlier reports with
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3 124 regards to established and recognized diagnostic criteria, use of validated clinical assessment tools and
4
5 125 electrophysiological or imaging-based target verification [10] led us to restrict the literature search to a
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7 126 publication date from 1990 onwards.

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9 127 We specifically aim to answer the following questions:

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11
12 128 What is the efficacy of lesional neurosurgical interventions on tremor severity in tremor due to PD, ET, MS and
13
14 129 midbrain/rubral origin for different lesioning techniques and targets according to published, peer-reviewed
15
16 130 studies?

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18
19 131 What is the prevalence rate of persistent side effects after unilateral lesional interventions for different lesioning
20
21 132 technique and target according to published, peer-reviewed studies?

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23 133 This will not only allow to objectively assess the safety and efficacy of existing lesional tremor treatment
24
25 134 approaches but also to compare novel, incision-less lesional interventions with this benchmark.

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31 136 **METHODS AND ANALYSIS:**

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33 137

34 138 **Protocol**

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36 139 The methods for this systematic review have been developed according to the recommendations from the
37
38 140 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement
39
40 141 [25]. This systematic review protocol has been registered in the International Prospective Register of Systematic
41
42 142 reviews (PROSPERO) on September 20th 2016: CRD42016048049. A PRISMA-P file is attached (see
43
44 143 Additional file 1).

45
46 144 Eligibility criteria

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48
49 145 Cohorts reporting a minimum of five patients of or above the age of 18 years with a tremor diagnosis of
50
51 146 confirmed aetiology, subjected to uni- or bilateral lesional functional neurosurgery in a central neuroanatomical
52
53 147 structure (thalamus, pallidum, subthalamic nucleus, alternative subcortical targets) by means of an intracerebral
54
55 148 lesion, either by incisional (placement of a stylette, leukotome, cryosurgery or radiofrequency (RF) probe after
56
57 149 skull opening) or incision-less (MRIGFUS, GK) means. Cases that received lesional functional neurosurgery in
58
59 150 more than one anatomical structure at the same time or non-lesional approaches including deep brain stimulation
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3 151 (DBS) will be excluded.
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5
6 152 Outcome Measures:

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8 153 As we expect only limited amount of data from controlled trials to be found, this protocol aims to assess
9
10 154 intervention effects by comparing pre- and post-interventional states. Primary outcome measure will be the
11
12 155 change in upper limb tremor severity from baseline to follow-up time points, as reported on a validated tremor
13
14 156 rating scale (United Parkinson's disease rating scale, part III (UPDRS III), clinical rating scale for tremor (CRST
15
16 157 [26,27]), Whiget tremor scale etc.). Results from controlled trials comparing lesional interventions to alternative
17
18 158 interventions, such as e.g. best medical treatment or deep brain stimulation will be included and discussed in a
19
20 159 narrative way as far as meaningful for comparison to lesional interventions. As we expect the literature to be
21
22 160 heterogeneous in terms of follow-up duration and applied tremor rating scales we aim to primarily summarize
23
24 161 the outcome as standardized mean difference (Hedge's g) [28] irrespective of follow-up duration. To limit bias
25
26 162 we will choose the follow-up time-point with the largest number of patients retained in the analysis.
27
28 163 Homogeneous cohorts (same tremor aetiology, intervention target and technique) will be grouped together for
29
30 164 subgroup-analysis if they consist of a minimum of n=2.

31
32 165 Secondary outcome measure will be the frequency of reported persistent side-effects after unilateral lesions per
33
34 166 indication and intervention group, calculated as % of cases per group. In addition, we aim to calculate the mean
35
36 167 rate of dysarthria and gait difficulties reported for unilateral vs. bilateral procedures. Homogeneous cohorts
37
38 168 (tremor aetiology, intervention target and technique) will be grouped together for analysis if they consist of a
39
40 169 minimum of n=2.

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44 171 Study design:

45
46 172 The choice of inclusion/exclusion criteria reflects that we expect very few randomized trials in this field.
47
48 173 Inclusion: Randomized controlled trials (RCTs), Meta-Analysis, case-control, prospective and retrospective case
49
50 174 series. Exclusion: Studies reporting results from mixed aetiologies (subjects of different aetiologies grouped
51
52 175 together) or mixed interventions (different anatomical targets grouped together). We will include peer-reviewed
53
54 176 articles without language restriction. Letters, abstracts and editorials will not be included (see Table 1).

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58 178 Information sources and search strategy:

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60 179 A full search of MEDLINE and Cochrane (ovid) database will be performed limited to time of publication
180
181 (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.

182

183

184 Search Strategy:

185

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 1 st January 1990 and 1 st February 2017	

186 Table 1. Planned In- and Exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	<ul style="list-style-type: none"> - 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 	<ul style="list-style-type: none"> - cases subjected to lesional functional neurosurgery in more than one anatomical structure at the same time - or stimulation techniques (deep brain stimulation)
Study design	<ul style="list-style-type: none"> - 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 	<ul style="list-style-type: none"> - studies reporting results from mixed aetiologies or mixed intervention (different anatomical targets or techniques)
Efficacy Outcome	<ul style="list-style-type: none"> - reporting tremor outcome on a validated tremor scale 	
Safety Outcome	<ul style="list-style-type: none"> - side effects after unilateral only interventions 	<ul style="list-style-type: none"> - cohorts including bilateral interventions
Type of publication	<ul style="list-style-type: none"> - Peer-reviewed articles without language restriction 	<ul style="list-style-type: none"> - Letters, abstracts and editorials

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2
3 187 Data collection:

4 188 Primary database searches will be performed by one researcher who will compile a list of non-duplicate studies
5
6 189 according to in- and exclusion criteria. In addition to the primary searches we will identify relevant studies from
7
8 190 the reference lists of primary search results. From this list, two researchers will independently compile a
9
10 191 definitive list of studies to be included in the safety and efficacy analysis – before analysis, lists will be
11
12 192 compared and discrepancies settled. Data will be extracted from original sources by use of a standardized
13
14 193 template. As we aim to cover publications from the past 26 years, which might cover interventions dating back
15
16 194 to >35 years we deem it unrealistic to compile data on individual participant basis, unless given in publications.

17
18 195

19 196 Data Items:

- 20
21 197 1. Publication details: title, authors, publication year
22
23 198 2. Design: pro- retrospective, randomization, blind-assessment, controlled;
24
25 199 3. Clinical details: cohort size, anatomical target, treatment technique, uni- or bilateral intervention,
26
27 200 guidance/targeting technique, tremor scale and item used, pre- and postinterventional tremor score
28
29 201 (mean ± standard deviation), follow-up duration, art / number and severity of transient and persistent
30
31 202 side-effects reported;

32 203 Quality assessment according to Jadad [29] and Newcastle Ottawa scale[30];
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34 204

35
36 205 Bias assessment:

37
38 206 If several follow-up time points are reported per cohort, the time-point with the largest number of subjects
39
40 207 retained will be chosen to minimize selection/reporting bias. We will assess the quality of RCTs (Jadad scale
41
42 208 [29]) and non-randomized trials (Newcastle-Ottawa Scale [30]) by means of standardized assessment tools and
43
44 209 will discuss the limitations of the data synthesis in terms of study and data quality. In addition to that, in the
45
46 210 discussion of results - depending on the overall quality of data – we will discuss potential shortcomings of our
47
48 211 source data, as retrospective analyses with incomplete follow-up tend to introduce bias.

49 212 A formal assessment of publication bias however only makes sense in the presence of a sufficient number (>10)
50
51 213 of homogeneous data sets [31]. As we expect the data compiled in this analysis to be of limited homogeneity we
52
53 214 do not plan to formally calculate bias assessments such as by means of Funnel plots, as this can result in
54
55 215 misleading results in small and heterogeneous data sets [31]. This shall only be calculated in case subgroups with
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57 216 more than 10 studies included are shown to have no substantial level of heterogeneity ($I^2 < 50\%$).

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3 218 Data synthesis and statistics:
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5 219 Aggregate data on pre-/post-interventional tremor severity will be extracted from publications or calculated from
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7 220 them in the form of mean \pm standard deviation for outcome variables per indication/intervention group per
8
9 221 publication. Data for continuous outcome measures will be used to calculate standardized mean difference
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11 222 (Hedge's g) values including 95% confidence intervals [28] and to compute Forest plots using the Meta-
12
13 223 Essentials workbook4 toolbox [32]. Based on study heterogeneity we will use a random-effects meta-analysis for
14
15 224 quantitative comparison. Heterogeneity between studies will be assessed using I^2 statistics, with an $I^2 > 50\%$
16
17 225 regarded as an indicator of substantial heterogeneity.

18 226 As we will analyse data from different tremor aetiologies and interventions, we will undertake subgroup analyses
19
20 227 by the following subgroups: PD tremor: RF ablation ventral intermedial (V.im.) nucleus, RF ablation Globus
21
22 228 pallidus internus (GPi), RF ablation subthalamic nucleus (STN), GK ablation V.im.; ET tremor: RF ablation
23
24 229 V.im., GK ablation V.im., MRIGFUS ablation V.im. MS tremor: RF ablation V.im., GK ablation V.im. Formal
25
26 230 subgroup analysis will be done in case of groups of a minimum of 2 studies per study intervention, target and
27
28 231 aetiology. We have not planned to restrict this meta-analysis to particular targeting modalities in order not to
29
30 232 fragment results, although we are aware that older modalities, such as ventriculography or CT-based approaches,
31
32 233 are not used anymore at least in the western hemisphere academic setting.

33 234 We will provide a narrative synthesis of results structured by aetiological category and intervention type and also
34
35 235 discuss the influence of study design and follow-up, taking GRADE guidelines into consideration [33]. We will
36
37 236 also discuss tremor recurrence in the narrative section of this review, as we expect only limited data on this in
38
39 237 the bulk of reports.

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41 239

42 240 **ETHICS AND DISSEMINATION:**

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44
45 241 The aim of this systematic review and meta-analysis is to summarize the data on consistency and efficacy of
46
47 242 lesional functional neurosurgical interventions for the treatment of tremor disorders. The recent development of
48
49 243 incision-less lesional functional neurosurgery techniques warrants this careful reassessment of the existing
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51 244 literature to guide future research into lesional interventions. Ethically, we consider it an obligation to
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53 245 summarize this data in a systematic manner to optimize treatment outcome for future patients. It will provide the
54
55 246 basis to compare the efficacy of lesional interventions across anatomical targets, tremor aetiologies and lesional
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57 247 techniques. Furthermore, the calculation of prevalence rates of persistent side-effects after unilateral lesional
58
59 248 interventions will allow for safety comparisons of established, incisional lesioning techniques and novel
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2
3 249 incision-less procedures, such as MRIGFUS and Gamma knife. This will allow a more unbiased evaluation of the
4
5 250 effects of bilateral interventions of the past and possible future.
6
7 251 We are committed to publish the results of this study in a peer-reviewed journal to distribute the outcome of this
8
9 252 work. To maximise data transparency, we aim to include the data extracted from published sources in our final
10
11 253 publication in the form of a table. This protocol, as well as it's registration and publication with the PROSPERO
12
13 254 database (no. CRD42016048049) documents our continuing efforts of transparent research.
14
15 255
16 256

17 257 **List of abbreviations:**

18
19 258 Clinical rating scale for tremor (CRST), deep brain stimulation (DBS), Essential Tremor (ET), Gamma knife
20
21 259 (GK), Globus pallidus internus (GPI), MRI-guided high-intensity focused ultrasound (MRIGFUS) Parkinson's
22
23 260 disease (PD), Multiple Sclerosis (MS), Preferred Reporting Items for Systematic Review and Meta-Analysis
24
25 261 Protocols (PRISMA-P), Randomized controlled trials (RCTs), subthalamic nucleus (STN), United Parkinson's
26
27 262 disease rating scale, part III (UPDRS III), ventral intermedial (V.im.) nucleus,
28
29 263

30 264 **Declarations:**

31
32 265 Ethics approval: not applicable
33
34 266

35
36 267 Data sharing statement: not applicable – research protocol only
37
38 268

39
40 269 Competing interest: The authors declare that they have no competing interests.
41
42 270

43
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45
46 272 commercial or not-for-profit sectors.
47
48 273

49 274 Author's contribution: SRS initialized and conceptualised the research plan for the proposed systematic
50
51 275 review and wrote the first manuscript draft. KB provided critical input on the proposed methodology and
52
53 276 statistical analysis and reviewed the manuscript for important intellectual content. JKK and JWC reviewed the
54
55 277 methodology and reviewed the manuscript for important intellectual content. GK supervised the project and
56
57 278 corrected the manuscript for important intellectual content. All authors approved of the final version of the
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59 279 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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