Author's response to reviews

Title: Aggravated stuttering following subthalamic deep brain stimulation in Parkinson's disease - two cases

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Author's response to reviews: see over
Dear Prof Korczyn,

Please thank the reviewers for their helpful comments on our paper. Both reviewers’ comments have been carefully addressed as described below.

I hereby confirm that both authors have read the manuscript, the paper has not been previously published, and is not under simultaneous consideration by another journal. In addition, all persons involved in the writing of the manuscript have been included on the author list.

I hope that the revised manuscript can be accepted for publication in BMC Neurology.

Sincerely,

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Reviewer: Harrison Walker

The cause of stuttering is unknown. This case report describes the occurrence of neurogenic (symptomatic) stuttering and the recurrence of developmental stuttering, respectively, in two patients who underwent bilateral subthalamic deep brain stimulation (STN-DBS) for advanced Parkinson’s disease (PD). One of these patients had a history of a prior thalamotomy in the left cerebral hemisphere prior to DBS surgery. This report is of interest because it implicates the basal ganglia (and its connections) in the pathogenesis of stuttering and adds to prior descriptions of both worsening and improvement of stuttering following STN DBS in patients with PD.

Major compulsory revisions:
1. Was speech assessed during spontaneous speech, during reading, or both? Did singing or choral speech diminish the speech abnormality, as is common in patients with developmental stuttering?

We agree with the reviewer that it is of interest to know how speech was assessed. In the described patients speech was assessed both during spontaneous speech and during reading. At least in patient 1 singing improved the speech abnormalities, and this information has been added to the revised manuscript.

2. Quantification of stuttering events in the various stimulation conditions with the percentage of syllables stuttered or a rating instrument such as the stuttering severity index would make it easier to interpret this manuscript. Additionally, quantification of various stuttering events (repetitions, prolongations, hesitations, etc...) would give the reader a better sense of the quality of the speech and how much the speech differed with DBS on and off.

All examinations of the patients were performed by neurologists that are members of the DBS team in our clinic. No formal rating instruments of stuttering have been used in these patients.

3. Were the ratings performed by speech pathologists or personnel trained in evaluating speech disorders?

See previous answer.

4. Were the patients truly blinded to the stimulation condition? This can be difficult, particularly when the DBS has dramatic symptomatic effects on motor function. Were efforts made to blind to the rater to tremor and other motor manifestations that might in effect unblind the rater to the stimulation condition? If not, this should be acknowledged in the manuscript.

The patients were unaware of the stimulation settings during testing of speech. However, as noted by the reviewer, due to the effects on motor function the patients might not have been completely blinded. More importantly, the rater assessed speech on a videotaped sequence of the patients’ faces and the effects of neurostimulation on other motor functions were thus not visible to the rater.

5. Also, it would be useful to know how Parkinsonian the patients' speech was. Was there hypophonia, palilalia, or tachyphemia for instance? Did bilateral DBS worsen Parkinsonian elements of the patients' speech, independent from any effect on stuttering?

Patient 1 had no hypophonia or other speech abnormalities than the stuttering after the performed surgery. However, he reported a history of abnormally rapid speech since his childhood. This information has been added to the manuscript. The manuscript already includes information on the presence of hypophonia and dysarthria in patient 2, these symptoms were not affected by neurostimulation.
7. It would be interesting to know the handedness of the subjects with respect to the lateralization of language function. PD is an asymmetric disease in terms of its motor manifestations, and it appears that in both patients in this report, the left hemisphere was more severely affected than the right hemisphere by PD because the motor symptoms were worse on the right than the left.

Both patients were right-handed, and this information has been added to the revised manuscript.

8. These patients underwent bilateral STN DBS. Did the authors test speech with one stimulator on at a time with "motor effective" settings? It seems very possible that one of the pair of stimulators (either in the right STN or the left STN) was actually driving the speech abnormality. If the speech abnormality were present only when both stimulators were on simultaneously at "motor effective" settings, this would be of interest as well.

Speech was tested with the stimulator switched on using the “motor effective” settings and off. We performed no tests of speech under unilateral stimulation. However, as described in the manuscript, in patient 1 the testing was also performed using reduced stimulation amplitudes leading to a partial improvement in stuttering.

9. The authors conclude "stimulation of the STN itself or to structures localized in the immediate proximity" relate to the development of stuttering. Although this may be the case, the STN is one node in a complex system with direct connections to and from various anatomical structures including cerebral cortex, other basal ganglia nuclei, and brainstem structures. I think it would be more appropriate to conclude that the stimulation of the STN, its afferent or efferent projections, and/or to other structures in the vicinity of the stimulating electrode relate to the alteration of speech in these patients.

We agree with the reviewer and have included this in the revision.

10. The authors did not cite an article with the opposite results of their findings. That case report described significant improvement in neurogenic stuttering associated with PD with unilateral left STN DBS (Walker HC et al, Journal of Speech Language and Hearing Research, 2009). The authors should explicitly discuss that there is some disagreement in the literature on this subject. How would the authors interpret their findings in the context of this result? At the least, I think the accumulated case reports argue for a role of the basal ganglia in the pathogenesis stuttering and that STN DBS appears to be able to modify it, either negatively or positively.

The reference has been included and discussed in the revised manuscript.

11. The authors seem to assume that neurogenic and developmental stuttering share the same pathogenesis. While it is certainly possible that they share some common mechanisms, the authors should acknowledge that they might in fact be different entities.

The authors agree with the reviewer that neurogenic and developmental stuttering may not share the same pathogenesis. The main purpose of the paper has been to describe the reversible worsening of both neurogenic and developmental stuttering, and this may indicate shared common mechanisms. We have tried to clarify this in the revision of the paper.

12. The authors conclude that the effect of the stimulators on motor function was clearly related to the effects on speech. Why would this necessarily be the case? Stuttering might be considered a bradykinesia of speech. If this were the case, why would DBS worsen speech yet help the arms and legs? I think the most that can be concluded is that stuttering and motor improvement in the limbs were associated with one another in these two cases - it remains possible that structures unrelated to motor function in the limbs were stimulated simultaneously at "motor effective" settings.

The authors agree with the reviewer and in the revised paper it is stated that the stuttering and motor improvements were associated in the two patients.
Minor essential revisions:
1. The authors should specify which contacts were used for monopolar stimulation on both sides of the brain.

This information is now added.

2. The authors argue on clinical grounds that the stimulators are in the vicinity of the STN. Was post-operative MRI performed on these patients? Were the microelectrode recordings typical for the STN region?

The peroperative microelectrode recordings were typical for the STN region, and information about this has been added to the paper. There are several safety issues with postoperative MRI after the implantation of the neurostimulator, which in our center is always performed in the same session as the lead implantation. Thus, post-operative MRI was not performed on these patients. However, the excellent clinical efficacy of the treatment indicates that the placement of the electrodes was appropriate.

Reviewer: F Klostermann

In their manuscript ‘Aggravated stuttering following subthalamic deep brain stimulation in Parkinson’s disease’ the authors report on two subjects who developed a stuttering speech disorder under DBS. Although the induction of this side effect by DBS appears altogether relatively seldom, the authors make clear that it was reliably and repeatedly assessed in a blinded fashion, depending on the stimulation state (only present in the on-condition). Since DBS neuromodulates specific nuclei within cortico-basal networks, the observation is of conceptual interest with respect to stuttering and I therefore support its publication.

Some minor points might, however, be revised:
1. The authors speak of a ‘relation’ between stuttering and stimulation induced motor improvements. They should avoid this term and choose a wording which indicates that both phenomena were observed together, causal relations being undefined.

We agree with the reviewer, and as mentioned in comments to the first reviewer we have in the revised paper stated that the two effects are associated, since the causal relationship is unknown.

2. What would the authors suggest conceptually the dissociation between motor improvement on the one hand and speech deterioration on the other hand might mean. Are speech and body motor systems neuroanatomically distinct, etc.? Are the conceptual accounts for basal ganglia roles for speaking / stuttering and body kinesia really different and why should we expect differential actions?

Both the results of our observations and the fact that dopamine antagonist generally improve stuttering and worsen parkinsonian limb symptoms indicate that speech and body motor symptoms are distinct. This information has been added to the revised paper.

3. The analogy between verbal dysfluency and stuttering appears unlikely. The authors observed a distinct phenomenon from the language-related impact of DBS on probably semantic or phonetic capacities.

In the revised version of the manuscript we have tried to clarify this analogy. Our main point is that if stuttering is aggravated by neurostimulation of the STN, such stimulation may also slightly impact motor functions of speech in patients without stuttering. This may influence the performance on verbal fluency tests, and the measured slight deterioration on such tests after STN-DBS might therefore not reflect executive dysfunction.
4. In this regard, the authors might avoid the classification of DBS-dependent stuttering as ‘language-related’ and prefer the term ‘speech-related’.

We agree with the reviewer and this has been changed in the revision.

5. Could the authors comment on the localisation of the DBS electrodes? One clinical remark: the UPDRS values of 8 and 12 (best on condition) appear extremely low for patients with a more than 20 years course of PD. They should check this again.

We have added information on the results of the microelectrode recording during the surgical procedure, indicating correct placement of the electrodes in the subthalamic nucleus. We agree that the presented UPDRS motor scores in the best on conditions are low, but we have again checked these values and they are correct. Both patients have early disease onset of PD, with mainly levodopa responsive motor symptoms complicated by the development of marked motor fluctuations.