Reversible Micrographia in Association with STN-DBS Therapy in a Patient with Parkinson's Disease

Dear Editor,

A 58-year-old male patient with Parkinson's disease (PD) had undergone subthalamic nucleus deep brain stimulation (STN-DBS) surgery one year ago due to refractory motor fluctuations including severe off periods and dyskinesia. It was learned that PD had manifested 15 years ago with slowing of his right leg and disruption in gait. Activation of DBS had provided marked relief from symptoms and the total levodopa dose was reduced from 1200 mg/day preoperatively to 400 mg/day postoperatively. However, although marked improvement in general daily living activities was observed, he suffered from severe deterioration in his writing that he realised soon after the activation of DBS. Of note, the writing problem persisted throughout the day and did not improve with levodopa doses. On admission to our polyclinic, he was receiving the medications of levodopa/benserazide 100/25 mg 4 × 1/2 TB, pramipexole 1 mg, and amandatine 100 mg daily. The extrapyramidal exam during the medication off state revealed bradymimia, bilateral rigidity, and bradykinesia that was prominent on the right side. Besides, mild gait difficulty and moderate postural instability were observed. Cranial computed tomography showed electrodes in bilateral subthalamic nucleus (STN) [Supplementary Figure 1]. The neuropsychological tests including standardized mini-mental sate examination, phonemic fluency, semantic fluency, forward–backward counting, and Stroop test were within normal limits. The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)-3 score during the medication off period was 19 points; however, evaluation of his writing revealed severe micrographia [Figure 1a]. Interestingly, after DBS was deactivated, his writing recovered substantially and micrographia resolved [Figure 1b]. Nevertheless, the MDS-UPDRS-3 score deteriorated to 42 points. The evaluation was reperformed a few minutes after the stimulation was reactivated, which again revealed the emergence of marked micrographia [Figure 1c]. The DBS settings were as follows: bilateral most-ventral monopolar active contacts, 1.8 V (right), 3.3 V (left), 50 μs (bilateral), 140 Hz (bilateral). To examine the association between stimulation and micrographia in a more detailed manner, we turned off the stimulation only on the left side, which provided improvement in micrographia. Nevertheless, unilateral deactivation of the stimulation on the right side did not provide an amelioration in writing [Figure 2]. Of note, reducing the left hemisphere stimulation voltage lead marked deterioration in the parkinsonian signs, whereas increment of the voltage by 0.3 V resulted in right lower limb dystonia. Alternative programming of DBS (different monopolar contacts, bipolar configurations) did not yield an improvement in micrographia. Taken together, considering the benefit of stimulation in general daily living activities, the patient was discharged with the same medical therapy while the stimulation was bilaterally active. However, reducing the left hemisphere stimulation voltage by 0.2 V provided mild improvement in micrographia without significant deterioration in the parkinsonian signs. The final settings were as follows: bilateral most-ventral monopolar active contacts, 1.8 V (right), 3.1 V (left), 50 μs (bilateral), 140 Hz (bilateral).

Herein, we illustrate an interesting patient with PD in whom DBS resulted in deterioration in writing ability that was compatible with micrographia, despite marked improvement in other Parkinsonian symptoms. Moreover, deactivation of the stimulation led to rapid resolution of micrographia and it reoccurred rapidly after reactivation of the stimulation, which all supported DBS-related, acute, and dynamic mechanisms. We think that our observation may give critical perspectives regarding the mechanisms underlying micrographia as well as those responsible for the efficacy of DBS.

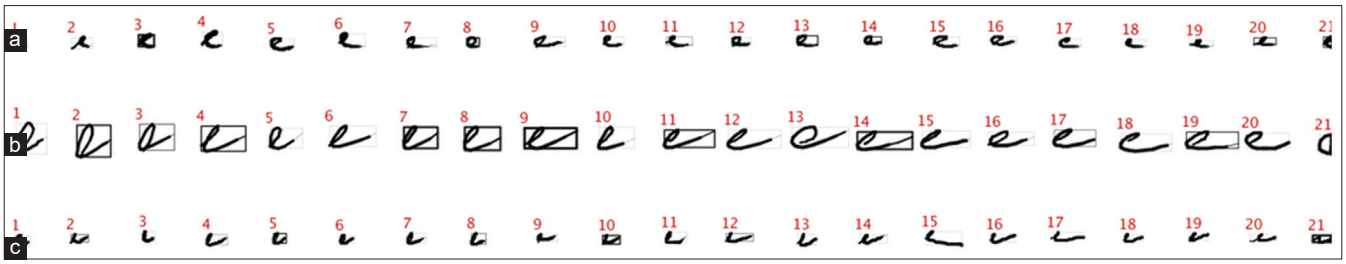

Figure 1: (a) The writing of the patient when the stimulation was "ON" shows micrographia. (b) The assessments soon after the stimulation was turned off show recovery from micrographia. (c) The assessments few minutes after the stimlation was reactivated, which again reveal marked micrographia

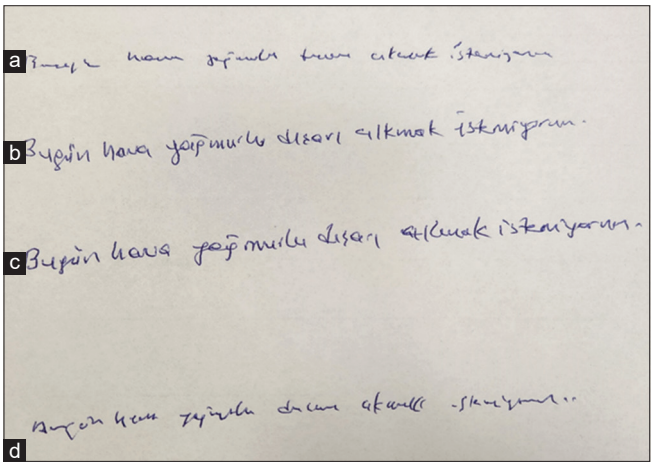

Figure 2: The serial assessments of the writing of patient show micrographia when the left hemisphere stimulation is active. Images of writing during the stimulation is bilateral 'ON' (a), only the right hemisphere is active (b), bilateral stim ulation is turned off (c), only the left hemisphere is active (d)

DBS is a critical treatment option for advanced-stage PD, which leads to a marked reduction in MDS-UPDRS motor scores, total levodopa dose, and improvement in the quality of life of patients.[1,2] However, it may lead to some side effects such as dysarthria, paresthesias, diplopia, eyelid opening, apraxia, depression, suicide, etc.[1,2] On the other hand, micrographia is strictly an atypical side effect.[3,4] Blahak *et al*.[3] reported micrographia induced by Globus pallidus internus-Deep brain stimulation (GPi-DBS) in 11 patients with dystonia. In this report, the authors concluded that micrographia reflects a mild hypokinetic syndrome directly induced by the stimulation.[3] They also referred to a previous patient-based questionnaire study,[5] which found that 10 out of 11 patients with GPi-DBS for cranial–cervical dystonia complained about at least mild hypokinetic symptoms including handwriting alterations. The authors hypothesized that alterations in GPi output activity by GPi-DBS might result in a modification of neuronal activity in the ascending pallido-thalamo-frontal pathways, which might be included in the pathophysiology of hypokinesia.[3] On the other hand, micrographia following STN-DBS has been reported in only a unique case.[4] The authors discussed that the simultaneous reduction in levodopa dose after surgery could be responsible for micrographia.[4] However, they also noted that the motor symptoms had improved despite micrographia, suggesting a mechanism other than hypokinesia.[4] In that case,[4] it is remarkable to state that micrographia was recognized postsurgery before the activation of DBS and there was no data regarding the impact of deactivation of DBS in the follow-up, questioning a dynamic association between micrographia and stimulation. However, we demonstrated the resolution of micrographia after deactivation of stimulation and its re-emergence after reactivation of the stimulation, which revealed a strong and dynamic association between the stimulation and micrographia. Similar to the case by Fearon *et al*.,[4] despite the emergence of micrographia, the stimulation provided improvement in motor symptoms including bradykinesia, rigidity, and gait impairment, supporting the hypothesis of a mechanism other than hypokinesia. Increased cognitive demand and visuospatial perception failure have been suggested to contribute to micrographia.[6] Considering that the learning effect would not allow to evaluate the dynamic effect of stimulation on cognition, we did not repeat the neuropsychological tests after the stimulation was deactivated. On the other hand, detailed neuropsychological assessments which also included the visuospatial functions performed during the stimulation "ON" period resulted in normal findings, reducing the possible role of cognitive mechanisms in this manifestation. Of note, we found that micrographia was associated with only the left hemisphere stimulation, confining the pathophysiology of micrographia to the left hemisphere function.

In a functional magnetic resonance imaging (MRI) study, Wu *et al*.[7] showed that constant micrographia was associated with decreased activity and connectivity in the basal ganglia motor circuit, and levodopa therapy was shown to improve micrographia by restoring the function of this circuit. However, in another study by Eklund *et al*.,[8] the authors found a correlation between micrographia severity and extrastriatal Iodine 123-radiolabeled 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane ([123I] FP-CIT) binding in their patients with PD. Besides, no difference in any micrographia measurement was found between levodopa-medicated and unmedicated PD patients ($P > 0.24$). They interpreted that these results might support the primarily nondopaminergic mechanism of micrographia in PD.[8] The emergence of micrographia in our

patient was inversely related to the other Parkinsonian signs such as bradykinesia and rigidity, which responded well to dopaminergic treatment. Besides, the writing of the patient did not ameliorate with dopaminergic treatment, which all suggested a nondopaminergic mechanism. However, which reversible mechanisms induced by STN-DBS might be involved in this intriguing manifestation of reversible micrographia? A primate study model showed that minor differences in the location of stimulation within STN could increase or decrease dopaminergic release to the striatum.[9] Besides, stimulated brain networks with STN-DBS are anatomically and functionally segregated within the basal ganglia thalamocortical system and are represented in distinct functional motor, associative, and limbic cortical regions.[10] Taken together, the emergence of micrographia and resolution of other parkinsonian signs in the upper and lower limbs may be related to the specific location of the STN-DBS electrodes that might result in distinct impacts in various anatomic regions. However, changing the contact sites of the left hemisphere DBS did not provide an amelioration in micrographia, contrasting with this hypothesis. Finally, the specific association with left hemisphere stimulation constitutes another crucial point for further deliberations. The deterioration in the verbal fluency, a measure of language function, is shown to occur particularly in patients with left hemisphere stimulation.[11] Of note, handwriting is not only a motor task, but additionally requires the function of intact language functions. Although we did not evaluate the pre- and post-DBS assessments of language functions, we can hypothesize that the left stimulation of STN-DBS might lead to micrographia by affecting the particular language areas localized in the left hemisphere via its possible effect in the hyperdirect pathway.[12]

In conclusion, we report micrographia as a dynamic and reversible side effect of STN-DBS for the first time in literature. We discuss the anatomically and functionally segregated networks within the basal ganglia thalamocortical system that may be distinctly activated according to the specific location of stimulation. The possible role of the affection of cortical language areas by STN-DBS is also discussed. Future studies investigating this manifestation in a systematic approach undergoing STN-DBS treatment might contribute substantially to our current knowledge regarding the pathophysiology of micrographia as well as the action of mechanisms of STN-DBS.

The procedure was performed under local anesthesia with microelectrode recording and test stimulation. Coordinates of the tip of the electrodes relative to the mid-commissural point were as follows:

	X	Y	Z	Anterior commissure (AC)–Posterior commissure (PC) distance
Left	−11.9	−2.1	−4.2	25.9 mm
Right	+12.1	−2.3	−3.9	

Consent to participate

Informed consent form has been obtained from the patient.

Consent for publication

Informed consent form for publication has been obtained from the patient.

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Conflicts of interest

There are no conflicts of interest.

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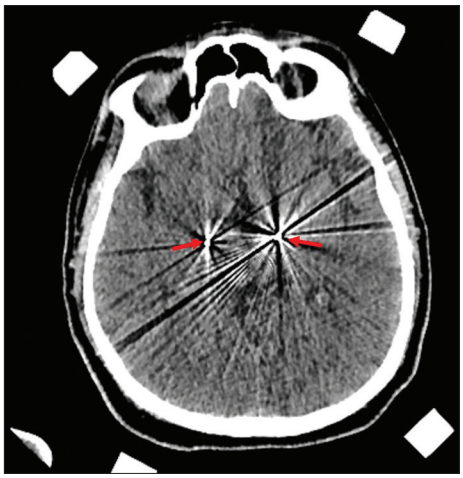

Supplementary Figure 1: Cranial computed tomography shows the bilateral electrodes of STN-DBS (arrows)