

Sensory processing deficits in Parkinson’s Disease: localizing auditory evoked p50 responses during awake deep brain stimulation surgery

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Abstract

Parkinson's Disease (PD) is a neurodegenerative disorder characterized by motor deficits, with secondary cognitive and sensory symptoms. Previous studies using magnetoencephalography (MEG) and electroencephalography (EEG) have revealed dysfunctions in sensory gating and processing that occur in PD. This study used intraoperative local field potentials (LFPs) to study dysfunction of auditory gating in patients undergoing awake deep brain stimulation surgery (DBS) to treat motor symptoms of PD. Intraoperative measurement of LFPs permits more precise spatial localization of sensory gating deficits and anatomical characterization of the implicated deep brain networks. Data were collected on eight DBS implantations, with LFP measurements of P50 auditory evoked potentials (AEPs) correlated to intraoperative imaging. We correlated P50 responses with neuroanatomical structures in the thalamus and basal ganglia, with abnormal responses originating primarily from within the subthalamic nucleus and the thalamic reticular nucleus. These results may improve understanding of the deep brain networks involved in PD. Additionally, detailed characterization of these networks will facilitate the development of DBS protocols for other disorders of dopaminergic dysregulation such as schizophrenia.

Introduction

DBS is indicated or has shown efficacy for several disorders, including Parkinson’s Disease (PD), Tourette Disorder, Essential Tremor, Dystonia, Obsessive-Compulsive Disorder, Major Depressive Disorder, and Schizophrenia. It’s most common and best studied use is in PD, as it is effective in the relief of the hallmark motor symptoms including bradykinesia and resting tremor. In the basal ganglia, the subthalamic nucleus (STN) and Globus Pallidus internus (Gpi) are approved DBS targets of Parkinson’s disease. .

Evidence suggests that DBS targeted at the STN in late PD modulates cortical auditory processing in addition to improving motor symptoms. Additionally, the presence of sensory processing abnormalities is predictive of freezing-of-gait in PD patients, suggesting a direct relationship between PD pathology and sensory processing deficits. Other studies have also noted a relationship between motor freezing-of-gait and sensory deficits. Further, DBS used chronically within the STN can rectify abnormal AEPs in PD patients and investigators have noted previously that DBS placement for ET and PD can incidentally improve auditory symptoms in comorbid tinnitus. It appears likely that rather than being isolated to motor symptoms, loss and dysfunction of dopamine signaling and PD also is a central cause of depression and apathy observed in the disease, emphasizing the central role of dopamine’s action in the STN for both motor and cognitive/psychological features of PD.

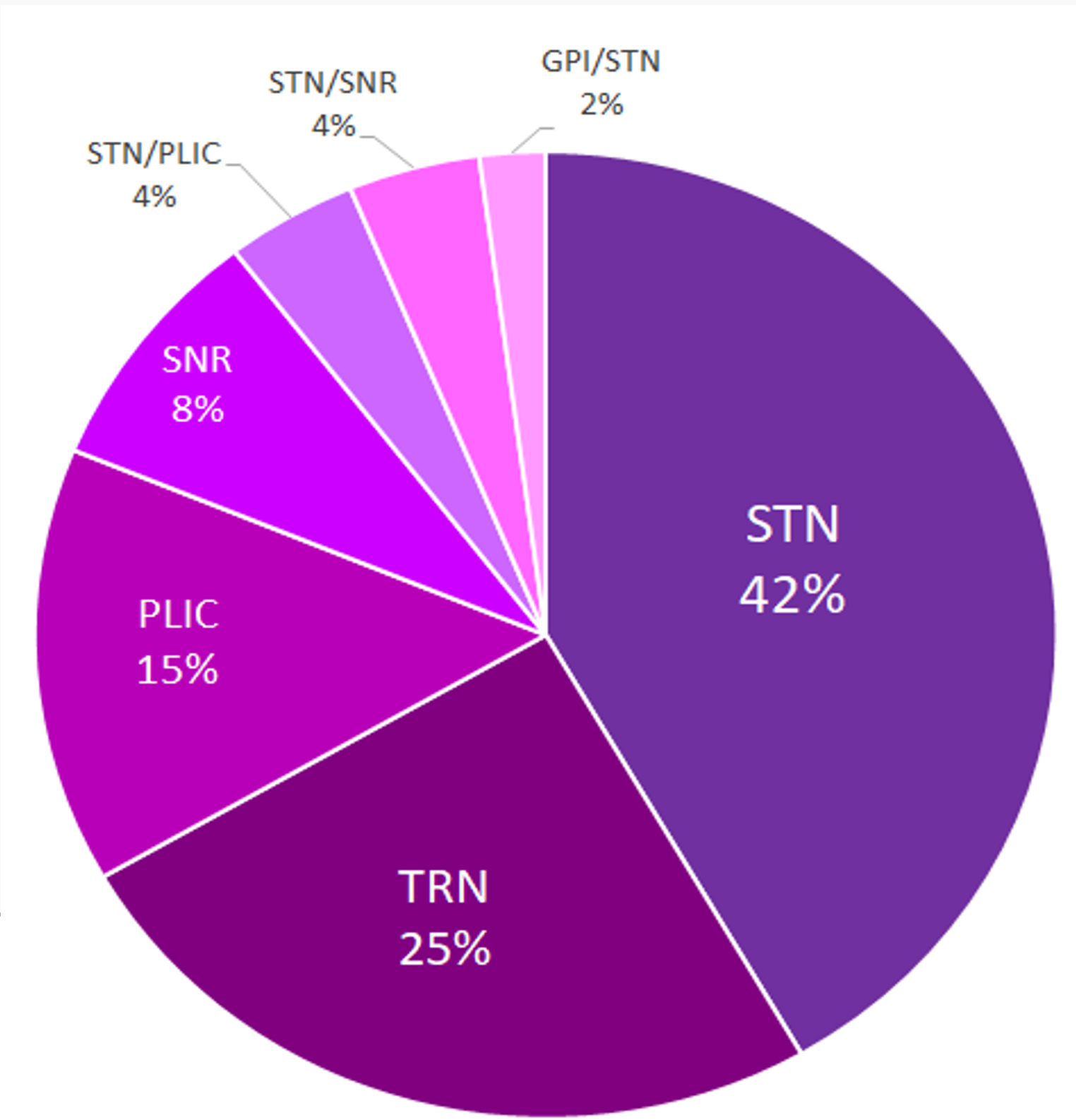
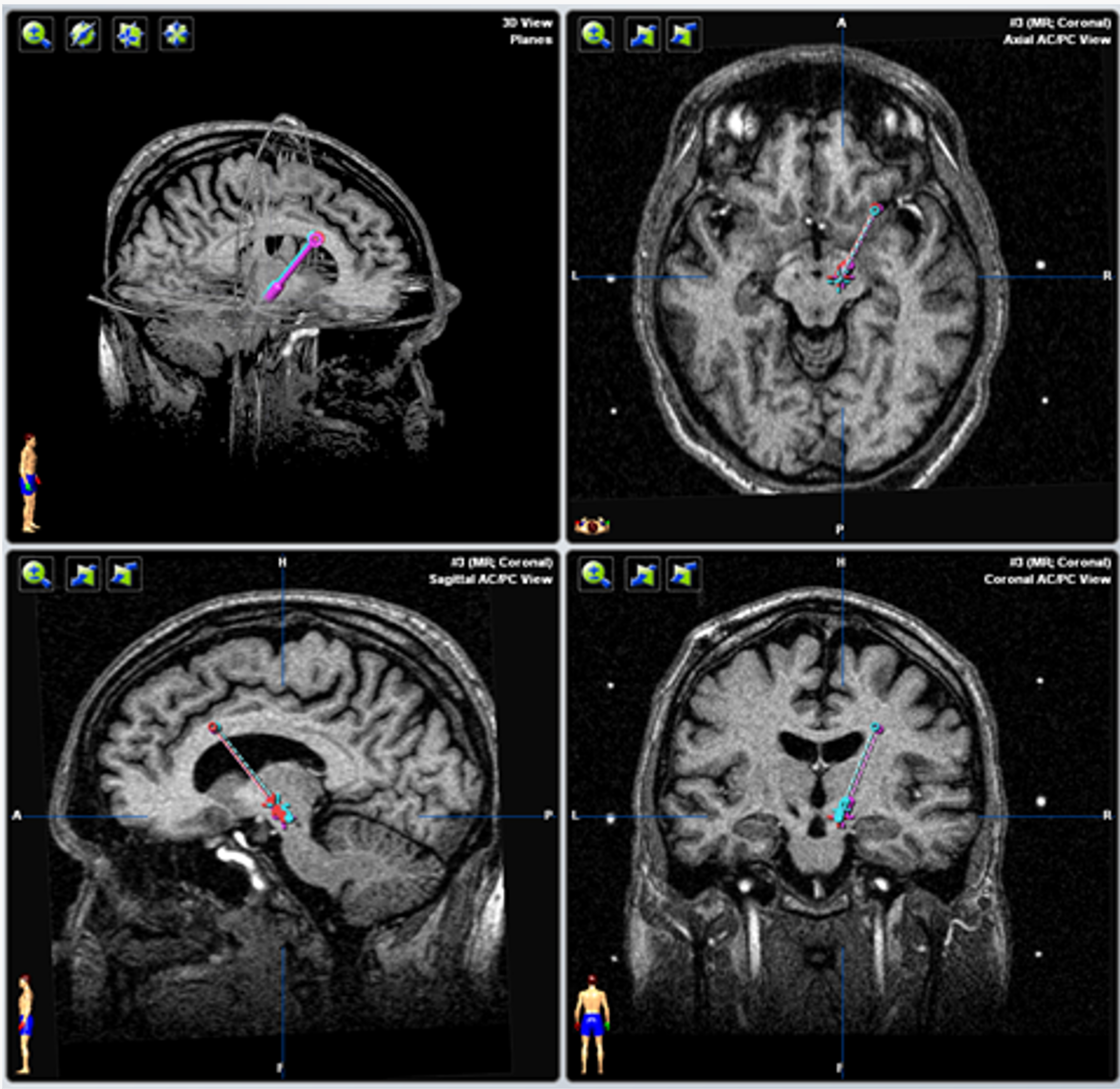
Local field potentials (LFP) used intraoperatively for anatomic identification has been validated in previous studies. Utilizing this technique while patients undergo DBS for PD in the STN or Gpi, P50 auditory evoked responses can be used to assess for sensory gating deficits and hopefully highlight potential targets for other disorders of dopaminergic dysregulation.

Methods

Patients who suffered from PD and had no hearing impairment were evaluated for DBS surgery. They reviewed the risks and benefits of intra-operative EEG and DBS lead implantation, and provided informed consent for participation. Pre-operative CT and MRI were obtained for surgical planning. The subthalamic nucleus was targeted using fused MRI and CT images, using standard stereotactic surgical planning software (iPlannet 3.0 Stereotaxy, Brainlab, Germany). In the operative room EEG electrodes were placed including Cz, Pz, Fpz, T4, right superior orbit, right lateral orbit, right ear (reference), and left ear (ground). For surgical targeting, three microelectrodes were advanced from the cortical entry site to the surgical target. Landmarks including the caudate nucleus and thalamus were identified by characteristic EEG findings, or sensory effects of macrostimulation. Paired auditory stimuli 500 ms apart were generated at every monitoring depth. EEG data for the subsequent AEPs were filtered at 10, 60, and 100 Hz. Peak μ V values were used to test for significant differences between amplitude of the AEP for the conditioning and test stimulus. Post-operatively, the same stereotactic planning software was used to confirm microelectrode track positioning with merged post-operative CT and MRI. Recording locations for AEPs were identified by their depth along the microelectrode trajectory. Three investigators separately performed neuroanatomical identification to correlate structures with AEP recording sites.

Results

Six patients met inclusion criteria and completed the study protocol. Of these six patients, three had bilateral subthalamic nucleus DBS implantation for a total of nine procedures with intra-operative LFP recordings.



Discussion

A preponderance of statistically significant aberrant P50 responses localize to the subthalamic nucleus, known to be an important site for monoamine transmission modulation, and converging site of many cortico-striatal-thalamic tracts implicated in dopamine related brain pathology. While its position in the brainstem does not immediately call to mind a role in emotional regulation, the primate subthalamic nucleus contains diverse projections to sensorimotor cortex, the limbic system, and associative cortical regions.

A major goal of this work is to lay groundwork for localizing the basis of aberrant sensory gating in the brain, to support the development of a DBS protocol for the treatment of schizophrenia. Currently, up to one third of patients with schizophrenia will not respond to standard anti-psychotic therapies, requiring treatment with clozapine. Approximately 60% of these patients will respond to clozapine, requiring intensive monitoring for the associated agranulocytosis and other side effects [9]. These patients urgently need improved treatment options. One patient at Johns Hopkins received bilateral substantia nigra pars reticulata implantation, with “reported immediate and complete resolution of chronic hallucinations in an amplitude dose-responsive fashion upon selective SNr stimulation initiation.” [10]. We observed abnormal P50 responses localizing to the SNR as well.

References

[1] Deuschl, G., Schade-Brittinger, C., Krack, P., Volkmann, J., Schäfer, H., Bötzel, K., ... & Gruber, D. (2006). A randomized trial of deep-brain stimulation for Parkinson disease. *New England Journal of Medicine*, 355(9), 896-908.

[2] Blumenfeld, Z., & Brontë-Stewart, H. (2015). High frequency deep brain stimulation and neural rhythms in Parkinson’s disease. *Neuropsychology review*, 25(4), 384-397.

[3] Airaksinen, K., Mäkelä, J. P., Taulu, S., Ahonen, A., Nurminen, J., Schnitzler, A., Pekkonen, E. (2011). Effects of DBS on auditory and somatosensory processing in Parkinson disease. *Human brain mapping*, 32(7), 1091-1099.

[4] Benabid, A. L., Pollak, P., Hoffmann, D., Gervason, C., Hommel, M., Perret, J. E., Gao, D. M. (1991). Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *The Lancet*, 337(8738), 403-406.

[5] Fearon, C., Butler, J. S., Newman, L., Lynch, T., & Reilly, R. B. (2015). Audiovisual processing is abnormal in Parkinson’s disease and correlates with freezing of gait and disease duration. *Journal of Parkinson disease*, 5(4), 925-936.

[6] Gault, J. M., Davis, R., Cascella, N. G., Saks, E. R., Corripio-Collado, I., Anderson, W.; Daskalakis, Z. J. (2018). Approaches to neuromodulation for schizophrenia. *J Neurol Neurosurg Psychiatry*, 89(7), 777-787.

[7] Gross, C., Rougier, A., Guehl, D., Boraud, T., Julien, J., & Bioulac, B. (1997). High-frequency stimulation of the globus pallidus internalis in Parkinson disease: a study of seven cases. *Journal of neurosurgery*, 87(4), 491-498.

[8] Gulberti, A., Hamel, W., Buhmann, C., Boelmans, K., Zittel, S., Gerloff, C., Moll, C.K. E. (2015). Subthalamic deep brain stimulation improves auditory sensory gating deficit in Parkinson’s disease. *Clinical Neurophysiology*, 126(3), 565-574.

[9] -Lally, J., & Gaughran, F. (2019). Treatment resistant schizophrenia–review and a call to action. *Irish journal of psychological medicine*, 36(4), 279-291.

[11] - Cascella, N., Butala, A. A., Mills, K., Kim, M. J., Salimpour, Y., Wojtasiewicz, T., ... & Anderson, W. (2021). Deep brain stimulation of the substantia nigra pars reticulata for treatment-resistant schizophrenia: a case report. *Biological psychiatry*, 90(10), e57-e59.