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Speech-Language Pathology as Applied Neuroscience: Precision Neurorehabilitation from Gene to Activity

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Abstract

Speech-Language Pathology is an applied discipline within neurology-based interdisciplinary neuroscience. Genes exist in cells, just as language exists in the brain, reflecting a homologous conceptual framework between molecular genetics and cognitive neuroscience. Clinical medicine, traditionally grounded in phenotypic observation, has progressively incorporated molecular aspects, including genetics. With advances in gene technologies, human research has shifted from primarily observational approaches to molecular and genetic investigations. Neurorehabilitation represents a translational framework in which genetically determined neural constraints are interpreted through activity-dependent plasticity to reconstruct speech, communication, and related functional chains, with the ultimate goal of maximizing activity and participation. Although advances in neurology, including disease-modifying therapies; gene therapies, nucleic acids therapeutics such as ASO, and immunotherapies, have rendered many neurological diseases increasingly treatable, functional recovery, activity and participation in daily life cannot be achieved through biological interventions alone. Future healthcare emphasizes personalized genomic information not only for prognostic prediction but also for the optimization of neurorehabilitation strategies, particularly during presymptomatic and prodromal stages. Importantly, genetic prognosis does not equate to functional and activity outcome. From a neurorehabilitation perspective, the coexistence of genetic prognosis, neurological functional prognosis, and activity-based prognosis underscores the enduring necessity of neurorehabilitation. This integrative perspective defines the core concept of precision neurorehabilitation, in which survival, and function, activity and participation as the ICF domains are addressed simultaneously.

Key words: gene expression, neurogenetics, electrophysiology, neurorehabilitation, precision

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I. Gene expressions of viral and human genome in neurogenetics

James D. Watson, who discovered the double helix structure of DNA in 1953 and later received the Nobel Prize, died in 2025 at the age of 97. Approximately seventy years after the elucidation of DNA structure, medicine has entered an era in which genetic information influences not only diagnosis and treatment but also reproductive decision-making. The indication for preimplantation genetic testing for monogenic disorders (PGT-M) has been defined as severe diseases manifesting in childhood, while the definition of "severity" itself has been continuously debated and revised from ethical, legal, and social issues (ELSI).

Members of the Herpesviridae family are representative neurotropic viruses.[1)] Herpes simplex virus (HSV) and varicella-zoster virus (VZV) directly infect neurons or glial cells, whereas Epstein–Barr virus (EBV) induces neurological disorders primarily through immune-mediated mechanisms rather than direct neuronal infection. To date, no convincing evidence supports primary neuronal infection by EBV. Neurological manifestations associated with HSV and VZV are largely attributable to viral reactivation from latency or to para- or post-infectious immune-inflammatory responses. EBV infects B lymphocytes and nasopharyngeal epithelial cells. The Herpesviridae genome is relatively large (approximately 125–235 kb) compared with that of typical RNA viruses (approximately 3-32 kb), reflecting the requirements for DNA replication and latent infection. In 1989, we demonstrated that transcription of BHLF-1, generally considered part of the lytic cascade, could also be detected during the initial phase of B-cell immortalization leading to latency.[2)-4)] Subsequent studies have identified distinct transcripts associated with lytic and latent cycles, citing our original findings.[5)] In addition, non-coding RNA transcripts have been shown to play pivotal roles in viral latency, suggesting potential therapeutic targets not only for viral infection but also for neurodegenerative diseases.

Spinal motor neuron–specific gene expression was first reported by our group using laser-captured microdissection (LCM) applied to autopsied lumbar spinal cords.[6)–10)] This study has been cited in numerous reviews and meta-analyses as a pioneering and concept-defining work, as it established both the feasibility and the scientific value of motor neuron–specific transcriptomic analysis in sporadic amyotrophic lateral sclerosis (ALS).[11)] With hundreds of subsequent citations, the study has become a key reference in ALS molecular research, serving as a foundation for later investigations in transcriptomics, systems biology, and comparative gene expression analysis. It has been widely referenced in studies addressing gene expression profiling, molecular pathology, and gene regulatory mechanisms in ALS.[12)–20)]

Importantly, the gene expression profiles of spinal motor neurons were markedly different from those of whole spinal cord tissue in sporadic ALS and were also distinct from those observed in induced pluripotent stem cell (iPSC)–derived motor neurons. The transcription of these genes and their protein products were subsequently confirmed by immunohistochemical analyses, thereby validating the original transcriptomic findings. The critical mis-regulated genes identified in this study were primarily associated with cytoskeletal organization, axonal transport, transcriptional regulation, and apoptotic pathways in sporadic ALS patients. These results provided direct molecular insights into degenerative processes occurring within motor neurons themselves, rather than reflecting secondary changes in heterogeneous whole spinal cord tissue. This series of LCM-based studies contributed to the establishment of the Japanese Consortium for Amyotrophic Lateral Sclerosis (JaCALS, Aichi Medical University), thereby providing an essential molecular foundation for subsequent longitudinal clinical and genetic research. Although LCM analysis was successfully performed on autopsied spinal cord tissue, its application to biopsied sural nerve specimens is fundamentally limited because such samples consist of a heterogeneous mixture of lower motor neuron axons, Schwann cells, fibroblasts, and vascular and connective tissue components.[21)–73)]

Gene therapy has been under development for many years; however, successful clinical applications have been limited. Nucleic acids therapeutics are applicable to some neurodegenerative diseases, which is defined genetically, instead of general gene therapy using vectors.[74)-77)] mRNA vaccine for Coronavirus is one of the most popular nucleic acids therapeutics. With respect to genetic testing, presymptomatic and prodromal diagnosis is technically possible but raises important ELSI considerations. Nucleic acids therapeutics are not available to a lot of genetic diseases. Preventive neurorehabilitation may play a pivotal role in the carrier state of late-onset autosomal dominant and autosomal or X-linked recessive inherited diseases.[78)] Moreover, personal genome information should not be regarded merely as determinants of prognosis, but rather as information

that optimizes rehabilitation strategies. Ethical issues are of paramount importance at a centered position among neurology, clinical genetics and neurorehabilitation (Fig. 1).

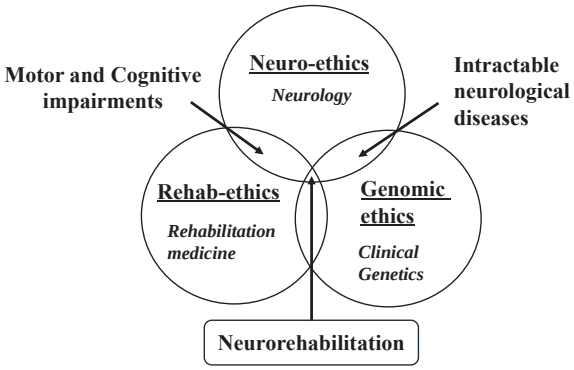

Figure 1. Ethical issues for neurorehabilitation in ethical, legal, and social issues (ELSI).

Neurorehabilitation lies at the intersection of three board-certified specialties. This schematic depicts the translational continuum from genetic information to neural function, activity, and participation. Genetic data inform prognosis but do not directly determine functional outcomes. Instead, neurorehabilitation operates within genetically and disease-specific neural constraints, leveraging activity-dependent plasticity to optimize real-world activity. Ethical, legal, and social issues (ELSI) intersect across all stages, particularly in presymptomatic and prodromal interventions. This framework highlights the complementary roles of genetic, neurological functional, and activity-based prognoses in precision neurorehabilitation. The author has these three board certifications.

II. Electrophysiology as functional biomarkers

Electrophysiological studies have long served as fundamental diagnostic tools in clinical neurology. Importantly, electrophysiology is not limited to diagnostic applications; it plays an increasingly important role in monitoring disease progression and evaluating therapeutic effects, including those of neurorehabilitation. Changes in electrophysiological parameters may precede detectable structural or functional alterations on neuroimaging and thus serve as sensitive biomarkers in clinical trials. In neurorehabilitation, electrophysiological measures are increasingly used to assess functional recovery, neural plasticity, and the effects of therapeutic interventions, thereby linking pathophysiological mechanisms to clinical outcomes.

Our group demonstrated that pain-related electrophysiological techniques using laser-evoked potentials (LEPs) selectively activate nociceptive Aδ fibers and enable evaluation of the spinothalamic system.[79)-84)] Studies in patients with cerebrovascular disease provided the earliest clinical evidence that nociceptive and non-nociceptive sensory pathways can be differentially impaired after stroke, establishing both conceptual and methodological foundations for subsequent LEP research. The application of LEP methodology to patients with dementia and other neurodegenerative disorders further expanded the clinical and theoretical implications of this work. In dementia, abnormalities in pain-related somatosensory evoked potentials (SEP) were observed despite relatively preserved peripheral sensory function, suggesting dysfunction at the level of cortical and subcortical pain integration rather than peripheral afferent transmission. These findings offered objective neurophysiological explanations for altered pain perception and atypical pain-related behaviors frequently observed in patients with cognitive impairment.

In peripheral neuropathies, pain-related SEP abnormalities were detected even when conventional sensory nerve conduction findings were relatively preserved, highlighting the selective vulnerability of small fibers and the limitations of standard electrophysiological assessments. Conversely, sensory conduction studies in cisplatin-induced neuropathy demonstrated preservation of small myelinated fibers with predominant involvement of large fibers, consistent with pathological findings. The integration of electrophysiology and neurorehabilitation thus represents a critical evolution in modern neurological care, shifting neurorehabilitation medicine toward activity-based interventions grounded in pathophysiological understanding of neurology.

III. Neurorehabilitation as activity-based translation

Neurorehabilitation is an interdisciplinary, activity-based medical field that aims to reduce activity limitation and enhance functional recovery in individuals with neurological disorders. It integrates principles from neurology, rehabilitation medicine, neuroscience, psychology, and allied health professions to address impairments in movement, cognition, communication, and swallowing. Rather than focusing solely on lesion localization or symptom control, neurorehabilitation emphasizes activity, participation, and quality of life in real-world contexts (Fig. 2).

Many hereditary neuromuscular disorders are classified as intractable neurological diseases. After disease onset, the primary clinical focus shifts toward neurological rehabilitation, whereas before onset, prenatal or presymptomatic diagnosis within the field of neurogenetics becomes relevant. In Japan, indications for preimplantation genetic testing for monogenic disorders (PGT-M) are defined as diseases that significantly impair daily life or threaten survival before adulthood and for which no effective preventive treatment exists at the time of application, or for which available treatments are highly specialized and invasive. According to an integrated national report published in September 2025, among 110 approved cases of 124 reviewed cases, the most frequently approved diseases were myotonic dystrophy, Duchenne muscular dystrophy, and Fukuyama congenital muscular dystrophy (Japan Society of Obstetrics and Gynecology). In addition to neuromuscular disorders, certain central nervous system diseases are also considered eligible for presymptomatic genetic diagnosis. From a neurorehabilitation perspective, the development of strategies to prevent or delay the onset of neurological signs and symptoms during presymptomatic and prodromal stages represents an emerging and critical frontier of intervention.

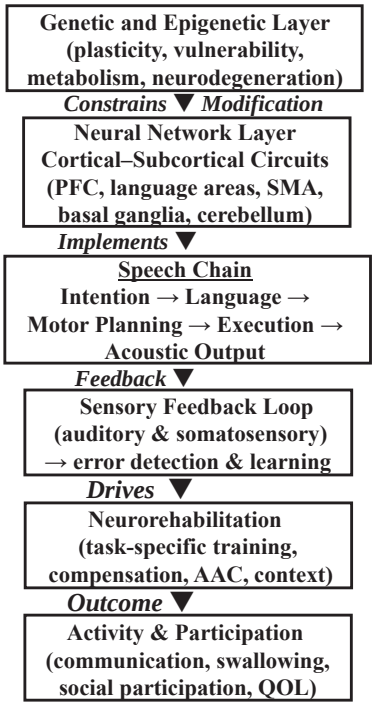

Figure 2. An integrated conceptual model linking genetics, the speech chain, and neurorehabilitation.

Genetic and epigenetic factors do not directly encode speech but define neural constraints such as plasticity, vulnerability, and metabolic capacity. Within these constraints, cortical–subcortical networks implement the speech chain from intention and language processing to motor execution and acoustic output. Sensory feedback loops enable error-based learning and drive activity-dependent plasticity. Neurorehabilitation strategically intervenes at multiple levels of the speech chain to optimize activity and participation outcomes under genetically determined neural conditions such as genetic polymorphism and epigenetic modification. "*Drives*" and "*Outcome*" are most important. PFC: prefrontal cortex; SMA: supplementary motor area; AAC: Augmentative and Alternative Communication.

1. Speech pathology

Speech is based on the speech chain, which includes auditory, perceptional, cognitive, and motor aspects. In speech production, the tongue represents the largest and most complex muscular organ involved. Vowel articulation is determined by tongue position, while consonant production depends on precise coordination of place and manner of articulation by tongue movements. From a developmental aspect, stop consonants produced through brief articulatory contact emerge earlier than fricatives, which require sustained airflow without contact. Thus, fricative production presupposes a more advanced level of motor control, including precise spatial regulation and temporal modulation. Articulatory development generally progresses in the order of stops, fricatives, affricates, and taps or flaps. These developmental stages can be objectively visualized using acoustic analysis, particularly sound spectrograms. In articulation disorders spanning childhood to adulthood, the functional one is designated during development though neurostructural networks changes with aging. Importantly, the neural control of articulation, spanning auditory feedback, central processing, and peripheral motor execution, is fundamentally shared across developmental stages and continues to mature over time. At present, it is challenging to visually and objectively evaluate tongue position and the degree of muscular tension during articulation. Accordingly, investigations employing quantitative tongue pressure measurement, ultrasonography, and magnetic resonance imaging (MRI) are required to elucidate the underlying neuromuscular mechanisms of articulatory control. Phonological processing ability has been implicated not only in articulation disorder and stuttering but also in reading and writing disorders, reflecting broader learning-related functions. From a developmental neuroscience perspective, functional articulation disorders in Japan should not be viewed solely as peripheral articulatory problems; rather, their potential associations with diverse forms of developmental higher brain dysfunction and neural network maturation warrant systematic investigation within neurorehabilitation frameworks.

In the larynx, dysfunction of the posterior cricoarytenoid muscle, the sole abductor of the vocal folds results in impaired glottic opening, lead to life-threatening airway compromise in bilateral closure. While multiple muscles contribute to glottic closure, abduction relies exclusively on this single muscle, rendering it particularly vulnerable to pathological conditions. Primary motor cortex for tongue is localized in the lower portion of precentral gyrus. Notably, paralytic conditions affecting the hand and tongue are rarely discussed in parallel from shared neurokinetic and neurophysiological aspects, despite their common neurological underpinnings. Ultimately, the goal of rehabilitation across disciplines is the restoration of activity and participation in daily life. Cortical and subcortical connections are not revealed clearly especially for oral, tongue, pharyngeal, and laryngeal regions. Future studies will concern subcortical white matter fibers including premotor cortex and insula.

The fields of neurophonetics and neuroacoustics are advancing rapidly under the progress of AI. Acoustic analysis has long been employed in speech research, and more recently, approaches based on nonlinearity and chaos theory have shown promise for characterizing complex speech dynamics.[85)-96)] It has recently been published that speech digital biomarker combined with fluid biomarkers predict cognitive impairment through machine learning. Neurofilament light chain is one of the blood biomarkers, indicating the severity of neurodegeneration. Biomarkers of acoustics, fluid and images are needed to intervene the presymptomatic and prodromal states.[97)-99)]

2. Language and cognitive pathology

Aphasia was conceptualized as a symptom-based disorder and anatomically discussed in Broca's and Wernicke's areas, which established correlations between clinical manifestations and focal brain lesions. Detailed neuroimaging analyses further clarified the anatomical substrates underlying aphasic syndrome. Despite these advances, many aspects of aphasia are resistant to a strict one-to-one correspondence between symptoms and lesions. Subsequently, intraoperative brain mapping in neurosurgical procedures has enabled direct comparison of neurological symptoms before, during, and after brain tumor resection. The introduction of diffusion tensor imaging (DTI) has further revolutionized aphasia research by allowing visualization of white matter pathways and their relationship to language function. Advances in automated tractography software have made it possible to estimate the anatomical localization of white matter tracts across the entire brain. Nevertheless, economic and temporal constraints associated with diffusion tensor tractography limit its routine longitudinal application. Wider utilization of DTI for evaluating therapeutic efficacy in acute care and rehabilitation settings remains an important future goal.[100)-116)]

In Japan, seven categories of higher brain dysfunctions are formally defined, including aphasia. Attention and executive functions occupy the base and the top of the hierarchical pyramid, respectively. Higher brain dysfunction is defined as resulting from organic brain lesions, whereas pediatric developmental disorders are not currently classified within this category and are instead considered forms of cognitive impairment. These conditions are often described as “invisible disabilities”, as they impose significant restrictions on daily activities. Visualization and quantification of subcortical white matter lesions beyond cortical damage alone are particularly valuable for prognostic assessment in neurorehabilitation aimed at recovery of activity. Such approaches as imaging biomarkers contribute directly to the development of neurorehabilitation strategies oriented toward recovery rather than compensation. Language rehabilitation strategies have been strongly influenced by psycholinguistic models, most notably the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) framework, which conceptualizes language processing through modular input and output pathways. In parallel with anatomical localization of symptoms, we adopted an approach that embeds functional language hubs directly within neuroanatomical structures, striving for conceptual consistency between PALPA-based models and brain imaging findings of neural network. Although the precise neural substrates underlying phonological, semantic, and orthographic input and output processes are incompletely defined, this integrated approach facilitates clinical interpretation of symptom–lesion–image relationships. Establishing systematic correspondence between PALPA-based language models and white matter tractography would allow detailed investigation of how functional reorganization of neural network occurs during cognitive rehabilitation. Such hodological integration may ultimately clarify mechanisms of neural plasticity underlying language recovery.

The improvement of task performance and generalization to everyday functioning for inattention in higher brain dysfunctions necessitate the incorporation of DAT (direct attention training), such as Attention Process Training (APT), with metacognitive strategy training, including time pressure management. The implementation of direct computer-based training is considered in acute rehabilitation for impaired working memory caused by acquired brain injury as well as in chronic stage. DAT in the acute phase may facilitate early improvement in higher brain functions and leads to further enhancement of activity of daily life in the chronic phase.

Recently, functional neurological disorder (FND) is noted as an active target for therapeutic intervention, rather than as a diagnosis of exclusion. These differentiation of functional disorders reflect ongoing debates regarding functional versus organic pathology as an issue long discussed within psychiatry as the differentiation between psychogenic and organic disorders. Since such conditions impose significant limitations and restrictions on activity and participation, respectively, neurorehabilitation and cognitive rehabilitation are essential components of management. Although the relationship between functional and organic pathology remains complex, future advances may allow most neurological conditions to be understood within a unified organic framework.

3. Swallowing pathology

Speech and swallowing share overlapping anatomical and neural substrates, yet they differ fundamentally in their control mechanisms. The oral phase of swallowing is primarily under voluntary control, whereas the pharyngeal and esophageal phases are largely reflexive. In contrast, speech production from expiratory control to glottic and pharyngeal modulation is essentially voluntary, although elements of automatization may exist within articulatory sequencing. Speech motor programs relate to the supplementary motor area, premotor cortex, and primary motor cortex, with execution mediated through the frontal aslant tract (FAT). Motor speech disorders include apraxia of speech (AOS), which occupies an interface between dysarthria and aphasia. Velopharyngeal competence (VPC) during articulation and the oral phase of swallowing is under voluntary control, whereas the pharyngeal phase of swallowing is triggered by reflexive mechanisms. Neurorehabilitation approaches aiming to simultaneously enhance both speech and swallowing functions have been developed; however, such strategies continue to be debated, and their efficacy is not universally accepted. The tongue, including its root portion, constitutes an exceptionally large muscular organ, despite only the tongue tip and dorsum being readily observable on visual inspection. At the level of motor execution, speech and swallowing share common effectors, namely the tongue, pharynx, soft palate, and larynx. While gross muscle strengthening exercises may overlap, task-specific motor sequence patterns differ substantially. Articulation requires highly refined and precise tongue movements, and swallowing demands stricter coordination of velopharyngeal function.

Sensory input from the soft palate and pharynx, which serves as the primary trigger for the swallowing reflex, is difficult to quantify clinically. Although sensory hypesthesia is frequently implicated in dysphagia, clinical assessment often focuses on the observable outcome of swallowing rather than on sensory dysfunction itself. Recently, interferential current stimulation (IFC) targeting the internal branch of the superior laryngeal nerve has been developed as neuromuscular electrical stimulation (NMES) and shown to improve delayed triggering of the swallowing reflex. However, the precise mechanisms by which central pattern generators (CPG) are activated under the sensory threshold of the pharynx remain incompletely understood.

Impaired opening of the upper esophageal sphincter (UES) and delayed swallowing onset in sensory abnormality lead to sarcopenic dysphagia, which is increasing with the aging population. Sarcopenic dysphagia, which is designated as decreased tongue pressure of biomarkers, is classified into two patterns between sarcopenia and dysphagia: one in which whole-body sarcopenia is followed by a swallowing disorder; and one in which the swallowing disorder with branchial muscle weakness is followed by malnutrition/whole-body sarcopenia. Despite these uncertainties, advances in neurophysiology and neuromodulation have expanded therapeutic options for dysphagia. Elucidating the interaction between sensory input, CPG, and motor output represents a critical challenge for future research in swallowing neurorehabilitation. The quantitative measures are a kind of biomarker for swallowing on the videofluoroscopic examination of swallowing study (VFSS).[117)-124)] Swallowing markers assessed by VFSS demonstrated that androgen deprivation using a luteinizing hormone–releasing hormone (LHRH) analogue suppresses the toxicity of the mutant androgen receptor in patients with spinal and bulbar muscular atrophy, providing the first evidence of a disease-modifying therapeutic effect with objectively measurable functional outcomes relevant to neurorehabilitation.[125)-132)]

IV. Conclusion

Neurorehabilitation can be conceptualized as a translational framework that reconstructs the speech and communication chain under genetically determined neural constraints through activity-dependent plasticity, with the ultimate goal of maximizing activity and participation. Future healthcare programs increasingly emphasize personalized genomic and epigenomic information not only for prognostic prediction but also for the optimization of neurorehabilitation strategies aimed at preventing or delaying the onset of neurological signs and symptoms during presymptomatic and prodromal stages. Advances in neurology, including disease-modifying therapies for neurodegenerative disorders, gene therapies, nucleic acids therapeutics, and immunotherapies have ushered in an era in which many neurological diseases are increasingly treatable, though not always curable. Because PGT-M is not applicable to all intractable neurological diseases and its indications are restricted, neurorehabilitation plays an indispensable role. Neurological diseases must therefore be understood through the coexistence of genetic prognosis, neurological functional prognosis, and activity-based prognosis. A future in which function, activity and participation, and survival are simultaneously optimized represents the shared goal of neurology, genetics, and rehabilitation medicine and defines the core concept of precision neurorehabilitation.

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