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Clinical Validity of Deep Brain Stimulation (DBS) and Gamma Knife Thalamotomy (GKT) Neurosurgical Therapeutic Techniques Treating Neurogenic Disorders

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Abstract

Increased progression of neurogenic disorders among elderly personnel is considered a top trend challenge for developed economies to standardize the life quality. Generally, Deep brain stimulation (an invasive neurosurgical technique) and Gamma Knife Thalamotomy (non-invasive radiosurgical therapeutic technique) are adopted to treat neurogenic disorders. Deep brain stimulation includes implantation of receptor compatible electrical devices in human brain, to generate type specific electrical signals to improve the impulse conduction capability of a motor neuron. Whereas, Gamma knife thalamotomy is adopted to target tumor specific cells by radiations to inhibit tumor genesis. Selection of either technique treating specific patient is considered is a key challenge faced by many neurosurgeons. Current study aims to evaluate the clinical validity and relative specificity of deep brain stimulation and gamma knife thalamotomy treating neurogenic disorders. NCBI/PubMed, Medline and neurosurgery Journal databases were retrieved from January 2008-upto November 2018. About 39 principle studies with complete demographic details were assessed and analyzed by using RISMA and Revman5.30 multiple tools. About 6, 724 patients from past ten years were enrolled. By following random effect data analysis tool at 95 % confidence interval moderate target specificity was observed for both techniques (heterogeneity Tau2 = 0.76; Chi2 = 8.08, I2 = 63 %). Whereas relative target specificity of DBS was recorded higher rather than GKT. Similarly, GKT was found safer in comparison to DBS. Calculated Risk ratio = 2.20 further assure the validity of both neurosurgical techniques. Even not a single neurosurgical therapeutic technique was found effective against inherited neurological disorders.

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Introduction

Increased progression of neurogenic disorders among elderly personnel is considered a top trend challenge for developed economies to standard the life quality (Lee JY *et al.*, 2005). Sometimes, uncontrolled progressiveness of disease causes neurological syndromes showing visible sign and symptoms of tremors, muscular stiffness, body imbalance, and bradykinesia due to loss of dopaminergic neurons.

Malignancies of Ventralis intermedius nucleus of the thalamus and sub-thalamus zona incerta are considered the major sites responsible for essential tremor and related disorders development (Koller WC *et al.*, 2001; Kondziolka *et al.,* 2000). Previously, medications were adopted to overcome visible sign and symptoms. But chronic side effects and receptor resistance against drugs left no choice of effectiveness against neurogenic disorders. Beside medications deep brain stimulation and gamma knife thalamotomy are recognized by many physicians as a promising therapeutic technique suppressing visible symptoms of neurogenic disorders like essential tremor.

Whereas patient selection criteria, adaptation of either or both neurosurgical techniques, target specificity and safety of chosen technique are still not standardized yet (Koller WC *et al.*, 2001; Kondziolka *et al.,* 2000). Our study is an effort to analyze comparative target specificity of both techniques, patient selection criteria and safety of either technique to draw an updated image of progress in the field of neurosurgery treating neurogenic disorders effectively.

Materials and methods

Search strategy

Careful research was carried out by using keywords deep brain stimulation, Gamma knife surgery, and neurological disorders to retrieve recent ten-year databases from NCBI/PubMed, Medline and Neurosurgery Journals timeframe of January 2008 up to November 2018. The studies published only in English language were included (Fig.1).Most of the studies were included from developed countries. First author affiliation was considered as the origin of the study for each included research. In case of more than one affiliation of the first author, primary affiliation was preferred.

Focused studies and analysis

Studies focusing other than deep brain stimulation and Gamma Knife surgical therapeutic techniques were excluded for further analysis. Out of a total 112 related articles and searched reports, only 39 studies met the inclusion criteria. Complete demographic details of each included research and outcomes were tabulated and analyzed by using multiple tools of Microsoft office Version 2010.

Results and discussion

The highest number of included studies (41%) were reported by US-based neurosurgical institutes, 15% German, and 8% were reported by Japanese institutes of neurosurgeries respectively. While 20 % of studies were from Sweden, Italy, France and Canada with an equal percentage (5%). similarly, an equal number of included studies (approx.3%) were reported by Netherland, Malaysia, Switzerland, United Kingdom, Belgium, and Saudi Arabia (Fig.2).

Table 1. Details of patients suffering from different neurological disorders, surgical treatment and target specificity a ten-year Analysis (2008-18).

Author	Country	Study Type	Neurological disorder	Cases	Surgical Technique	Target selectivity/ Outcomes
Shabbir Hussain I. (2018).	USA	LTE	ETS	ND	DBS	DBS is the best option to overcome the progression of ET. But genetically associated could not overcome effectively.
Holslag, Joost *et al.*, 2017.	Netherland.	OA	ETS	44	DBS	DBS is more effective against Zona incerta target as compared to VIM.
Tuleasca Constantin *et al.*, 2017.	Switzerland	LTE	ETS	01	DBS + GKT	Combined surgery could overcome tremor, but recurrence phenomenon of tremor is unknown.
Ravikumar, V. K *et al.*, 2017.	USA	RA	ETS	958	DBS+ MRI guided surgery.	MRI guided focused thalamotomy more effective and littler expensive.

Higuchi, Y *et al.*, 2017.	Japan	RA	ETS	540	GKT	Only long-term studies could clear or prove Gamma knife specificity.
T. Witjas, R *et al.*, 2016.	France.	RA	ETS	835	GKT	GKT is the best available technique to overcome tremor disability.
Dembek, T. A *et al.*, 2016.	Germany.	OA	ETS	16	DBS	DBS is more effective against Zona incerta target as compared to VIM
Alomar, S. *et al.*, 2016.	Saudi Arabia.	RA	SD	2, 320	DBS	Deep brain stimulation is less effective against speech therapy disorders.
Cho, K. R., *et al.*, 2015.	Korea	OA	IT	7	GKT	GKT is the superior technique against VIM as compared to all other techniques
Hedera P *et al.*, 2014.	USA	Book chapter	Dystonia and ET	ND	DBS	Dystonia tremor can be treat by targeting VIM, but adverse reactions should be overcome finding specific sub thalamic targets
Mehanna R *et al.*, 2014	USA	OA	RF	3	Double DBS	No significant results were obtained due to the small sample size and statistical issues.
Deuschl G. 2013.	Germany.	Concept Paper	ETS	ND	MRgFUS+ DBS+ GKT	MRgFUS is a potential technique against neurological disorders, But clinical values need to understand.
Takamitsu Y *et al.*, 2013	Japan	PRR	Comatose brain injury	21	DBS+ SCS	Recovery of motor function following SCS is higher as compared with DBS.
Franzini Angelo *et al.*, 2013	Italy.	PRR	MR	7	DBS	DBS proves best against mental retardation against post hypothalamic target site.
Alexander S *et al.*, 2013.	USA	PRR	TR DP	129	DBS	DBS gives promising results initially against treatment-resistant depression.
Hemmings Wu *et al.*, 2013.	Belgium.	PRR	AN	4	DBS	It provides new directions for restoring weight. Therefore, future application of DBS to explore new targets helps to restore psychiatric disorder.
Stéphan Chabardès *et al.*, 2013.	France.	PRR	CD+ Obesity	4	DBS	DBS with GKT can produce promising results for future research to control weight gain.
Laxton Adrian W *et al., 2013*.	Canada.	PRR	ND	3	DBS	Limited studies are done on Dementia.
Chopra A *et al.*, 2013.	USA	RA	ETS	539	DBS	DBS is safe, and effective against both VIM and PSA.
Voges, J *et al.*, 2012.	Germany.	PRR	Alcohol addiction	5	DBS	DBS counter devices can be used to control the periodic stimulation of the brain followed by drugs.
Lozano A. M *et al.*, 2012.	Canada.	Commentary	ETS	5	DBS	Repeating DBS for VIM as well as Zona incerta could improve essential tremor.
Romanelli P *et al.*, 2012.	Italy.	PRR	Epilepsy	ND	DBS+ Radiosurgery	Drug-resistant epilepsy can be treated by DBS
Michael T. Barbe *et al.*, 2011.	Germany	OA	ETS	21	DBS	VIM and PSA are promising targets of DBS.
Blomstedt P *et al.*, 2011	Sweden	OA	ETS	68	DBS	DBS is independent of age and gender. Its 89% specific for PSA.
Deuschl G. 2011	Germany	Context	ETS	ND	DBS	DBS with medications is effective.
Parvizi J *et al.*, 2011	USA	OA	Brain lesions	100	MRI	Extent of epileptic seizures determines lesion.
Elaimy AL *et al*, 2011	USA	RA	ETS	364	GKT	GKT 80-100 % safe and efficient.
Deuschl G *et al.*, 2011.	Germany	RA	ETS	ND	DBS	DBS reduces tremor up to 90%.
Steven M. *et al.*, 2011	USA	OA	DP	45 Rats	DBS	DBS induces behavioral improvements
Mark K. 2011	USA	RA	NDS + obesity	ND	DBS	Many applications mechanism needs to be understood.
Pezeshkian P *et al.*, 2011	USA	OA	ND	52	DBS+ MRI	No significant difference among both imaging techniques.
A. Follett *et al.*, 2010	USA	OA	PD	299	DBS	In the case of both pallidal and subthalamic targets similar improvements in DBS.
Etienne M *et al.*, 2010	UK	OA	MD	165	DBS	DBS technique is systemic error free technique.
Lim S.Y *et al.*, 2010	Malaysia	OA	ETS	18	GKT	Moderate efficacy.
Young R.F *et al.*, 2010	USA	OA	ETS	172	GKT	It is a safe and effective alternative to DBS surgery
Greenberg B.D *et al.*, 2009.	USA	RA	OCD	ND	DBS	Longer patients follow up is necessary for pre and post DBS analysis
Greenberg B.D *et al.*, 2008.	USA	OA	CD	4	DBS	DBS is reliable against obsessive compulsive disorders.
Terao T.*et al.*, 2008.	Japan	Case Report	ETS	01	GKT+DBS	GKT can be used for DBS devices implantation as well. MRI assessed drawbacks of GKT are false positive results.
Hariz G.M *et al.*, 2008.	Sweden	OA	ETS	19	DBS	DBS is relevant to ET control, but not much specific.

Abbreviations: LTE = letter to the editor, PRR = Peer review reports, ETS = Essential tremor syndrome, OCD = obsessive-compulsive disorder, OR = original article, RA = review Article, ND = not determined, RF = Refractory tremor, CD = compulsive disorder. MD = movement disorder, PD = Parkinson's disease, DP = depression, NDS = neurological disorders, AN = Anorexia nervosa, MR = Mental retardation, SD = Speech disorder, IT = Intractable tremor.

A total number of 6724 patients were enrolled during the past ten years of neurosurgical advancement at 39 world class neurosurgical institutes for effective treatment against neurological disorders. About 38.96 % patients seeking neurosurgical treatment were from United States while rest of 61.04 % were enrolled from other parts of the world (Table.1). Neurological disorders were classified as Essential tremor syndrome (ETS), Speech disorders (SD), Mental retardation (MR), Obsessive-compulsive disorder (OCD), Refractory tremor (RF), compulsive disorder (CD), depression (DP), General neurological disorders (NDS), Intractable tremor (IT) and Anorexia nervosa (AN) associated disorders.

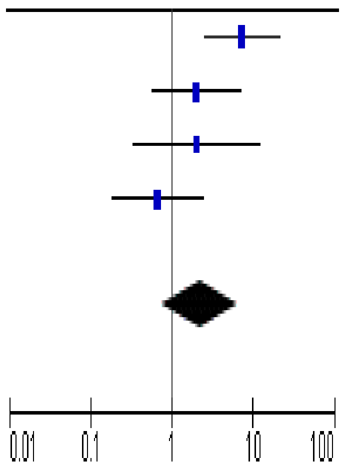
Table 2. Forest and funnel plot of comparison, Limitations of DBS and GKT towards Enhanced target Specificity.

Studies reporting Target specificity <70·80 % for Zona Incerta, VIM. Non.target specificity						Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	*N,* Random, 95% CI
Deep Brain Stimulation	22	25	3	25	29.0%	7.33 [2.51,21.41]
Gamma Knife Thalomotomy	4	6	2	6	26.1%	2.00 [0.56, 7.09]
DBS+ GKT	2	3	1	3	19.2%	2.00 [0.33, 11.97]
DBS +Other	2	5	3	5	25.7%	0.67 [0.18, 2.42]
Total (95% CI)		39			39.100.0%	2.20 [0.74, 6.50]
Total events	30		9	39		

Heterogeneity: Tau== 0.76; Chi'= 8.08,
df= 3 (P = 0.04); 1'= 63%

Test for overall effect: Z= 1.42 (P = 0.16)

Risk Ratio
N, Random, 95% CI



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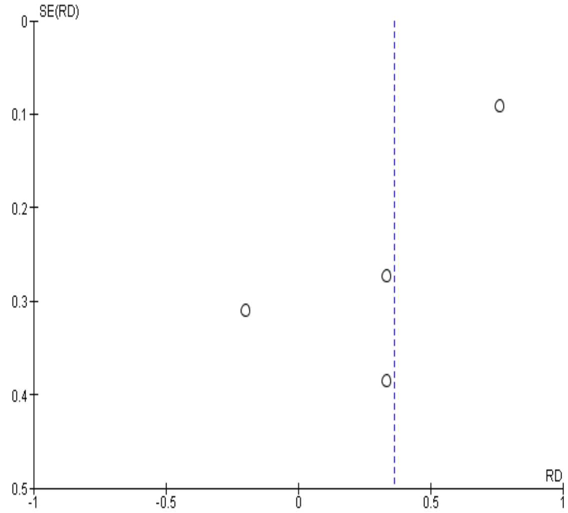

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Approximately 53.5 % cases were suffering from ETS, 34.5 % from Speech disorders and 12 % of cases were suffering from OCD, RF, IT and AN respectively (Table.1). Commonly surgical techniques are adopted to overcome Essential tremor, mental retardation, and speech disorders when medications become no more choice of treatment to cope with the severity and extent of the disorders.

In 2011 Steven M. *et al.* recruited 45 rats and came to know that, Deep brain stimulation surgical technique is an effective option to improve animal behavior by altering motor neuron functions. A recent study conducted by Holslag, Joost *et al.* focusing on 44 Essential tremor patients, reported DBS a valid treatment option, which specifically targets zona incerta of the thalamus. While Young R.F *et al.* in 2010 highlighted a non-invasive technique Gamma Knife surgery a superior option over DBS for the treatment of Essential tremor.Our target specificity analysis based on 25 DBS based published studies, Six GKT based studies, 3 with mixed studies (DBS + GKT), and five studies based on DBS with other surgical techniques showed 88% specificity of DBS against Zona incerta and VIM. Only three studies reported DBS not much specific but still relevant to control essential tremor. Specificity analysis of GKT based on six studies was 66%. In case of mixed surgical approach, results were improved up to 1% Specificity. Studies based on DBS combined with other radiosurgical techniques reported 40% specificity (Fig. 3 & Table. 2).

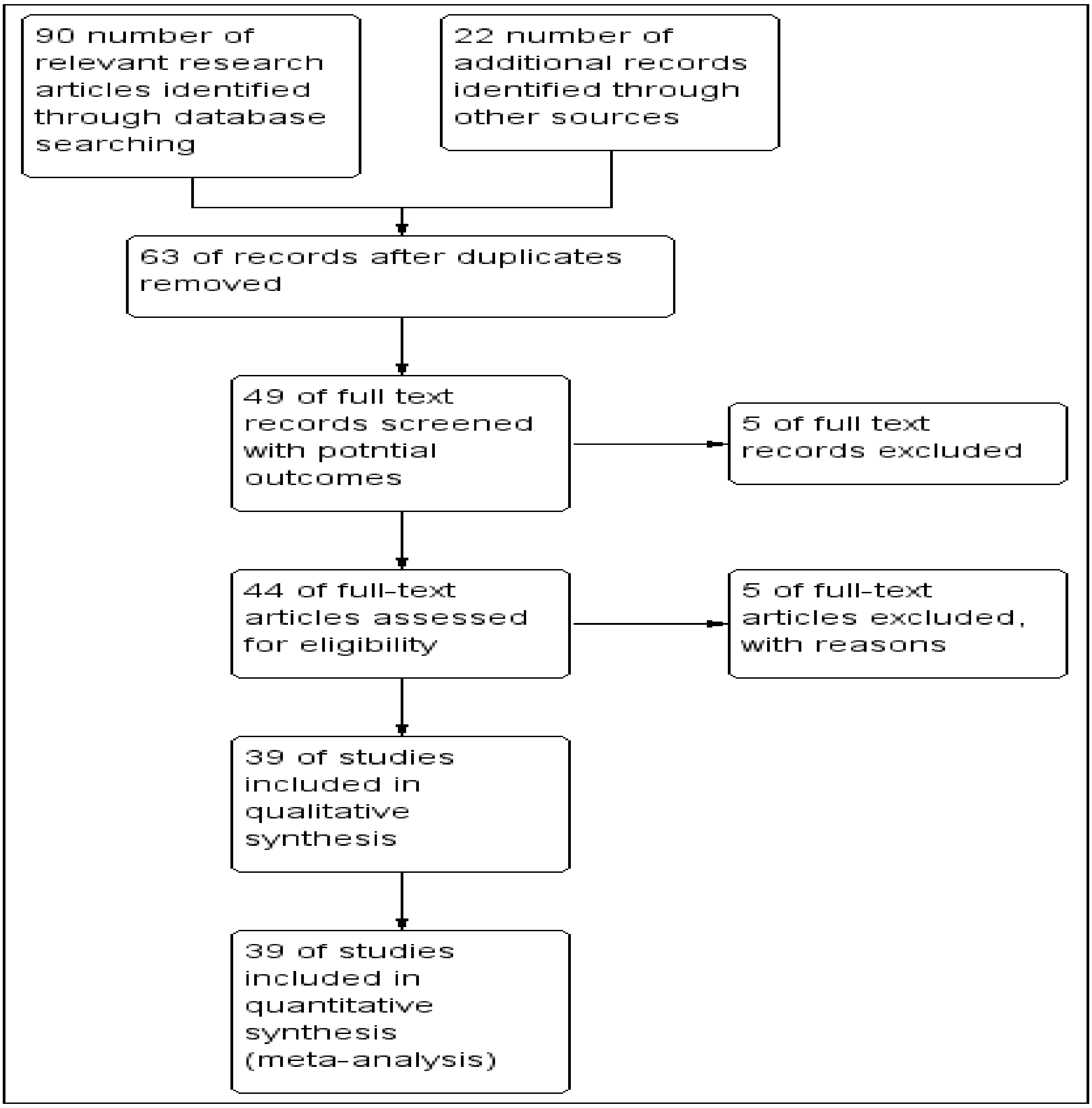
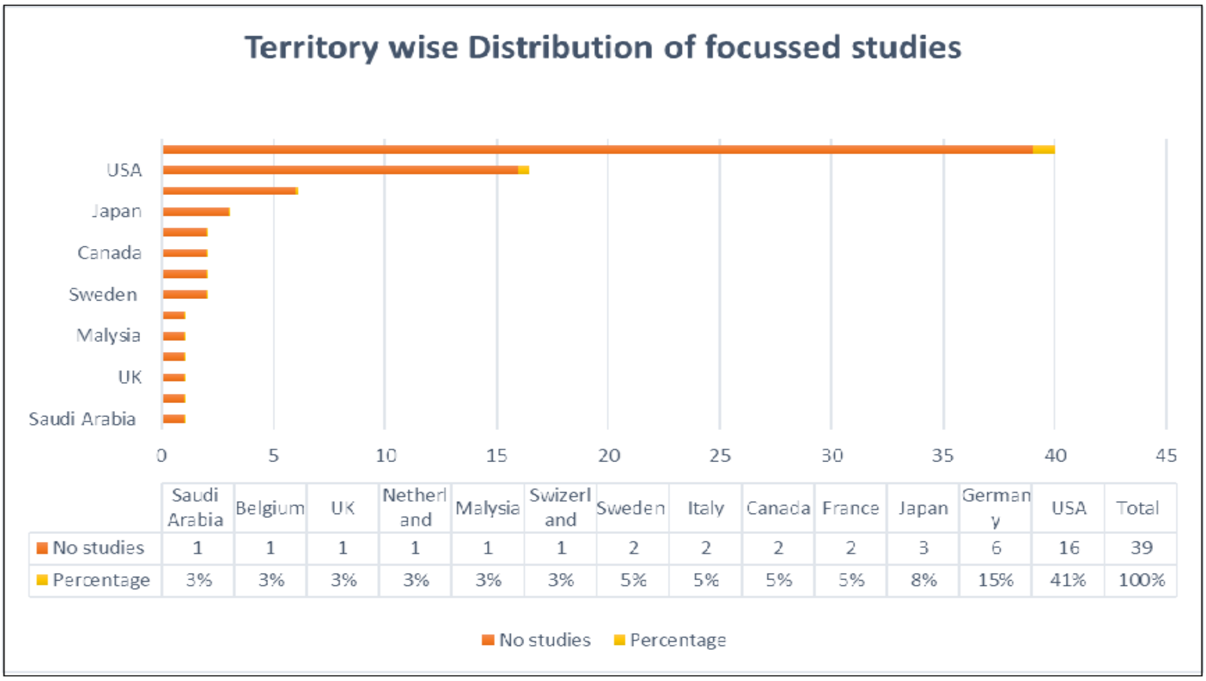


Fig. 1. Literature Search Strategies and studies inclusion and exclusion criteria.

Based on relative specificity of GKT with respect of DBS, Gamma knife thalamotomy is 80-100% safe, and is an efficient, available technique to overcome neurological disorders including Essential tremor.

By following random effect analysis model at 95 % confidence interval moderate target specific heterogeneity $Tau^2 = 0.76$; $Chi^2 = 8.08$, $I^2 = 63$ % was observed. Calculated Risk ratio = 2.20 further assure the validity of both neurosurgical techniques (Table. 2). our review reported DBS a best final stage treatment option against chronic neurological disorders while Gamma knife surgery a safe method for acute phase neurological disorders including essential tremor. Improvements in motor neuron function are possible by DBS to overcome brain disorders as well. While neurogenic disorders associated with inherited carcinomas could not be treated with DBS effectively. Current study highlights the comparative specificity of DBS and Gamma knife thalamotomy surgical techniques against Essential tremor and relative neurological disorders. Similarly, current progress in surgical techniques against neurological disorders was assessed, and the reason being that a significant number of acquired carcinomas associated with motor neuron dysfunction were characterized.

In 2010, Lim S.Y *et al.* conducted a study on 18 Malaysian Patients and reported GKT as a moderate, and efficient technique against ET. Limitations of combined (DBS+GKT) neurosurgical techniques about the unknown recurrence of essential tremor. Only two studies supported Radiosurgical guided DBS to overcome essential tremor and drug-resistant epilepsy as shown in Table. 2.



	Saudi Arabia	Belgium	UK	Netherland	Malysia	Swizerland	Sweden	Italy	Canada	France	Japan	Germany	USA	Total
No studies	1	1	1	1	1	1	2	2	2	2	3	6	16	39
Percentage	3%	3%	3%	3%	3%	3%	5%	5%	5%	5%	8%	15%	41%	100%

Fig. 2. Number and percentage of reported studies during 2008-2018 focusing DBS and GKT for the treatment of Neurological disorders.

From three other limitations-based studies, one highlighted no visible difference on a combined approach, the second one focused on the repeated, and double DBS surgery is expensive, and third one. During our analysis, the net specificity of all available neurosurgical techniques was about 65. 25 % (Table.2). Similarly, DBS among speech disorders also showed no improvements due to the involvement of inherited factors (Alomar S *et al.*, 2016). While target specificity of DBS against zona incerta and VIM is promising to overcome essential tremor up to 90 %, in case of repeated DBS, no visible improvements are observed against refractory tremor (Mehanna R *et al.*, 2014). As reported by Lozano A. M *et al.* in 2012 that repeated DBS could not improve VIM and Zona incerta function while in 2010, Greenberg B.D *et al.* emphasized on the importance of long patient follow up studies on repeated DBS, which could be beneficial to Obsessive-compulsive disorders (OCD). Three years ago, M.D. Cho K.R *et al.* GKT a superior technique in comparison to other available technique.

In 2016, Higuchi. Y *et al.* highlighted in his review that only longterm studies could undoubtedly prove the specificity of GKT. In the same year, Witjas. T *et al.* reported GKT as the best available technique for treatment of neurological disorders including tremor disability.

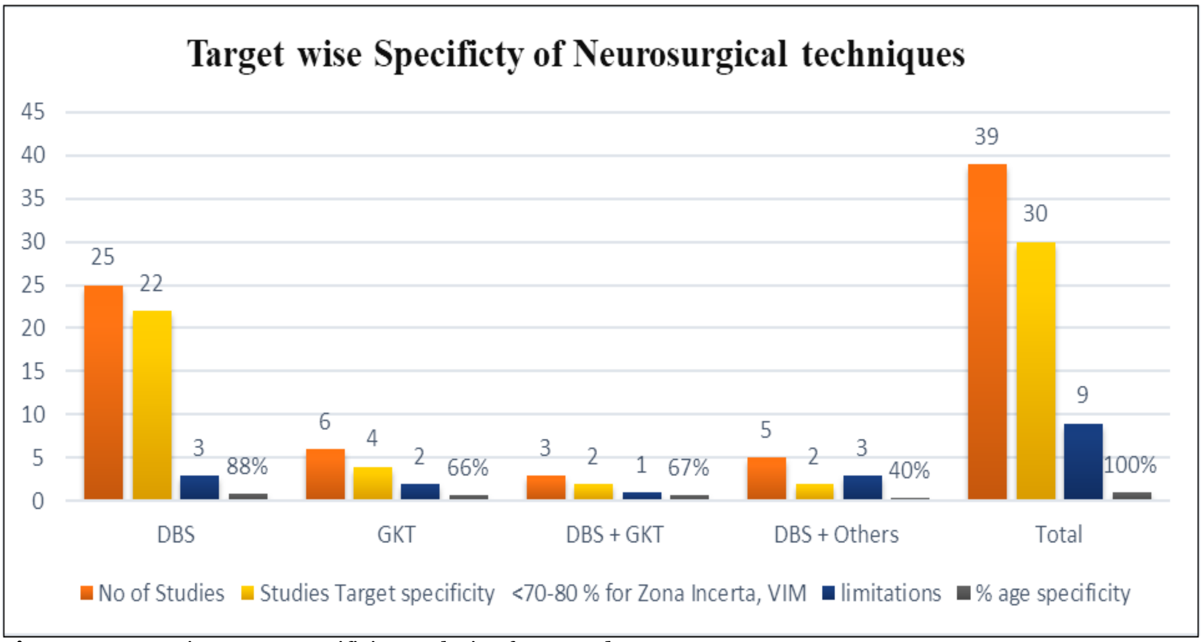


Fig. 3. Comparative target specificity analysis of DBS and GKT.

Conclusion and recommendations

Despite significant efforts from European countries, lack of compact neurosurgical advancements are the biggest challenges for the developed world to overcome neurological disorders. Both DBS and GKT are effective to treat neurological disorders with moderate heterogeneity (Tau2 = 0.76) and least risk ratio (Risk ratio = 2.2) at 95% confidence interval to overcome essential tremor and related neurological disorders. From elative target specificity, Deep brain stimulation is more target specific rather than GKT. But, in case of inherited neurological disorders, both seem to be least effective. We highly recommend Gene stimulation based specific neurosurgical techniques to overcome such disorders from our future generations. Similarly, developing nations should also take bold steps like awareness programs to stop the transmission of affected genes further? Future research on the molecular mechanism of neurological targets identification by using Laser-induced breakdown spectroscopy (LIBS) and Gene stimulation based neurosurgical techniques are needed to improve the quality of life among aged patients.

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Competing interest:

The authors declare no conflict of interest.

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