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Reply to: Cognitive effects of deep brain stimulation in *GBA*-related Parkinson's disease

Gian Pal, MD, MS[1,2], **Graziella Mangone, MD, PhD**[3], **Bichun Ouyang, MD**[2], **Debra Ehrlich, MD**[4], **Rachel Saunders-Pullman, MD**[5], **Susan Bressman, MD**[5], **Roy N. Alcalay, MD, MS**[6], **Karen Marder, MD**[6], **Jan Aasly, MD**[7], **Maral Mouradian, MD**[1,8], **Sharlet Anderson, PhD**[2], **Bryan Bernard, PhD**[2], **Glenn Stebbins, PhD**[2], **Sepehr Sani, MD**[9], **Mitra Afshari, MD, MPH**[2], **Leo Verhagen, MD, PhD**[2], **Rob M.A. de Bie, MD, PhD**[10], **Tom Foltynie, MD, PhD, MRCP**[11], **Deborah Hall, MD, PhD**[2], **Jean-Christophe Corvol, MD, PhD**[3], **Christopher G. Goetz, MD**[2]

[1]Department of Neurology, Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ, USA

[2]Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA

[3]Sorbonne Université, Assistance Publique Hôpitaux de Paris, Inserm, CNRS, Institut du Cerveau – Paris Brain Institute – ICM, Pitié-Salpêtrière Hospital, Department of Neurology, Centre d'Investigation Clinique Neurosciences, Paris, France

[4]Parkinson's Disease Clinic, Office of the Clinical Director, NIH/NINDS, Bethesda, MD, USA

[5]Department of Neurology, Mount Sinai Beth Israel, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[6]Department of Neurology, College of Physicians and Surgeons, Columbia University Medical Center, New York, NY, USA

[7]Department of Neurology, St. Olavs Hospital and Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, 7030, Norway

[8]Robert Wood Johnson Medical School Institute for Neurological Therapeutics, Rutgers Biomedical and Health Sciences, Piscataway, NJ, USA

[9]Department of Neurosurgery, Rush University Medical Center, Chicago, IL, USA

[10]Amsterdam University Medical Centers, University of Amsterdam, Department of Neurology, Amsterdam Neuroscience, Amsterdam, Netherlands

[11]Department of Clinical & Movement Neurosciences, UCL Institute of Neurology, London, UK

We thank Weill and colleagues for their valuable comments.[1] Their observations corroborate our findings of cognitive decline post-DBS in PD patients carrying *GBA* mutations (*GBA*-PD) and they, like us, question the long-term risk-to-benefit of bilateral subthalamic nucleus

Corresponding Author: Gian Pal, MD, MS, Rutgers-Robert Wood Johnson Medical School, 125 Paterson Street, New Brunswick, NJ 08901, Phone: (732) 235-7733, gian.pal@rutgers.edu.

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deep brain stimulation (STN-DBS) in these patients. They caution, however, against a potential bias introduced by our use of non-operated *GBA*-PD patients accessed through the Parkinson's Progression Marker's Initiative (PPMI)[2], as these patients may have had a milder clinical profile than the *GBA*-PD patients who underwent STN-DBS, and we acknowledge this limitation of our study. While it is correct that mean disease duration and follow-up time were both longer in the *GBA*-PD group with DBS compared with those without DBS, we statistically corrected for both factors and utilized two different techniques in our analysis, linear mixed modeling and propensity score weighting, both yielding similar results. Propensity score weighting is particularly useful to account for systematic differences between non-randomized groups in observational studies.[3, 4] Even with their corroboration of our overall findings, we agree that further replication testing are needed, and only the use of prospective controlled studies would allow for definitive conclusions.

Currently, genetic testing for *GBA* mutations is not standard of care as part of the DBS pre-operative process, and the Weil et al. observations further support our recommendation that *GBA* testing and counseling be considered pre-operatively, if available. We do not claim that STN-DBS be categorically avoided in *GBA*-PD patients, rather approached cautiously, and *GBA* status may be a factor that is useful when considering the risk-benefit profile of STN-DBS. It remains to be explored whether treatments such as globus pallidus internus DBS (GPi-DBS) or other device-aided non-neurosurgical therapies result in better cognitive outcomes than STN-DBS in *GBA*-PD patients.[5] Integrating *GBA* status into decision-making for DBS and potentially other device-aided therapies is likely to foster further studies of other genetic mutations on treatment outcomes as part of the overall effort to move towards precision medicine in PD.

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