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Emergence of Deglutology, a Transdisciplinary Field

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Oropharyngeal dysphagia is a well-known manifestation of a large number of acute and chronic neurologic disorders including Parkinson's disease (PD), and is associated with pulmonary complications as a leading cause of mortality in these patients¹. Symptoms of dysphagia in PD patients poorly correlate with objective video fluoroscopic findings²; in addition, age, severity and duration of the disease are not reliable predictors of dysphagia³. Deglutitive dysfunction in PD does not improve with levodopa therapy⁴⁻⁶, and may occasionally deteriorate with dopamine precursor therapy². The exact underlying neurogenic mechanisms of swallowing dysfunction in PD are not well established and involvement of non-dopaminergic mechanisms has been suggested⁶. Recent comprehensive postmortem neuropathologic studies of PD patients have indicated that brain pathology (Lewy neurites and Lewy bodies) in PD originates in the olfactory bulb and visceromotor projections of dorsal nucleus of the glossopharyngeal and vagal nerves in medulla oblongata years prior to involvement of nigrostriatal pathway and onset of somatomotor dysfunction⁷. Furthermore, these histopathologic observations have shown atrophic and denervated pharyngeal constrictors and cricopharyngeus myofibers⁸; axonal degenerative changes in vagal and sympathetic motoneurons innervating pharyngeal constrictors and cricopharyngeus⁹, along with degenerative changes of predominantly sensory internal superior laryngeal branch of the vagus nerve¹⁰. Collectively these central and peripheral autonomic sensorimotor impairments in dysphagic PD patients may explain compromised cough reflex¹¹, delayed swallow reflex^{3, 12}, pharyngeal peristaltic incoordination^{3, 13} and incomplete UES relaxation^{3, 14}. Together these mechanistic abnormalities contribute to self-reported dysphagia (28-41%)¹⁵, objective videofluoroscopic metrics of dysphagia (77-87%)¹⁵ and ultimately aspiration pneumonia (11-45%) in PD patients^{16, 17}. Current dysphagia management in PD patients is unsatisfactory. A number of approaches including dietary modification and swallowing maneuvers¹⁶, dopaminergic and anticholinergic pharmacotherapy¹⁸, expiratory muscle strengthening¹⁹, video based biofeedback therapy²⁰, cricopharyngeal myotomy²¹ and cricopharyngeus Botulinum toxin injection²² have all been utilized with variable outcomes, necessitating further research to devise pathophysiology based therapeutic modalities²³.

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Tangible progress in management and treatment of neurogenic dysphagia including those due to PD has been slow because of the inability to identify and address the fundamental alterations in various organs that are affected in these patients. Remedying this shortcoming requires collaboration among experts from multiple fields applying a transdisciplinary approach. Contribution of diverse scientific disciplines such as biophysics, neuroimaging, neuroscience, neurology, otolaryngology, gastroenterology and speech language pathology is needed to fully bring the cutting edge advances in their respective disciplines to the field of swallowing disorders. This convergence of disciplines has the potential to shift our focus from merely mechanical peripheral assessment and management strategies of deglutition utilizing video fluoroscopy, manometry and electromyography to a more comprehensive approach that adds the understanding of mechanisms of brainstem control and the cortical modulator effects on deglutition. Better understanding of neuronal mechanisms also may allow us to formulate therapeutic approaches beyond mere rehabilitation to effective interventions inducing neuroplasticity and metaplasticity at cellular and neuronal network levels.

Over the past two decades, our understanding of the human brain function has extended beyond traditional brain lesion studies and its associated behavioral deficits. Simple yet incomplete structure-function relationship that traditionally attributed a specialized relatively independent function (e.g. movement of a muscle) to a distinct brain region (a segment of motor cortex), has not been able to elucidate complex and coordinated behaviors that depend critically on often transient interactions of not only distant brain regions but also brain networks²⁴. Initial application of noninvasive functional neuroimaging techniques such as functional magnetic resonance imaging^{25, 26}, positron emission tomography^{27, 28}, and magnetic encephalography²⁹ extended the classic structure-function observations to humans in-vivo. Recent expansion of imaging technology such as structural^{30, 31} and functional^{32, 33} connectivity techniques, and sophisticated analytical concepts like graph theoretical analysis³⁴ have allowed deeper and broader investigation of dynamic functions of neuronal networks. Moreover, modern and safe noninvasive brain stimulation techniques in humans such as Transcranial magnetic stimulation (TMS)³⁵ and transcranial direct current stimulation (tDSC³⁶) not only have offered unique understanding of brain network organization and dynamism³⁷, but also have shown potential therapeutic applications³⁸. TMS can be applied in single or paired pulse paradigms or repetitive trains of stimulation³⁷. Strong evidence suggests that human TMS protocols induce cortical plasticity comparable to NMDA-receptor dependent glutamatergic long-term potentiation (LTP)-like and long-term depression (LTD)-like effects seen in animal models³⁹. The NMDA receptor antagonists effectively block the facilitatory or inhibitory effects of TMS protocols in humans⁴⁰, that depend on the underlying state of the targeted brain region⁴¹. Michou et al. in the current issue of this publication have utilized TMS to evaluate cortical excitability in PD patients, investigating neurophysiologic mechanisms of dysphagia off and on dopaminergic therapy⁴². They show that embracing non-invasive brain stimulation along with neurotransmitter modulation open tremendous opportunities in translational neurosciences, allowing us to address fundamental issues in neurogenic dysphagia patients such as those affected by PD.

Functional magnetic resonance imaging ^{43, 44}, positron emission tomography ^{45, 46}, and magnetic encephalography ⁴⁷ have all confirmed the role of cortex in volitional and reflexive swallow ⁴⁸⁻⁵⁰. Although a consistent ensemble of brain regions (sensorimotor, cingulate and insular cortices, lateral prefrontal and parietal regions) has been identified in governance of deglutition ^{51, 52}, the specific role of distinct brain regions and their interactions await further study. Functional connectivity of swallowing network and interactions of involved brain regions has just been recently described for resting state and during swallowing ⁵³⁻⁵⁵. These findings may enhance our understanding of the physiology of deglutition. In addition, interventional investigations such as peripheral sensory ⁵⁶ and central cortical stimulation ⁵⁷ of the deglutitive apparatus have not only enriched our understanding of pathophysiology of neurogenic dysphagia but also have opened the possibility to induce enduring cortical neuroplasticity and behavioral swallow improvement ^{58, 59}.

As evidenced by recent findings, the pathobiology of neurogenic dysphagia in general and in Parkinson's disease specifically extends beyond the boundary of any single discipline. Effective management of this disorder requires convergence of several basic and clinical disciplines in a collaborative and complimentary fashion, approaching the deglutition and its disorders in its entirety from the neurons of the cerebral cortex to the muscle fibers of the pharynx and esophagus with a physiologic and pathophysiologic perspective. Michou et al, have used this “deglutology” approach in their study entitled “characterization of corticobulbar pharyngeal neurophysiology in dysphagic patients with Parkinson's disease” in this issue of *Clinical Gastroenterology and Hepatology*. This is a welcome approach and the authors are congratulated for taking on this important task.

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References

1. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology*. 1967; 17:427–42. [PubMed: 6067254]
2. Bushmann M, Dobmeyer SM, Leeker L, Perlmutter JS. Swallowing abnormalities and their response to treatment in Parkinson's disease. *Neurology*. 1989; 39:1309–14. [PubMed: 2797454]
3. Ali GN, Wallace KL, Schwartz R, DeCarle DJ, Zagami AS, Cook IJ. Mechanisms of oral-pharyngeal dysphagia in patients with Parkinson's disease. *Gastroenterology*. 1996; 110:383–92. [PubMed: 8566584]
4. Calne DB, Shaw DG, Spiers AS, Stern GM. Swallowing in Parkinsonism. *The British journal of radiology*. 1970; 43:456–7. [PubMed: 5429083]
5. Menezes C, Melo A. Does levodopa improve swallowing dysfunction in Parkinson's disease patients? *Journal of clinical pharmacy and therapeutics*. 2009; 34:673–6. [PubMed: 20175800]
6. Hunter PC, Cramer J, Austin S, Woodward MC, Hughes AJ. Response of parkinsonian swallowing dysfunction to dopaminergic stimulation. *Journal of neurology, neurosurgery, and psychiatry*. 1997; 63:579–83.
7. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of aging*. 2003; 24:197–211. [PubMed: 12498954]

8. Mu L, Sobotka S, Chen J, Su H, Sanders I, Adler CH, Shill HA, Caviness JN, Samanta JE, Beach TG. Altered pharyngeal muscles in Parkinson disease. *Journal of neuropathology and experimental neurology*. 2012; 71:520–30. [PubMed: 22588389]
9. Mu L, Sobotka S, Chen J, Su H, Sanders I, Adler CH, Shill HA, Caviness JN, Samanta JE, Beach TG. Alpha-synuclein pathology and axonal degeneration of the peripheral motor nerves innervating pharyngeal muscles in Parkinson disease. *Journal of neuropathology and experimental neurology*. 2013; 72:119–29. [PubMed: 23334595]
10. Mu L, Sobotka S, Chen J, Su H, Sanders I, Nyirenda T, Adler CH, Shill HA, Caviness JN, Samanta JE, Sue LI, Beach TG. Parkinson disease affects peripheral sensory nerves in the pharynx. *Journal of neuropathology and experimental neurology*. 2013; 72:614–23. [PubMed: 23771215]
11. Ebihara S, Saito H, Kanda A, Nakajoh M, Takahashi H, Arai H, Sasaki H. Impaired efficacy of cough in patients with Parkinson disease. *Chest*. 2003; 124:1009–15. [PubMed: 12970031]
12. Ertekin C, Tarlaci S, Aydogdu I, Kiylioglu N, Yuceyar N, Turman AB, Secil Y, Esmeli F. Electrophysiological evaluation of pharyngeal phase of swallowing in patients with Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society*. 2002; 17:942–9. [PubMed: 12360543]
13. Eadie MJ, Tyrer JH. Alimentary Disorder in Parkinsonism. *Australasian annals of medicine*. 1965; 14:13–22. [PubMed: 14271784]
14. Palmer ED. Dysphagia in Parkinsonism. *JAMA : the journal of the American Medical Association*. 1974; 229:1349.
15. Kalf JG, de Swart BJ, Bloem BR, Munneke M. Prevalence of oropharyngeal dysphagia in Parkinson's disease: a meta-analysis. *Parkinsonism & related disorders*. 2012; 18:311–5. [PubMed: 22137459]
16. Robbins J, Gensler G, Hind J, Logemann JA, Lindblad AS, Brandt D, Baum H, Lilienfeld D, Kosek S, Lundy D, Dikeman K, Kazandjian M, Gramigna GD, McGarvey-Toler S, Miller Gardner PJ. Comparison of 2 interventions for liquid aspiration on pneumonia incidence: a randomized trial. *Annals of internal medicine*. 2008; 148:509–18. [PubMed: 18378947]
17. Yamamoto T, Kobayashi Y, Murata M. Risk of pneumonia onset and discontinuation of oral intake following videofluorography in patients with Lewy body disease. *Parkinsonism & related disorders*. 2010; 16:503–6. [PubMed: 20584622]
18. Jost WH. Gastrointestinal dysfunction in Parkinson's Disease. *Journal of the neurological sciences*. 2010; 289:69–73. [PubMed: 19717168]
19. Troche MS, Okun MS, Rosenbek JC, Musson N, Fernandez HH, Rodriguez R, Romrell J, Pitts T, Wheeler-Hegland KM, Sapienza CM. Aspiration and swallowing in Parkinson disease and rehabilitation with EMST: a randomized trial. *Neurology*. 2010; 75:1912–9. [PubMed: 21098406]
20. Manor Y, Mootanah R, Freud D, Giladi N, Cohen JT. Video-assisted swallowing therapy for patients with Parkinson's disease. *Parkinsonism & related disorders*. 2013; 19:207–11. [PubMed: 23131836]
21. Born LJ, Harned RH, Rikkers LF, Pfeiffer RF, Quigley EM. Cricopharyngeal dysfunction in Parkinson's disease: role in dysphagia and response to myotomy. *Movement disorders : official journal of the Movement Disorder Society*. 1996; 11:53–8. [PubMed: 8771067]
22. Restivo DA, Palmeri A, Marchese-Ragona R. Botulinum toxin for cricopharyngeal dysfunction in Parkinson's disease. *The New England journal of medicine*. 2002; 346:1174–5. [PubMed: 11948283]
23. van Hooren MR, Baijens LW, Voskuilen S, Oosterloo M, Kremer B. Treatment effects for dysphagia in Parkinson's disease: A systematic review. *Parkinsonism & related disorders*. 2014; 20:800–807. [PubMed: 24794097]
24. Shafi MM, Westover MB, Fox MD, Pascual-Leone A. Exploration and modulation of brain network interactions with noninvasive brain stimulation in combination with neuroimaging. *The European journal of neuroscience*. 2012; 35:805–25. [PubMed: 22429242]
25. Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Ugurbil K. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance

- imaging. Proceedings of the National Academy of Sciences of the United States of America. 1992; 89:5951–5. [PubMed: 1631079]
26. Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proceedings of the National Academy of Sciences of the United States of America. 1992; 89:5675–9. [PubMed: 1608978]
 27. Phelps ME, Mazziotta JC, Kuhl DE, Nuwer M, Packwood J, Metter J, Engel J Jr. Tomographic mapping of human cerebral metabolism visual stimulation and deprivation. Neurology. 1981; 31:517–29. [PubMed: 6972013]
 28. Mazziotta JC, Phelps ME, Miller J, Kuhl DE. Tomographic mapping of human cerebral metabolism: normal unstimulated state. Neurology. 1981; 31:503–16. [PubMed: 6972012]
 29. Cohen D. Magnetoencephalography: detection of the brain's electrical activity with a superconducting magnetometer. Science. 1972; 175:664–6. [PubMed: 5009769]
 30. Ciccarelli O, Catani M, Johansen-Berg H, Clark C, Thompson A. Diffusion-based tractography in neurological disorders: concepts, applications, and future developments. Lancet neurology. 2008; 7:715–27.
 31. Voss HU, Schiff ND. MRI of neuronal network structure, function, and plasticity. Progress in brain research. 2009; 175:483–96. [PubMed: 19660675]
 32. Van Dijk KR, Hedden T, Venkataraman A, Evans KC, Lazar SW, Buckner RL. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. Journal of neurophysiology. 2010; 103:297–321. [PubMed: 19889849]
 33. Fox MD, Snyder AZ, Zacks JM, Raichle ME. Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. Nat Neurosci. 2006; 9:23–5. [PubMed: 16341210]
 34. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. Nature reviews Neuroscience. 2009; 10:186–98.
 35. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985; 1:1106–7. [PubMed: 2860322]
 36. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. The Journal of physiology. 2000; 527(Pt 3):633–9. [PubMed: 10990547]
 37. Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG. Noninvasive brain stimulation: from physiology to network dynamics and back. Nature neuroscience. 2013; 16:838–44.
 38. Hummel F, Celnik P, Giraux P, Floel A, Wu WH, Gerloff C, Cohen LG. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain : a journal of neurology. 2005; 128:490–9. [PubMed: 15634731]
 39. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron. 2005; 45:201–6. [PubMed: 15664172]
 40. Stefan K, Kunesch E, Benecke R, Cohen LG, Classen J. Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. The Journal of physiology. 2002; 543:699–708. [PubMed: 12205201]
 41. Pasley BN, Allen EA, Freeman RD. State-dependent variability of neuronal responses to transcranial magnetic stimulation of the visual cortex. Neuron. 2009; 62:291–303. [PubMed: 19409273]
 42. Michou E, Hamdy S, Harris M, Vania A, Dick J, Kellett M, Rothwell J. Characterization of Corticobulbar Pharyngeal Neurophysiology in Dysphagic Patients With Parkinson's Disease. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2014
 43. Birn RM, Bandettini PA, Cox RW, Jesmanowicz A, Shaker R. Magnetic field changes in the human brain due to swallowing or speaking. Magn Reson Med. 1998; 40:55–60. [PubMed: 9660553]
 44. Hamdy S, Mikulis DJ, Crawley A, Xue S, Lau H, Henry S, Diamant NE. Cortical activation during human volitional swallowing: an event-related fMRI study. Am J Physiol. 1999; 277:G219–25. [PubMed: 10409170]

45. Zald DH, Pardo JV. The functional neuroanatomy of voluntary swallowing. *Ann Neurol.* 1999; 46:281–6. [PubMed: 10482257]
46. Hamdy S, Rothwell JC, Brooks DJ, Bailey D, Aziz Q, Thompson DG. Identification of the cerebral loci processing human swallowing with H2(15)O PET activation. *J Neurophysiol.* 1999; 81:1917–26. [PubMed: 10200226]
47. Watanabe Y, Abe S, Ishikawa T, Yamada Y, Yamane GY. Cortical regulation during the early stage of initiation of voluntary swallowing in humans. *Dysphagia.* 2004; 19:100–8. [PubMed: 15382798]
48. Martin RE, Goodyear BG, Gati JS, Menon RS. Cerebral cortical representation of automatic and volitional swallowing in humans. *J Neurophysiol.* 2001; 85:938–50. [PubMed: 11160524]
49. Toogood JA, Barr AM, Stevens TK, Gati JS, Menon RS, Martin RE. Discrete functional contributions of cerebral cortical foci in voluntary swallowing: a functional magnetic resonance imaging (fMRI) “Go, No-Go” study. *Exp Brain Res.* 2005; 161:81–90. [PubMed: 15536553]
50. Kern MK, Jaradeh S, Arndorfer RC, Shaker R. Cerebral cortical representation of reflexive and volitional swallowing in humans. *Am J Physiol Gastrointest Liver Physiol.* 2001; 280:G354–60. [PubMed: 11171617]
51. Soros P, Inamoto Y, Martin RE. Functional brain imaging of swallowing: an activation likelihood estimation meta-analysis. *Hum Brain Mapp.* 2009; 30:2426–39. [PubMed: 19107749]
52. Babaei A, Ward BD, Ahmad S, Patel A, Nencka A, Li SJ, Hyde J, Shaker R. Reproducibility of swallow-induced cortical BOLD positive and negative fMRI activity. *American journal of physiology Gastrointestinal and liver physiology.* 2012; 303:G600–9. [PubMed: 22766854]
53. Babaei A, Siwiec RM, Kern M, Douglas Ward B, Li SJ, Shaker R. Intrinsic functional connectivity of the brain swallowing network during subliminal esophageal acid stimulation. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society.* 2013; 25:992–e779. [PubMed: 24251873]
54. Babaei A, Ward BD, Siwiec RM, Ahmad S, Kern M, Nencka A, Li SJ, Shaker R. Functional connectivity of the cortical swallowing network in humans. *Neuroimage.* 2013; 76:33–44. [PubMed: 23416253]
55. Lowell SY, Reynolds RC, Chen G, Horwitz B, Ludlow CL. Functional connectivity and laterality of the motor and sensory components in the volitional swallowing network. *Experimental brain research Experimentelle Hirnforschung Experimentation cerebrale.* 2012; 219:85–96.
56. Hamdy S, Jilani S, Price V, Parker C, Hall N, Power M. Modulation of human swallowing behaviour by thermal and chemical stimulation in health and after brain injury. *Neurogastroenterol Motil.* 2003; 15:69–77. [PubMed: 12588471]
57. Hamdy S, Aziz Q, Rothwell JC, Power M, Singh KD, Nicholson DA, Tallis RC, Thompson DG. Recovery of swallowing after dysphagic stroke relates to functional reorganization in the intact motor cortex. *Gastroenterology.* 1998; 115:1104–12. [PubMed: 9797365]
58. Gow D, Rothwell J, Hobson A, Thompson D, Hamdy S. Induction of long-term plasticity in human swallowing motor cortex following repetitive cortical stimulation. *Clin Neurophysiol.* 2004; 115:1044–51. [PubMed: 15066528]
59. Jayasekaran V, Singh S, Tyrrell P, Michou E, Jefferson S, Mistry S, Gamble E, Rothwell J, Thompson D, Hamdy S. Adjunctive functional pharyngeal electrical stimulation reverses swallowing disability after brain lesions. *Gastroenterology.* 2010; 138:1737–46. [PubMed: 20138037]