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# Accuracy of intracranial electrode placement for stereoencephalography: A systematic review and meta-analysis

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## Abstract

Objective: Stereoencephalography (SEEG) is a procedure in which electrodes are inserted into the brain to help define the Epileptogenic Zone. This is performed prior to definitive epilepsy surgery in patients with drug resistant focal epilepsy when non-invasive data are inconclusive. The main risk of the procedure is haemorrhage occurring in 1-2% of patients. This may result from inaccurate electrode placement or a planned electrode damaging a blood vessel that was not detected on the pre-operative vascular imaging. Proposed techniques include the use of a stereotactic frame, frameless image guidance systems, robotic guidance systems and customized patient specific fixtures.

Methods: Using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines a structured search of the PubMed, Embase and Cochrane databases identified studies that involve: 1) SEEG placement as part of the pre-surgical work up in patients with 2) drug resistant focal epilepsy in which 3) accuracy data has been provided.

Results: 326 publications were retrieved of which 293 were screened following removal of duplicate and non-English language studies. Following application of the inclusion and exclusion criteria 15 studies were included in the qualitative and quantitative synthesis of the meta-analysis. Accuracies for SEEG electrode implantations have been combined using a random effects meta-analysis and stratified by technique.

Significance: The published literature regarding accuracy of SEEG implantation techniques is limited. There are no prospective controlled clinical trials comparing different SEEG implantation techniques. Significant systematic heterogeneity exists between the identified studies preventing any meaningful comparison between techniques. The recent introduction of robotic trajectory guidance systems has been suggested to provide a more accurate method of implantation, but supporting evidence is limited to Class 3 only. It is important that new techniques are compared to the previous 'gold-standard' through well designed and methodologically sound studies before they are introduced into widespread clinical practice.

Bullet points:

- Currently used surgical techniques for SEEG include frame-based, frameless and robotic applications.

- A PRISMA systematic review and meta-analysis of the literature revealed 15 studies eligible for quantitative analysis.
- Studies supporting accuracy of implantation techniques are limited to Class 3 evidence with significant heterogeneity preventing meaningful comparison.
- There is a need for well-designed prospective control studies comparing different SEEG implantation techniques to guide future clinical practice.

## Introduction

Stereoencephalography (SEEG) is a procedure that was developed by Talairach and Bancaud[1] and is undertaken as part of the pre-surgical evaluation of patients in whom non-invasive investigations are unable to accurately define the Epileptogenic zone (EZ). The EZ can be defined as the "minimal area of the cortex that must be resected to produce seizure-freedom"[2]. As part of the investigations prior to epilepsy surgery patients undergo detailed non-invasive clinical, neurophysiological, neuropsychological, neuropsychiatric and multi-modal imaging investigations[3]. If these non-invasive investigations are concordant and the EZ can be accurately determined, such as in most cases of hippocampal sclerosis, then the patient can safely undergo surgery with good clinical outcomes[4]. In cases where non-invasive investigations are non-concordant, invasive intracranial recordings are required, which may take the form of subdural grid, SEEG electrode insertion or both[5]. A recent meta-analysis has highlighted that the main complications associated with SEEG include intracranial haemorrhage, infection, implant malfunction and malposition[6]. Before SEEG electrode insertion trajectories are carefully planned with prior

knowledge of the critical neurovascular structures[7,8]. Computer aided planning has been employed in this regard to determine the safest trajectories that maximize grey matter sampling whilst ensuring a safe distance from vasculature[9,10]. Understanding the accuracy of the implantation method is necessary to incorporate a safe threshold away from blood vessels during trajectory planning. Cardinale et al, following a prospective analysis of 500 patients in which 6496 electrodes were implanted, calculated a safe distance of 2.88 mm based on the mean entry point error (0.86 mm) with the addition of 3 standard deviations (3 x 0.54 mm) and the probe radius (0.4 mm)[11]. This therefore provides a 99% estimate of confidence that a safe trajectory can be implanted should any vessels be greater than this distance away. Accuracy of SEEG implantations is therefore paramount for electrode implantation as the corridors for implantation between cerebral vasculature are narrow, especially when multiple electrodes are implanted. Another potential consequence of inaccurate electrode placement is the inability to achieve electrophysiological recordings from the intended anatomical brain region. Target points for SEEG electrodes are chosen based on the hypothesis generated from the summation of information provided by the non-invasive investigations. The SEEG recordings help to define the epileptogenic zone and hence, the region for resection that will result in seizure freedom. Electrode malposition therefore exposes patients to the risks of SEEG unnecessarily, and of failure to achieve identification of the epileptogenic zone. The published literature describes a number of different techniques including the use of a stereotactic frame, frameless image guidance, robotic trajectory guidance and custom patient specific fixture systems. A recent review of the history of SEEG techniques and those used in high-volumes centres

has recently been published[12]. We aimed to undertake a meta-analysis of all the published literature in which patients with refractory focal epilepsy that have undergone SEEG implantation to determine which provides the most accurate when compared to the preoperative planned trajectories. This will guide surgeons as to which technique is safest and aid in determining a safe threshold when planning SEEG trajectories.

## Methods

The meta-analysis was registered with the PROSPERO database and was assigned the registration number CRD42016047839 through which the review protocol can be reviewed.

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[13] a structured search of the PubMed, Embase and Cochrane databases was undertaken. The last date of the search was undertaken on the 16/09/16. Eligibility for inclusion in the meta-analysis include peer reviewed publications in which full length English language manuscripts were available through electronic indexing comprising:

1. Pre-clinical or clinical studies of patients with refractory focal Epilepsy
2. Undergoing SEEG implantation as part of pre-surgical evaluation
3. The technique for insertion has been described
4. Post-implantation imaging has been performed (CT or MRI)
5. The method for measurement of deviation from the planned trajectory has been described
6. The accuracy of the implantation has been measured from the post-operative imaging

Two independent researchers applied the search criteria using the search terms:

- ((drug resist*) OR refractory) AND epilepsy
- (((stereoencephalography) OR stereo EEG) OR SEEG) OR depth electrode)

In total 328 studies were identified. Following removal of duplicate and non-English language studies 296 manuscripts' titles and abstracts were screened. After applying the eligibility criteria, there were 35 articles that were analyzed. A comparison of the articles for inclusion between the two independent researchers was undertaken and revealed high concordance between the identified studies. Any discrepancy was resolved through mutual review and involvement of the senior author. The remaining 17 studies were included in the qualitative and 15 in the quantitative synthesis. (See Figure 1)

Figure 1: PRISMA 2009 Flow diagram

Figure 1 Legend: Summary of search strategy

Data extraction was performed using a table with a predefined set of criteria. The risk of bias and methodological quality of the included studies was calculated using the methodological index for non-randomized studies (MINORS) in which rating scores out of 16 and 24 for non-comparative and comparative studies respectively are generated[14]. Low scores suggest methodologically flawed studies. There was good internal consistency between the ratings from the two independent assessors as defined by a Cronbach's alpha of 0.86. Mean accuracy of implantation results for entry point or target point error were combined using an inverse variance method and stratified by technique. Studies were weighted

from random effects analysis. Statistical analysis was performed using SPSS 24 and Stata (Version 14).

## Results

### Study quality

From the 17 studies included in the qualitative synthesis one study was preclinical, one study contained a combination of pre-clinical and clinical results and the remaining studies were all clinical. In the majority of studies (11/17) no comparison between different techniques of implantation was undertaken. From the remaining 6 studies, 5 compared outcome results to retrospective data sets (historical cohorts) and the single preclinical study compared two robotic trajectory guidance systems prospectively. One of the studies by Gonzalez-Martinez et al [15] used previously published data as a historical comparison for a prospective study and therefore appears twice (once for the stand-alone results and again for the comparison). Two studies were removed from the quantitative analysis because the method used to assess accuracy was deemed sufficiently different to prevent any meaningful results comparison. (See Table 1)

Table 1: Summary of Data Synthesis

Calculated MINORS scores were a median 9/16 for non-comparative and 15.5/24 for the comparative studies suggesting that studies had significant methodological flaws. Included studies provided Level 3 evidence for individual case control studies and Level 4 evidence for case-series. No randomized control trials in this area were identified. No studies included blinding or provided a

prospective power calculation. Follow up periods were adequate for the purposes of accuracy determination in all cases as for inclusion eligibility all accuracy data was derived from the post-operative imaging. From the comparative studies, control groups were rarely adequately balanced with regards to baseline characteristics.

## Accuracy measurement

No consistent means of measuring accuracy within the published studies was identified. Error between the planned and implanted trajectories was measured using Euclidian distance in 8/17 studies and lateral deviation in 5/17. A single study [16] combined both measures using lateral deviation for the entry point and Euclidian distance for the target point and one study did not specify how the errors were measured [17].

## Accuracy data

See Figure 2 – Forest Plot for a) Entry Point and b) Target Point

Figure 2 Legend: Forest plot a) Entry point b) Target point accuracy based on operative implantation technique. Mean (solid diamond) and 95% confidence interval (solid line) provided with percentage weighting based on inverse variance method. Group (subtotal) and overall mean with 95% confidence interval for mean (hollow diamond) provided with statistic (I-squared) and p-value for heterogeneity showing significant heterogeneity between robotic and frameless studies preventing meaningful comparison.

From all the studies accuracy data has been provided for 13 different implantation systems (5 frameless, 3 frame-based, 3 robotic trajectory guidance and one patient specific custom frame system). Two studies were excluded from the quantitative analysis, as the method of accuracy was determined as distance from the edge of an anatomical structure opposed to distance from the planned trajectory[18,19].

The combined accuracy of the:

a) Frameless systems were Entry Point (EP) Error mean 2.45 mm (0.39, 4.51 95% CI) and Target Point (TP) error mean 2.89 mm (2.34, 3.44 95% CI).
b) Frame-based systems were EP error mean 1.43 mm (1.35, 1.51 95% CI) and TP error mean 1.93 mm (1.05, 2.81 95% CI).
c) Robotic trajectory guidance systems were EP error 1.17 mm (0.80, 1.53 95% CI) and TP error 1.71 mm (1.66, 1.75 95% CI).

## Discussion

### Accuracy measures

Entry point error is the difference in the actual from the planned position at which the electrode passes through the skull. This can be affected by mis-registration of the neuronavigation system, inaccurate alignment and deflection during drilling. Target point error is the difference in the actual from the planned position of the electrode at the target site. Target point accuracy is affected by the angle at which the electrode passes through the skull (even when the entry point is accurate), deflection of the electrode at the dura or within the brain, rigidity of the electrode and depth to which the introducer is inserted. The choice

of insertion technique has a greater effect on the entry point error but the stability of the system will also effect the angle of entry, which in turn has a direct impact on the target point accuracy. The entry and target point accuracies are based on the segmentation of the electrode positions on the post-operative CT scan and have been measured in a variety of ways, although Euclidean distance and lateral deviation were most commonly used. Comparison of accuracies between the two methods can lead to inaccuracy as the Euclidean distance takes into account depth inaccuracies, whilst lateral deviation does not. Given that Euclidean distance was used in 8/17 and lateral deviation in 5/17 studies this introduces significant heterogeneity and prevents meaningful comparisons between studies using different accuracy measures. Given that none of the compared techniques for the implantation of SEEG electrodes directly affect depth error, as this is surgeon controlled some authors advocate the use of lateral shift over Euclidean distance. We were unable to consider studies that used lateral deviation and Euclidean distance separately due to the small number in the literature and have therefore opted to amalgamate them whilst recognizing the imprecision that this introduces. A uniform rating scale is required to facilitate accurate comparisons between different studies. There is a large variation in the number of patients and electrodes in the published studies ranging from 6 electrodes in 3 patients[20] to 1050 electrodes in 81 patients[11]. To account for this the studies in the meta-analysis were weighted using an inverse variance method. The overall incidence of haemorrhage from SEEG electrode implantation is estimated to be 0.18% per electrode[6]. Given the relatively small numbers of studies and variable complication reporting in some studies we are unable to correlate accuracy with haemorrhage rate.

**Frame-based systems**

Five studies provided accuracy data for the Leksell, Fischer-Leibinger and Talairach frame-based systems. All studies were retrospective and data were provided as historical control groups for the comparison to frameless[20,21] and robotic trajectory guidance systems, ROSA[15,22] and Neuromate[11], providing Level 3 evidence. Hou et al[23] used a frameless system involving the Navigus tool in a prospective cohort of 36 patients in which 173 electrode were implanted compared to historical use of the Leksell frame in 28 patients for the insertion of 62 electrodes. Surface tracing registration was used for the frameless system and did not reveal any significant difference in the overall electrode accuracy between the frameless and Leksell frame accuracies. The use of surface tracing is thought to be less accurate to bone fiducials and could have reduced the accuracy of the frameless implantation technique. There was a significant reduction in the time taken for electrode implantation from 34.5 to 19.4 minutes using the frameless system, compared to frame-based. This represents the only published study in which the baseline characteristics of the case and control groups have been matched. Ortler et al[20] compared the Fischer-Leibinger frame in 6 patients with the frameless Vogele-Bale-Hohner maxillary fixation system in 3 patients for the purpose of bilateral longitudinal hippocampal electrode insertion. There was no difference in accuracy found between the two systems with the Fischer-Leibinger and Vogele-Bale-Hohner systems providing EP errors of 2.17 mm+/-2.19 (Mean +/- SD) and 1.37 mm+/-0.55 (Mean +/- SD) respectively and TP errors of 2.43 mm+/-0.98 (Mean +/- SD) and 1.80 mm+/-0.39 (Mean +/- SD) respectively. The overall number of patients in the study was

very small and there was a lack of a prospective power calculation. As such it likely the study was inadequately powered to detect a clinically significant difference.

Cardinale et al[11] compared a historical cohort of 37 patients that had undergone 517 electrode insertions using the Talaraich stereotactic frame with 81 patients undergoing 1050 electrodes using the Neuromate robotic trajectory guidance system. There was a significant improvement in both the entry and target point accuracy with the Neuromate robotic system over the historical cohort of patients implanted with the Talairach frame ($p<2.2x10^{16}$). Entry point error reduced from a median of 1.43 mm (IQR 0.91-2.21) to 0.78 mm (IQR 0.49-1.08). In a similar study by Gonzalez-Martinez et al[22] the implantation of 1245 electrodes in 100 patients using the ROSA robotic trajectory guidance system was compared with a historical cohort of 100 patients implanted with 1310 electrodes using the Leksell frame. EP error was not significantly different between the two methods. No target point error was provided for the Leksell frame historical cohort. Historical comparison data in this study was provided as a means of reference and not for formal statistical comparison. The calculated heterogeneity statistic for EP accuracy between frame-based systems was 0%. Excluding the small study by Ortler et al[20], the remaining studies had very tight confidence intervals suggesting valid comparisons can be made between frame-based techniques.

## Frameless systems

The frameless systems included in the analysis include the Vertek arm (Medtronic)[17,24,25], Varioguide (BrainLab)[26,27], Navigus tool (Medtronic)[21] and

the Guide Frame-DT (Medtronic)[28]. A single study compared the use of the iSYS1 robotic trajectory guidance system for the insertion of 93 electrodes in 16 patients with a historical cohort using the Vertek arm frameless technique[24]. The number of patients and baseline characteristics of the historical cohort was not specified. There was a 40% reduction in the EP error from 3.5 mm+/-1.5 (Mean +/- SD) with the Vertek arm to 1.54 mm+/-0.8 (Mean +/- SD) with the iSYS1 robotic trajectory guidance system. TP error was reduced by 20% from 1.82 mm+/-1.1 (Mean +/- SD) to 3.0 mm+/-1.9 (Mean +/- SD). Historical comparison data in this study were provided as a means of reference and not for formal statistical comparison. All other studies using frameless systems were case-series in which accuracy data was measured and therefore provides Level 4 evidence. The calculated heterogeneity statistic for frameless techniques included in the meta-analysis was 98.9% suggesting significant heterogeneity exists between individual studies that prevents any meaningful comparisons between the different frameless techniques. Combined accuracy data is provided for different frameless techniques, but the significant heterogeneity between the studies prevents any meaningful conclusions from being drawn.

## Robotic guidance systems

The robotic trajectory guidance systems include the ROSA[22], Neuromate[11] and iSYS1[24].

As stated previously comparisons between the robotic trajectory guidance systems has been with retrospective frame-based and frameless systems. A single preclinical prospective comparison between a robotic arm using different guidance systems (Polaris and Optotrak) has been published[29]. Twelve

electrodes were inserted into a single phantom using each technique. This device however is not clinically available and therefore are no clinical publications of its use to date. There have been no prospective clinical comparisons of robotic trajectory guidance systems with other techniques or between robotic trajectory guidance systems. The calculated heterogeneity statistic for robotic techniques included in the meta-analysis was 99.4% suggesting significant heterogeneity exists between individual studies that again prevents any meaningful comparisons between the different robotic techniques. Combined accuracy data is provided for different robotic techniques, but the significant heterogeneity between the studies prevents any meaningful conclusions from being drawn.

## Conclusion

The accuracy of SEEG electrode implantation using a variety of techniques has been published. Studies to date are mostly single center case series providing Level 4 evidence. Some studies have provided comparisons between different implantation techniques, but all clinical comparisons have been of retrospective cohorts (Level 3), with variable study quality. Calculated heterogeneity statistics suggest meaningful comparisons between studies can only occur between different frame-based techniques and not between frameless or robotic techniques. The lack of a uniform measure of accuracy likely contributes to this heterogeneity and reduces the validity of the pooled data such that no meaningful conclusions can be drawn. There is some limited evidence suggesting that robotic trajectory guidance systems may provide greater levels of accuracy compared to both frameless and frame-based systems, but the studies are of low quality and provide low levels of evidence. There is therefore a need for high

quality prospective control trials between different SEEG implantation techniques to define which methods provide the highest levels of accuracy.

Ethical Publication: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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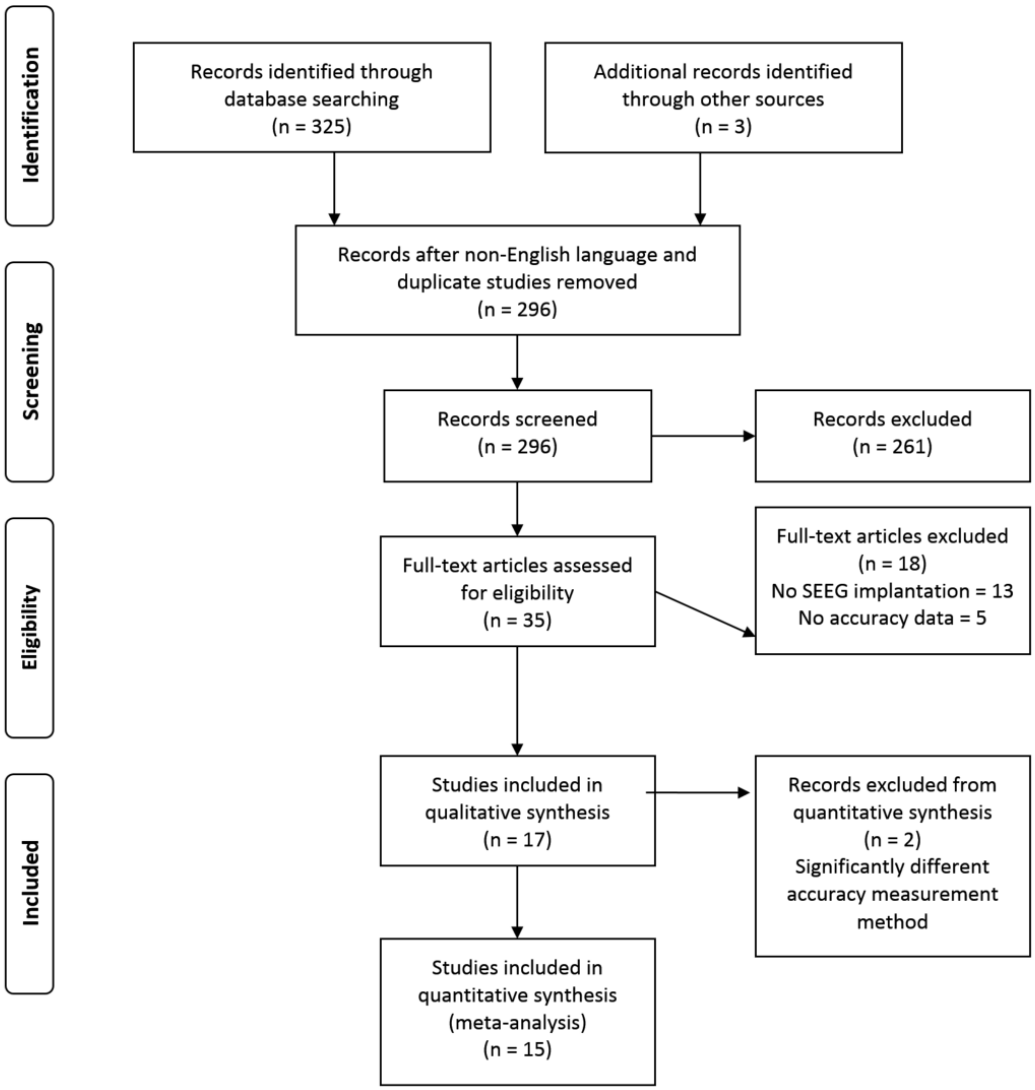
Figure 1: PRISMA 2009 Flow Diagram




*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Figure 2a

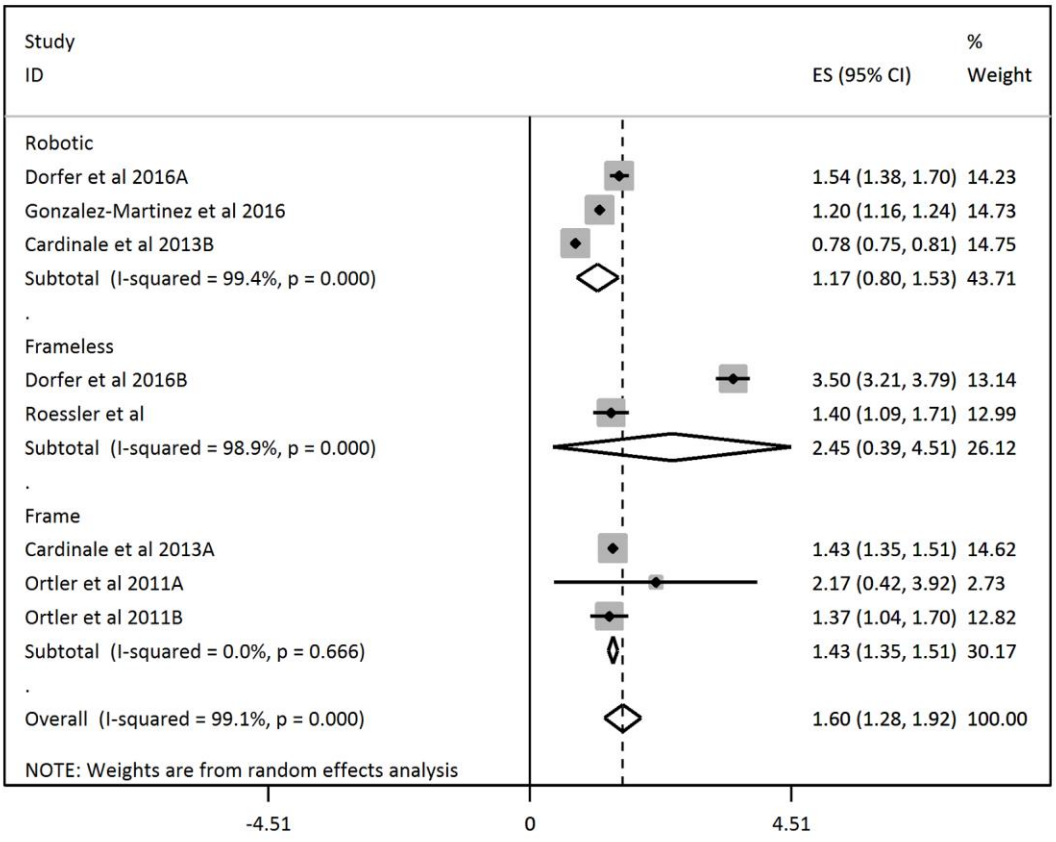
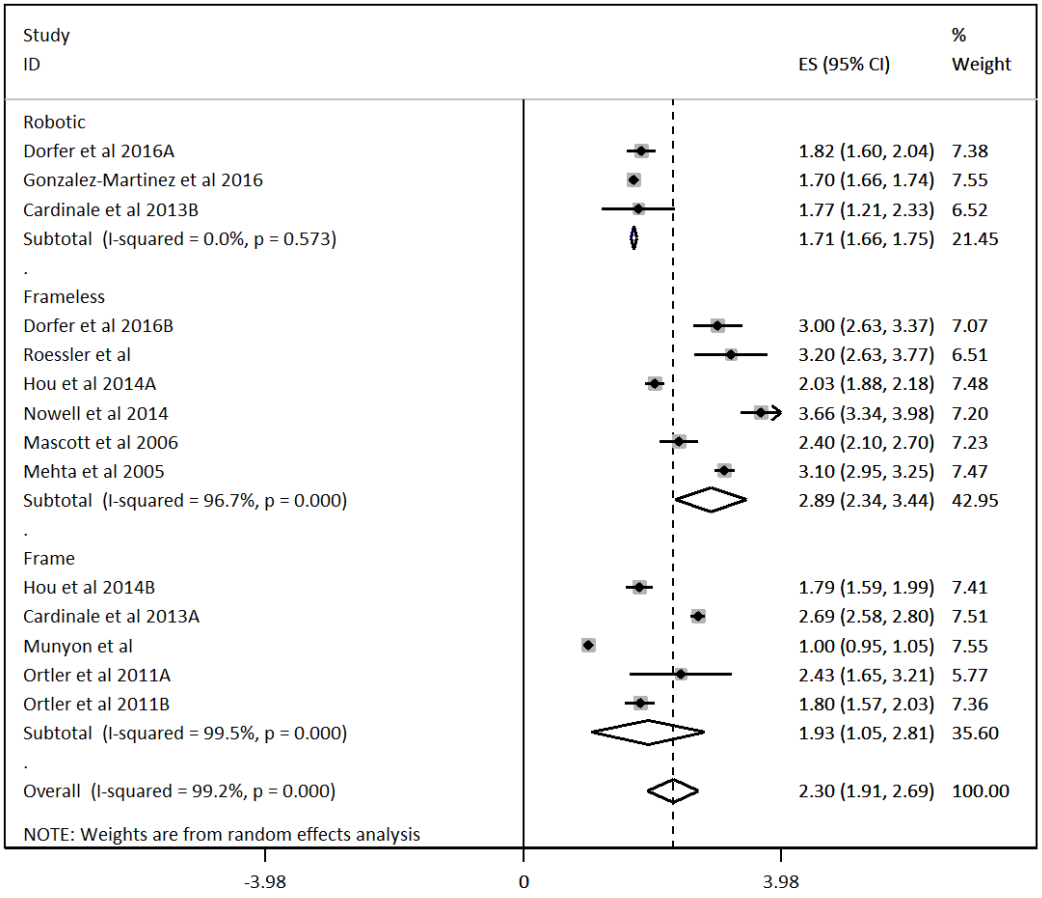

Study
ID
ES (95% CI)
%
Weight
Robotic
Dorfer et al 2016A
1.54 (1.38, 1.70) 14.23
Gonzalez-Martinez et al 2016
1.20 (1.16, 1.24) 14.73
Cardinale et al 2013B
0.78 (0.75, 0.81) 14.75
Subtotal (I-squared = 99.4%, p = 0.000)
1.17 (0.80, 1.53) 43.71
.
Frameless
Dorfer et al 2016B
3.50 (3.21, 3.79) 13.14
Roessler et al
1.40 (1.09, 1.71) 12.99
Subtotal (I-squared = 98.9%, p = 0.000)
2.45 (0.39, 4.51) 26.12
.
Frame
Cardinale et al 2013A
1.43 (1.35, 1.51) 14.62
Ortler et al 2011A
2.17 (0.42, 3.92) 2.73
Ortler et al 2011B
1.37 (1.04, 1.70) 12.82
Subtotal (I-squared = 0.0%, p = 0.666)
1.43 (1.35, 1.51) 30.17
.
Overall (I-squared = 99.1%, p = 0.000)
1.60 (1.28, 1.92) 100.00
NOTE: Weights are from random effects analysis
-4.51
0
4.51

Figure 2b


Study
ID
ES (95% CI)
%
Weight
Robotic
Dorfer et al 2016A 1.82 (1.60, 2.04) 7.38
Gonzalez-Martinez et al 2016 1.70 (1.66, 1.74) 7.55
Cardinale et al 2013B 1.77 (1.21, 2.33) 6.52
Subtotal (I-squared = 0.0%, p = 0.573) 1.71 (1.66, 1.75) 21.45
.
Frameless
Dorfer et al 2016B 3.00 (2.63, 3.37) 7.07
Roessler et al 3.20 (2.63, 3.77) 6.51
Hou et al 2014A 2.03 (1.88, 2.18) 7.48
Nowell et al 2014 3.66 (3.34, 3.98) 7.20
Mascott et al 2006 2.40 (2.10, 2.70) 7.23
Mehta et al 2005 3.10 (2.95, 3.25) 7.47
Subtotal (I-squared = 96.7%, p = 0.000) 2.89 (2.34, 3.44) 42.95
.
Frame
Hou et al 2014B 1.79 (1.59, 1.99) 7.41
Cardinale et al 2013A 2.69 (2.58, 2.80) 7.51
Munyon et al 1.00 (0.95, 1.05) 7.55
Ortler et al 2011A 2.43 (1.65, 3.21) 5.77
Ortler et al 2011B 1.80 (1.57, 2.03) 7.36
Subtotal (I-squared = 99.5%, p = 0.000) 1.93 (1.05, 2.81) 35.60
.
Overall (I-squared = 99.2%, p = 0.000) 2.30 (1.91, 2.69) 100.00
NOTE: Weights are from random effects analysis
-3.98
0
3.98