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ORIGINAL ARTICLE

The incidence of seizures following Deep Brain Stimulating electrode implantation for movement disorders, pain and psychiatric conditions

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Abstract
Deep Brain Stimulation (DBS) for neuromodulation is now commonplace. However little is known about the incidence of either procedural related seizures or epilepsy following chronic DBS. This study aims to provide estimates of these complications for movement disorders, pain and psychiatric conditions. A literature review was performed. Because searches using the terms seizure, epilepsy, and deep brain stimulation revealed only papers dealing with experimental and clinical application of DBS to treat chronic seizures disorders, a search strategy trawling through papers that described clinical case series of DBS was used. Thirty-two papers were reviewed that described stereotactic placement of DBS electrodes for movement disorders, pain syndromes and psychiatric conditions with cohorts of $n > 5$. Sixteen of these papers describing at least 1418 DBS electrode placements in 1254 patients did not mention seizures as a complication (i.e., it was not possible to know whether seizures had or had not occurred). In 16 papers, describing at least 2101 electrode placements in 1555 patients, seizures were described in 42 patients (incidence 2.7%). The range of seizure incidence varied from 0% (three series encompassing 317 patients and 576 electrode placements) up to 10% ($n = 130$) and 13% ($n = 15$). The reasons for this variance were not obvious. At least 74% of seizures occurred around the time of electrode implantation and many of these patients also suffered intracranial hemorrhage. Follow up times were variable (range 6mths to 5 years). The analysis was complicated by multiple publications from some centres with duplication of some data. The quality of literature on seizures following DBS insertion for neuromodulation is highly variable. Analysis of the available data, after making corrections for publication of duplicate data, suggests strongly that the risk of seizures associated with DBS placement is probably lower than 2.4% (95% CI 1.7 to 3.3 %). The risk of postprocedural seizures associated with chronic deep brain stimulation is even lower with best estimates around 0.5% (95% CI .02 to 1.0%).

Key words: *Deep brain stimulation, Parkinson's disease, essential tremor, pain obsessive-compulsive disease, seizure, epilepsy.*

Introduction

Functional stereotactic surgery using Deep Brain Stimulation (DBS) is now widely used for a range of movement disorders and pain conditions, and is being evaluated in the treatment of some mood and psychiatric disturbances, refractory epilepsies, Tourette's syndrome, cluster headache and eating disorders.[1–5] The spectrum of procedural and chronic complications associated with DBS is relatively well documented and includes *inter alia* intracranial hemorrhage, infection, hardware failure, and mood disturbances.[6] Since the procedure involves cortical puncture and traversing subcortical brain tissue to attain a mesodiencephalic or pallidal target one would expect a certain risk of seizures and epilepsy as a complication of the procedure. Paradoxically however there is increasing experimental and clinical work on the use of DBS to treat certain refractory epilepsies.[3,5]

The aim of this study was to ascertain what is the risk of periprocedural seizures and what is the risk of epilepsy being caused by chronic DBS for the common movement disorders (Parkinson's Disease, essential tremor, multiple sclerosis, dystonias), for certain chronic pain conditions and obsessive compulsive disorder. The raison d'etre for this paper arose because of two issues contemporaneous. One was to provide for the United Kingdom's Driver and Vehicle Licensing Authority (DVLA) some idea of the incidence of epilepsy following DBS so that driving regulations in the UK could be based upon the best available evidence. The second reason was the occurrence of a delayed chronic seizure disorder in an 18-year-old male who had bilateral Gpi DBS implantation for DYT1+ dystonia, an extremely

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rare complication in the senior author's (IRW) experience.

Methods

An electronic literature review was performed on PubMed using the specified search terms seizures, epilepsy, Deep Brain stimulation, Parkinson's Disease, essential tremor, dystonia, pain, complication, hematoma.

Searches using the terms seizure, epilepsy, and deep brain stimulation revealed only papers dealing with experimental and clinical application of DBS to treat chronic seizures disorders. Therefore a search strategy trawling through the senior author's large database of clinical papers on functional and stereotactic surgery for the incidence of seizures in clinical case series of $n > 5$ of DBS was used. Additional papers were searched on PubMed from references that looked appropriate. Data was analysed using non-parametric statistics.

Results

Thirty-two papers were retrieved that described stereotactic placement of DBS electrodes for Parkinsons Disease, essential tremor, multiple sclerosis, dystonia and pain syndromes with cohorts $n > 5$ (Table I). Sixteen of these papers describing at least 1418 DBS electrode placements in 1254 patients did not mention seizures as a complication (i.e., it was not possible to know whether seizures had or had not occurred).

In 16 papers describing at least 2099 electrode placements in 1555 patients, seizures were described in 42 patients (2.7%). The range of seizure incidence varied from 0% (three series encompassing 239 patients and 420 electrode placements) to as high as 10% ($n = 130$) and 13% ($n = 15$). However in the 2 papers where seizures occurred in relatively large numbers of patients (10 and 8), both described data from Lozano's group in Toronto,[7,8] so there is almost certainly duplication of some data. If one assumed that all 10 patients having seizures from that centre in Seijo's paper[8] included all from the earlier Venkatraghagen paper,[7] then correction of data (-8 patients from the seizure total, -110 patients from the overall patient number) suggests an incidence of 35 seizures in 1445 patients (2.4%, 95% CI 1.7–3.3). Many of these patients who suffered periprocedural seizures also suffered from intracranial hemorrhage[8] as a complication of surgery, but many with an ICH did not have a seizure[9] (Table I).

If it is assumed that all seizures that did not have a specified periprocedural or immediate postoperative incidence ($n = 7$) were delayed then at least 75% (95% CI 55-89%) of seizures occurred around the time of implantation of the electrode. The estimated incidence of delayed seizures is therefore around 0.5% (95% CI 0.02 to 1.0%).

Follow-up times in the various series were variable (range 6 months to 5 years).

Discussion

A simple electronic literature search for the incidence of seizures or epilepsy after DBS implantation for neuromodulative purposes was not particularly useful because of the large experimental neuroscience literature encompassing DBS, and the use of DBS for control of some seizure disorders. Therefore a strategy of reviewing larger series of DBS patients was adopted and these papers searched for incidence of seizure disorder, timing of the seizures and whether the seizures were associated with other surgical complications such as intracranial hematoma.

Such information in many series, unfortunately, was either absent or if present, difficult to time precisely or relate to periprocedural complications.[8,9] There was also a large variation in the reported incidence of seizure complications. This suggests that at best the figures obtained from the review are estimates. However a further paper found after initial submission of this report described 2 cases or epilepsy in 86 cases (2.3%).[38] This figure is identical to that found in our literature review and suggests that although our report does not have the authority of a meta-analysis the figures are as good as can be derived from current data.

Unfortunately the data gives no insight into why the incidence of periprocedural seizures was so variable between series. Factors that theoretically could influence seizure occurrence such as the use of ventriclography, microelectrodes, the amplitude, duration and frequency of macroelectrode or DBS electrode stimulation of the awake patient when testing for neurophysiological responses are not available. Indeed both from Grenoble,[10,12,15] where the use of both ventriculography and microelectrode recording is known to be extensive, and a paper looking at specific complications of microelectrode[9] use, seizures were not mentioned as a complication. Conversely the incidence of seizures from Lozano's group in Toronto, where microelectrode use is widespread, was high.[8]

Perhaps the best-quality data was the prospective data submitted to the FDA for regulatory purpose by the DBS manufacturers Medtronic (Medtronic, Minneapolis) (www.Fda.Gov/cdrh/pmajul97.html).[37] Procedural related seizures occurred in 1.2% of 424 patients (95% CI 0.5%–2.7%). There were no seizures in this data associated with chronic stimulation. Interestingly in the independent audit performed after 4 years in a large number of Parkinsonian patients having bilateral STN DBS implantation, although there were numerous adverse side effects epilepsy or seizures were not documented.[6]

Some of the papers covered in the review were from the same centres but describing cases cohorts of different sizes. It is therefore possible that there is

TABLE I.

Ref	Author	Patient (n)	Electrodes (n)	Disease	Position	Seizure Incidence	When	ICH incidence	F/UP
10	Benabid *et al.* 1991	32	43	PD, ET	VIM	NM	–	0	13 m
11	Blond *et al.* 1992	14	NS	PD, ET	VIM	NM	–	NM	15.2 m
12	Benabid *et al.* 1993	87	126	PD, ET, MS	VIM	NM	–	3.4% (3 pts)	5 y
13	Caparros-Lefebvre *et al.* 1993	10	14	PD	VIM	NM	–	NM	27 m
14	Siegfried *et al.* 1994	60	73	PD + others	VIM, VPL, Gpi	NM	–	NM	NM
15	Benabid *et al.* 1996	117	177	PD, ET + others	VIM	0	–	5.1% (6 pts)	NM
16	Koller *et al.* 1997	53	59	PD + ET	STN	1.6% (1 pt)	post op	3.4% (2 pts)	12 m
17	Kumar *et al.* 1997	68	NS	Various pain syndromes	PVG, VPl and VPm	2.9% (2 pts)	procedure related	NM	NM
18	Tronnier *et al.* 1997	6	12	PD	GPi	NM	–	NM	6.5 m (mean)
19	Limousin *et al.* 1999	111	NS	PD + ET	VIM	NM	–	2.7% (3 pts)	12 m
20	Taha *et al.* 1999	23	42	PD, ET, MS	VIM	NM	–	0	10 m (mean)
21	Schuurman *et al.* 2000	35	NS	PD, ET, MS	VIM	NM	–	5.7% (2 pts)	2 y (mean)
22	Krauss *et al.* 2001	94	123	PD, ET + 7 (MS)	STN	NM	–	1% (1 pt)	11.9 m (mean)
23	European PD study group 2001	143	277 leads	PD	STN + GPi	2.8% (4 pts)	NM	4.9% (7 pts)	6 m
24	Hooper *et al.* 2002	15	13	MS	VIM, VOP	13% (2 pts)	one week, 8 weeks	13% (2 pts)	12 m
7	Venkatraghaven *et al.* 2002	172	NS	PD, ET, Dystonia	STN, VIM, Gpi	4.6% (8 pts)	periprocedural	not stated	
25	Yiani *et al.* 2002	25	50	Dystonias	GPi	NM	–	NM	12 m (mean)
26	Krack *et al.* NEJM 2003	49	98	PD	STN	4% (2 pts)	"transient"	20% (8 pts)	5 y
27	Coubes *et al.* 2004	31	62	Dystonias	GPi	0	–	0	2 y
9	Binder *et al.* 2005	280	481	all movement disorders'	STN, Gpi, VIM	NM	–	5.7% (16 pts)	12 m
28	Bittar *et al.* 2005	12	24	Dystonias	GPi	0	–	0	2 y
29	Vidailhet *et al.* 2005	22	44	Dystonia	GPi	NM	–	4.5% (1 pt)	12 m
30	Deuschl *et al.* 2006	78	156	PD	STN	0*	–	0%	6 m
31	Goodman *et al.* 2006	100	191	PD	STN	3% (3 pts)	"periprocedural"	2.0% (2 pts)	12 m
32	Guehl *et al.* 2006	44	NS	PD	STN	NM	–	4.5% (2 pts)	12 m
33	Hamani *et al.* 2006	21	29	Pain	PAG + PVG + Vc	5% (1 pt)	perioperative	NM	not clear
34	Owen S. 2006	15	NS	Post stroke pain	PAG, VPL	NM	–	NM	27 months (av)
8	Seijo *et al.* 2007	130	252	PD	STN	10% (13 pts)	all within first 24 hrs	6.9% (9 pts)	37 m (mean)
35	Tabbal *et al.* 2007	110	219	PD	STN	0	–	0.9% (1 pt)	12 m
36	Tir *et al.* 2007	100	200	PD	STN	NM	–	8% (8 pts)	12 m
2	Greenberg *et al.* 2008	26	52	OCD	VIC/VS	3.8% (1 pt)	procedure related	7.6% (2 pts)	12 m
37	Medtronic Activa FDA data	424	NS	PD + ET	VIM	1.2% (5 pts)	procedure related	3.1% (13 pts)	variable

some duplication of data. For example the data (n = 117) from one paper by Benabid and colleagues[15] almost certainly covers two early papers on the same topic.[10,12] The papers by Blond[11] and Caparros-Lefebre[13] may also contain the same patients as may those of from the Aziz's Oxford group.[25,28] However in all these papers there was no mention of seizures so the data does not contribute to the estimates made.

Adjustments to the estimates were made in the results because of the contribution of patients from Toronto probably being cross referred. It is also possible that there was also double counting of some patients described in The European tremor trial,[23] where there were 4 cases of seizure, and the Medtronic FDA data[37] where there were 5 cases. Adjusting the data for potential double counting within this cohort reduces the number of seizures to 31 in 1308 patients. However this gives an overall seizure estimate of 2.4% with 95% CI of 1.6 to 3.3%, which is almost identical to the unadjusted estimate.

Given these caveats and shortcomings with much of the literature, patients may be counselled preoperatively that the seizure risk is relatively low at around 2.5%, irrespective of the indication for the DBS, that it is largely periprocedural, and that the likelihood of a chronic seizure disorder occurring is extremely low at around 0.5%. Additionally patients should be able to resume driving once they have recovered from their DBS surgery, unless there are other contra-indications to driving.

Declaration of interest: IRW is a member of The Secretary of States Advisory Panel on Driving and Diseases of the Nervous System. All other authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1 Anderson WS, Lenz FA. Surgery insight: Deep brain stimulation for movement disorders. *Nat Clin Pract Neurol* 2006;2(6): 310–20.
2 Greenberg BD, Gabriels LA, Malone DA Jr, Rezai AR, Friehs GM, Okun MS, *et al*. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Mol Psych* 2008;May 20:[Epub ahead of print].
3 Halpern CH, Samadani U, Litt B, Jaggi JL, Baltuch GH. Deep brain stimulation for epilepsy. *Neurotherapeutics* 2008;5(1): 59–67.
4 Laćan G, De Salles AA, Gorgulho AA, Krahl SE, Frighetto L, Behnke EJ, *et al*. Modulation of food intake following deep brain stimulation of the ventromedial hypothalamus in the vervet monkey. Laboratory investigation. *J Neurosurg* 2008; 108(2):336–42.
5 Velísek L, Velísková J, Moshé SL. Electrical stimulation of substantia nigra pars reticulata is anticonvulsant in adult and young male rats. *Exp Neurol* 2002;173(1):145–52.
6 Hariz MI, Rehncrona S, Quinn NP, Speelman JD, Wensing C; Multicentre Advanced Parkinson's Disease Deep Brain Stimulation Group. Multicenter study on deep brain stimulation in Parkinson's disease: an independent assessment of reported adverse events at 4 years. *Mov Disord* 2008;23(3):416–21.
7 Venkatraghavan L, Manninen P, Mak P, Lukitto K, Hodaie M, Lozano A. Anesthesia for functional neurosurgery: review of complications. *J Neurosurg Anesthesiol* 2006;18(1):64–7.
8 Seijo FJ, Alvarez-Vega MA, Gutierrez JC, Fdez-Glez F, Lozano B. Complications in subthalamic nucleus stimulation surgery for treatment of Parkinson's disease. Review of 272 procedures. *Acta Neurochir* (Wien). 2007;149(9):867–75, discussion 876.
9 Binder DK, Rau GM, Starr PA. Risk factors for hemorrhage during microelectrode-guided deep brain stimulator implantation for movement disorders. *Neurosurgery* 2005;56(4):722–32; discussion 722–32.
10 Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, Perret JE, de Rougemont J. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet* 1991;337(8738):403–6.
11 Blond S, Caparros-Lefebvre D, Parker F, Assaker R, Petit H, *et al*. Control of tremor and involuntary movement disorders by chronic stereotactic stimulation of the ventral intermediate thalamic nucleus. *J Neurosurg* 1992;77(1):62–8.
12 Benabid AL, Pollak P, Seigneuret E, Hoffmann D, Gay E, Perret J. Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. *Acta Neurochir Suppl* (Wien). 1993;58:39–44.
13 Caparros-Lefebvre D, Blond S, Vermersch P, Pécheux N, Guieu JD, Petit H. Chronic thalamic stimulation improves tremor and levodopa induced dyskinesias in Parkinson's disease. *J Neurol Neurosurg Psych* 1993;56(3):268–73.
14 Siegfried J, Lippitz B. Chronic electrical stimulation of the VL-VPL complex and of the pallidum in the treatment of movement disorders: personal experience since 1982. *Stereotact Funct Neurosurg* 1994;62(1–4):71–5.
15 Benabid AL, Pollak P, Gao D, Hoffmann D, Limousin P, Gay E, *et al*. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. *J Neurosurg* 1996;84(2):203–14.
16 Koller W, Pahwa R, Busenbark K, Hubble J, Wilkinson S, Lang A, *et al*. High frequency unilateral thalamic stimulation in the treatment of essential and Parkinsonian tremor. *Ann Neurol* 1997;42(3):292–9.
17 Kumar K, Toth C, Nath RK. Deep brain stimulation for intractable pain: a 15-year experience. *Neurosurgery* 1997; 40(4):736–46; discussion 746–7.
18 Tronnier VM, Fogel W, Kronenbuerger M, Steinvorth S. Pallidal stimulation: an alternative to pallidotomy? *J Neurosurg* 1997;87(5):700–5.
19 Limousin P, Speelman JD, Gielen F, Janssens M. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. *Neurol Neurosurg Psych* 1999; 66(3):289–96.
20 Taha JM, Janszen MA, Favre J. Thalamic deep brain stimulation for the treatment of head, voice, and bilateral limb tremor. *J Neurosurg* 1999;91(1):68–72.
21 Schuurman PR, Bosch DA, Bossuyt PM, Bonsel GJ, van Someren EJ, de Bie RM, *et al*. comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. *N Engl J Med* 2000;342(7):461–8.
22 Krauss JK, Simpson RK Jr, Ondo WG, Pohle T, Burgunder JM, Jankovic J. Concepts and methods in chronic thalamic stimulation for treatment of tremor:technique and application. *Neurosurgery* 2001;48(3):535–41; discussion 541–3.
23 The Deep-Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's Disease. *NEJM* 2001:345:956–63.
24 Hooper J, Taylor R, Pentland B, Whittle IR. A prospective study of thalamic deep brain stimulation for the treatment of movement disorders in multiple sclerosis. *Br J Neurosurg* 2002;16(2):102–9.
25 Yianni J, Bain P, Giladi N, Auca M, Gregory R, Joint C, *et al*. Globus pallidus internus deep brain stimulation for dystonic conditions: a prospective audit. *Mov Disord* 2003;18(4): 436–42.

26 Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, Koudsie A, *et al*. P. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 2003;349(20):1925–34.
27 Coubes P, Cif L, El Fertit H, Hemm S, Vayssiere N, Serrat S, Picot MC, *et al*. Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: long-term results. *J Neurosurg* 2004;101(2):189–94.
28 Bittar RG, Burn SC, Bain PG, Owen SL, Joint C, Shlugman D, Aziz TZ. Deep brain stimulation for movement disorders and pain. *J Clin Neurosci* 2005;12(4):457–63.
29 Vidailhet M, Vercueil L, Houeto JL, Krystkowiak P, Benabid AL, Cornu P, *et al*. French Stimulation du Pallidum Interne dans la Dystonie (SPIDY) Study Group. Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. *N Engl J Med* 2005;352(5):459–67.
30 Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, *et al*. German Parkinson Study Group, Neurostimulation Section. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006; 31;355(9):896–908.
31 Goodman RR, Kim B, McClelland S 3rd, Senatus PB, Winfield LM, Pullman SL *et al*. Operative techniques and morbidity with subthalamic nucleus deep brain stimulation in 100 consecutive patients with advanced Parkinson's disease. *J Neurol Neurosurg Psych* 2006; 77(1): 12–17.
32 Guehl D, Cuny E, Benazzouz A, Rougier A, Tison F, Machado S, *et al*. Side-effects of subthalamic stimulation in Parkinson's disease: clinical evolution and predictive factors. *Eur J Neurol* 2006;13(9):963–71.
33 Hamani C, Schwalb JM, Rezai AR, Dostrovsky JO, Davis KD, Lozano AM. Deep brain stimulation for chronic neuropathic pain: long-term outcome and the incidence of insertional effect. *Pain* 2006;125(1–2):188–96.
34 Owen SL, Green AL, Stein JF, Aziz TZ. Deep brain stimulation for the alleviation of post-stroke neuropathic pain. *Pain* 2006;120(1–2):202–6.
35 Tabbal SD, Revilla FJ, Mink JW, Schneider-Gibson P, Wernle AR, de Erausquin GA, Perlmutter JS, Rich KM, Dowling JL. Safety and efficacy of subthalamic nucleus deep brain stimulation performed with limited intraoperative mapping for treatment of Parkinson's disease. *Neurosurgery* 2007;61(3 Suppl):119–27; discussion 127–9.
36 Tir M, Devos D, Blond S, Touzet G, Reyns N, Duhamel A, *et al*. Exhaustive, one-year follow-up of subthalamic nucleus deep brain stimulation in a large, single-center cohort of Parkinsonian patients. *Neurosurgery* 2007;61(2):297–304; discussion 304–5.
37 www.fda.gov/cdrh/pmajul97.html US Food and Drug administration summary of Safety and Effectiveness for Medtronic Activa Tremor control system, Washington, DC.
38 Beric A, Kelly PJ, Rezai A, Sterio D, Mogliner A, Zonenshayn M, Kopell B. Complications of deep brain surgery. *Stereotactic Functional Neurosurg* 2001: 77;73–78.