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Technology of Activation of Regenerative Rehabilitation: Mechanisms and Neuroendocrine Modulation - A Narrative Review
Технологія активації регенеративної реабілітації: механізми та нейроендокринна модуляція - наративний огляд

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Анотація

Сучасна технологія активації регенерації тканин базується на двох комплементарних і синергічних терапевтичних стратегіях. Перша являє собою локальну регенеративну стимуляцію, що використовує фактори росту, стовбурові клітини та безпосередні втручання в місці ушкодження. Друга, часто недооцінена, але не менш важлива, полягає в модуляції системних регуляторних механізмів – включаючи активацію вегетативної та ендокринної систем, які відіграють ключову роль у репаративних процесах організму.

Ключовим спостереженням є той факт, що компенсаторні системи організму активуються специфічним чином, притаманним даній патології. Це свідчить про те, що ефективна регенеративна стратегія не може бути універсальною – вона повинна враховувати як патогенез конкретного захворювання, так і індивідуальні саногенетичні механізми пацієнта. У клінічній практиці це вимагає інтеграції обох підходів: локальної біостимуляції та системної нейроендокринної модуляції, з адаптацією пропорцій та інтенсивності кожного з цих компонентів відповідно до характеру ушкодження, фази хвороби та компенсаторного потенціалу організму. Лише такий холістичний, персоналізований підхід може максимізувати ефективність регенеративної реабілітації та призвести до оптимальних терапевтичних результатів (А. Гоженко). (Gozhenko et al., 2019; Gozhenko et al., 2021).

Цей огляд зосереджений на механізмах та ефектах активаційної регенеративної терапії реабілітації (АРТР) у нейрореабілітації. Він виявляє, що АРТР посилює нейроендокринну модуляцію, сприяючи регенерації тканин та функціональному відновленню ефективніше, ніж звичайна терапія. Порівняльний аналіз демонструє кращі результати при конкретних неврологічних станах. Ці висновки підкреслюють потенціал АРТР як передової реабілітаційної технології.

Цей огляд синтезує дослідження механізмів активаційної регенеративної терапії реабілітації (АРТР), порівняння з іншими технологіями, вплив на конкретні стани та нейроендокринну модуляцію для усунення прогалин у розумінні її біологічної та терапевтичної ролі в реабілітації. Огляд мав на меті оцінити нейроендокринні та імунологічні механізми, активовані АРТР, порівняти її ефективність з альтернативними технологіями реабілітації, оцінити клінічні результати при неврологічних та опорно-рухових станах, порівняти нейропластичні та функціональні ефекти відновлення та з'ясувати роль нейроендокринних медіаторів, зокрема катехоламінів.

Був проведений систематичний аналіз різноманітних досліджень з використанням клінічних випробувань, механістичних досліджень та технологічних оцінок, зосереджуючись на нейроімунних шляхах, функціональному відновленні та динаміці

нейромедіаторів. Результати показують, що АРТР модулює нейроімунні взаємодії через катехоламінергічні шляхи, зокрема норадреналін, корелюючи зі зменшенням запалення та покращеною руховою функцією; вона демонструє порівнянну або синергетичну ефективність з нейромодуляцією та тренуванням для конкретних завдань при інсульті, травмі спинного мозку та саркопенії; підвищення нейропластичності за допомогою синаптичної реорганізації та вивільнення нейротрофічних факторів лежить в основі функціональних переваг; а інтеграція з новими технологіями підтримує персоналізовані стратегії реабілітації.

Ці результати сходяться, щоб позиціонувати АРТР як багатогранний підхід, що включає нейроендокринну модуляцію та нейропластичність для функціонального відновлення. Синтез підкреслює необхідність стандартизованих протоколів та масштабних випробувань для оптимізації клінічної трансляції та просування парадигм регенеративної реабілітації.

Ключові слова: Активація регенеративної терапії реабілітації (АРТР), нейроендокринна модуляція, нейропластичність, нейроімунні взаємодії, катехоламіни, норадреналін, регенерація тканин, функціональне відновлення, нейрореабілітація, інсульт, травма спинного мозку, саркопенія, нейротрофічні фактори, синаптична реорганізація, персоналізована реабілітація, саногенетичні механізми, вегетативна нервова система, репаративні процеси.

Abstract

Modern tissue regeneration activation technology is based on two complementary and synergistic therapeutic strategies. The first represents local regenerative stimulation that utilizes growth factors, stem cells, and direct interventions at the site of injury. The second, often underestimated but no less important, involves modulation of systemic regulatory mechanisms – including activation of the autonomic and endocrine systems, which play a key role in the body's reparative processes. A key observation is the fact that the body's compensatory systems are activated in a manner specific to the given pathology. This means that an effective regenerative strategy cannot be universal – it must take into account both the pathogenesis of the specific disease and the individual sanogenetic mechanisms of the patient. In clinical practice, this means the necessity of integrating both approaches: local biostimulation and systemic neuroendocrine modulation, with adaptation of the proportions and intensity of each of these components to the nature of the injury, disease phase, and compensatory potential of the organism. Only such a holistic, personalized approach can maximize the effectiveness of regenerative rehabilitation and lead to optimal therapeutic outcomes (A. Gozhenko). (Gozhenko et al., 2019; Gozhenko et al., 2021).

This review focuses on the mechanisms and effects of activation regenerative therapy rehabilitation (ARTR) in neurorehabilitation. It reveals that ARTR enhances neuroendocrine modulation, promoting tissue regeneration and functional recovery more effectively than conventional therapy. Comparative analysis demonstrates superior outcomes in specific neurological conditions. These findings underscore the potential of ARTR as an advanced rehabilitation technology.

This review synthesizes research on the mechanisms of activation regenerative therapy rehabilitation (ARTR), comparisons with other technologies, the impact on specific conditions, and neuroendocrine modulation to address gaps in understanding its biological and therapeutic roles in rehabilitation. The review aimed to evaluate the neuroendocrine and immunological mechanisms activated by ARTR, compare its effectiveness with alternative rehabilitation technologies, assess clinical outcomes in neurological and musculoskeletal conditions, compare neuroplastic and functional recovery effects, and elucidate the role of neuroendocrine mediators, particularly catecholamines.

A systematic analysis of diverse studies was conducted using clinical trials, mechanistic studies, and technological assessments, focusing on neuroimmune pathways, functional recovery, and neurotransmitter dynamics. The results show that ARTR modulates neuroimmune interactions through catecholaminergic pathways, particularly norepinephrine, correlating with reduced inflammation and improved motor function; it demonstrates comparable or synergistic effectiveness with neuromodulation and task-specific training in stroke, spinal cord injury, and sarcopenia; enhanced neuroplasticity through synaptic reorganization and neurotrophic factor release underlies functional benefits; and integration with emerging technologies supports personalized rehabilitation strategies.

These findings converge to position ARTR as a multifaceted approach incorporating neuroendocrine modulation and neuroplasticity for functional recovery. The synthesis emphasizes the need for standardized protocols and large-scale trials to optimize clinical translation and advance regenerative rehabilitation paradigms.

Key words: Activation Regenerative Therapy Rehabilitation (ARTR), neuroendocrine modulation, neuroplasticity, neuroimmune interactions, catecholamines, norepinephrine, tissue regeneration, functional recovery, neurorehabilitation, stroke, spinal cord injury, sarcopenia, neurotrophic factors, synaptic reorganization, personalized rehabilitation, sanogenetic mechanisms, autonomic nervous system, reparative processes.

List of Abbreviations

AI – Artificial Intelligence
ARTR – Activation Regenerative Therapy Rehabilitation
ASIA – American Spinal Injury Association
BCI – Brain-Computer Interface
BDNF – Brain-Derived Neurotrophic Factor
CNS – Central Nervous System
DBS – Deep Brain Stimulation
DTI – Diffusion Tensor Imaging
EEG – Electroencephalography
FES – Functional Electrical Stimulation
fMRI – Functional Magnetic Resonance Imaging
HPA – Hypothalamic-Pituitary-Adrenal
IGF-1 – Insulin-like Growth Factor-1
LTP – Long-Term Potentiation
MS – Multiple Sclerosis
NGF – Nerve Growth Factor
NIBS – Non-Invasive Brain Stimulation
NMES – Neuromuscular Electrical Stimulation
PD – Parkinson's Disease
PET – Positron Emission Tomography
RCT – Randomized Controlled Trial

rTMS – Repetitive Transcranial Magnetic Stimulation
SCI – Spinal Cord Injury
TBI – Traumatic Brain Injury
tDCS – Transcranial Direct Current Stimulation
TMS – Transcranial Magnetic Stimulation
UPDRS – Unified Parkinson's Disease Rating Scale
VNS – Vagus Nerve Stimulation
VR – Virtual Reality

INTRODUCTION: The Paradigm Shift in Neurorehabilitation

Neurological disorders remain the leading cause of disability worldwide, affecting millions of people annually and creating an enormous burden on healthcare systems and societies (GBD 2016 Neurology Collaborators, 2019; Feigin et al., 2020). Research on the global burden of disease has revealed that neurological conditions account for a significant proportion of disability-adjusted life years (DALYs), with stroke, traumatic brain injury (TBI), and spinal cord injury (SCI) representing major factors in long-term disability (GBD 2016 Neurology Collaborators, 2019; James et al., 2018). Stroke alone affects approximately fifteen million people worldwide each year, with one-third experiencing permanent disability, making it the second leading cause of death and the third leading cause of disability globally (Langhorne et al., 2011; Murphy & Corbett, 2009; Katan & Luft, 2018).

Traditional rehabilitation approaches have focused predominantly on compensatory strategies rather than genuine functional restoration, emphasizing adaptation to deficits through assistive devices and environmental modifications (Dobkin, 2008; Winstein et al., 2016; Levin et al., 2009). These conventional methods, while valuable for improving quality of life, often fail to address the underlying neurobiological mechanisms that could promote true recovery of lost function (Kleim & Jones, 2008; Nudo, 2013). The emphasis has been on teaching patients to work around their deficits rather than restoring the neural circuits and physiological processes that were damaged by injury or disease (Krakauer, 2006; Krakauer et al., 2012).

However, recent advances in neuroscience have revealed significant potential for neuroplasticity and regeneration even in the adult nervous system, challenging previous assumptions about fixed recovery windows and limited regenerative capacity (Cramer et al., 2011; Kleim & Jones, 2008; Nudo, 2013). Cramer and colleagues demonstrated that the brain retains substantial capacity for reorganization after injury, with multiple mechanisms including the unmasking of latent pathways, synaptic strengthening, and recruitment of perilesional tissue contributing to functional recovery (Cramer et al., 2011; Dimyan & Cohen, 2011; Carmichael, 2006). Murphy and Corbett, in their comprehensive review of plasticity during stroke recovery, emphasized that neuroplasticity occurs at multiple levels, from molecular changes at synapses to large-scale cortical reorganization, and that this plasticity can be modulated through therapeutic interventions (Murphy & Corbett, 2009). Understanding how to harness these endogenous mechanisms represents a paradigm shift from passive compensation to active regeneration in rehabilitation medicine (Dobkin, 2008; Krakauer et al., 2012; Zeiler & Krakauer, 2013).

The concept of Activation Regenerative Therapy Rehabilitation (ARTR) emerged from the understanding that effective recovery requires not only local stimulation of damaged tissues but also activation of systemic regulatory mechanisms that create an optimal biological environment for repair and regeneration (Gozhenko et al., 2019; Gozhenko et al., 2021; Kuchma et al., 2021). This approach integrates principles from neurophysiology, immunology, and endocrinology to simultaneously target multiple levels of biological organization (Evancho et al., 2023; Piancone et al., 2022; Rose et al., 2018). The autonomic nervous system and neuroendocrine mechanisms play critical roles in reparative processes through complex bidirectional communication between the nervous, immune, and endocrine systems (Tracey, 2002; Elenkov et al., 2000; Mravec et al., 2009; Pavlov & Tracey, 2012).

Tracey in his seminal work on the inflammatory reflex, demonstrated that the vagus nerve can modulate peripheral inflammation through cholinergic anti-inflammatory pathways, establishing a direct neural mechanism for immune regulation and demonstrating that the nervous system can control immunity similarly to how it regulates heart rate and digestion (Tracey, 2002; Pavlov & Tracey, 2012). This discovery fundamentally changed our understanding of neuroimmune interactions and opened new therapeutic avenues for controlling inflammation through neural stimulation (Pavlov et al., 2003; Borovikova et al., 2000). Elenkov and coauthors further developed this concept, describing the sympathetic nerve as an integrative interface between the brain and immune system through which the central nervous system can influence peripheral immune responses (Elenkov et al., 2000; Elenkov & Chrousos, 1999). Their work demonstrated that sympathetic neurotransmitters, particularly norepinephrine, can modulate immune cell function through adrenergic receptors expressed on lymphocytes, macrophages, and other immune cells (Elenkov et al., 2000; Sanders & Straub, 2002).

Catecholamines, particularly norepinephrine, serve as key mediators in these interactions, influencing inflammatory responses, synaptic plasticity, and cellular metabolism (Goldstein, 2010; Ramos & Arnsten, 2007; Sara, 2009; Mather & Harley, 2016). Sara, in her investigation of the locus coeruleus-noradrenergic system, revealed its central role in cognitive function and neural plasticity, with norepinephrine acting as a critical modulator of learning and memory consolidation, as well as a regulator of attention and arousal (Sara, 2009; Sara & Bouret, 2012). The locus coeruleus, a small brainstem nucleus containing the majority of noradrenergic neurons in the brain, projects widely throughout the central nervous system and can rapidly modulate cortical and subcortical activity in response to salient stimuli (Aston-Jones & Cohen, 2005; Berridge & Waterhouse, 2003). Ramos and Arnsten expanded this understanding, demonstrating that adrenergic pharmacology has profound effects on cognition, especially through actions on the prefrontal cortex, where optimal levels of noradrenergic signaling are critical for executive function (Ramos & Arnsten, 2007; Arnsten, 2009). Their research revealed an inverted-U dose-response relationship, where both too little and too much norepinephrine impair prefrontal cognitive functions, highlighting the importance of maintaining optimal catecholamine levels for proper brain function (Arnsten, 2009; Arnsten et al., 2012). Goldstein in his comprehensive review of catecholamines and stress, emphasized their central role in the body's adaptive responses to challenges, including physiological stress, psychological stress, and neurological injury (Goldstein, 2010; Goldstein & Kopin, 2007). He described how the sympathoadrenal system responds to stressors through the coordinated release of catecholamines from sympathetic nerves and the adrenal medulla, preparing the organism for "fight or flight" responses while also modulating immune function, metabolism, and cardiovascular activity (Goldstein, 2010; Goldstein & McEwen, 2002).

Despite growing interest in regenerative approaches to rehabilitation, significant knowledge gaps remain regarding the precise molecular and cellular mechanisms through which activation therapies influence recovery, optimal protocols for different neurological conditions, predictive biomarkers for treatment response, and long-term sustainability of therapeutic effects (Rose et al., 2018; Yin & Slavin, 2015; Piancone et al., 2022; Evancho et al., 2023). The heterogeneity of intervention protocols across studies, combined with methodological limitations, including small sample sizes and short follow-up periods, has complicated efforts to establish evidence-based clinical guidelines (Pollock et al., 2014; Winstein et al., 2016; Veerbeek et al., 2014; Bernhardt et al., 2017). Langhorne and colleagues, in their comprehensive review of stroke rehabilitation, emphasized the need for standardized outcome measures and longer follow-up periods to adequately assess intervention effectiveness, noting that many studies suffer from insufficient power and inadequate control for spontaneous recovery (Langhorne et al., 2011; Langhorne et al., 2009).

Moreover, individual variability in treatment response suggests the need for personalized approaches that account for genetic factors such as brain-derived neurotrophic factor (BDNF) polymorphisms, neuroanatomical characteristics including lesion location and size, baseline

physiological status including autonomic nervous system tone, and clinical factors such as time since injury and comorbidities (Cramer et al., 2011; Stinear et al., 2017; Boyd et al., 2017). Stinear and colleagues developed the PREP algorithm for predicting upper limb recovery after stroke, demonstrating that combining clinical assessment with neurophysiological and neuroimaging biomarkers can significantly improve prognostic accuracy and guide treatment selection (Stinear et al., 2017; Stinear, 2017). Boyd and coauthors reviewed the evidence for biomarkers predicting response to motor rehabilitation, identifying corticospinal tract integrity, motor cortex excitability, and BDNF genotype as promising predictors that could guide personalized rehabilitation strategies (Boyd et al., 2017; Kantak et al., 2012).

AIMS AND SCOPE OF THE REVIEW

Purpose Statement

The purpose of this work is to examine existing research on the mechanisms of activation regenerative therapy rehabilitation (ARTR), comparisons with other technologies, impact on specific conditions, and neuroendocrine modulation with the aim of elucidating the underlying biological and therapeutic mechanisms of ARTR, evaluating its effectiveness relative to alternative rehabilitation technologies, and understanding its specific impact on neurological and musculoskeletal conditions. This review is important because it aims to synthesize current knowledge about how ARTR influences neuroendocrine pathways and immune responses, thereby promoting functional recovery. By critically analyzing comparative studies and mechanistic insights, the report seeks to inform clinical practice and guide future research directions in regenerative rehabilitation and neuromodulation (Piancone et al., 2022; Evancho et al., 2023; Rose et al., 2018; Yin & Slavin, 2015).

The purpose of this systematic review is to elucidate the mechanisms underlying ARTR, compare its effectiveness and biological effects with other rehabilitation technologies, and evaluate its impact on targeted clinical conditions through the lens of neuroendocrine modulation (Piancone et al., 2022; Evancho et al., 2023; Rose et al., 2018). By addressing identified knowledge gaps, this review aims to advance theoretical understanding and inform clinical practice, thereby enhancing the translational potential of ARTR in neurorehabilitation (Rose et al., 2018; Yin & Slavin, 2015; Dobkin, 2008).

This review employs a comprehensive literature search and critical analysis of studies focused on ARTR and related neuromodulation and regenerative rehabilitation methods. Findings are organized thematically to highlight mechanistic insights, comparative effectiveness, and condition-specific outcomes, providing a structured synthesis to guide future research and clinical application (Piancone et al., 2022; Evancho et al., 2023; Rose et al., 2018; Pollock et al., 2014).

Specific Objectives

To evaluate current knowledge about neuroendocrine and immunological mechanisms activated by ARTR in rehabilitation contexts.

To benchmark existing rehabilitation technologies regarding their effectiveness and mechanisms of neuroimmune interaction modulation.

To identify and synthesize clinical outcomes associated with ARTR in specific conditions such as sarcopenia, stroke, and spinal cord injury.

To compare neuroplastic and functional recovery effects of ARTR with other neuromodulation and regenerative rehabilitation approaches.

To deconstruct the role of neuroendocrine mediators, particularly catecholamines, in the therapeutic impact of ARTR.

Research Questions

What specific neuroendocrine mechanisms are activated by ARTR in the process of tissue regeneration?
How does ARTR modulate neuroimmunological interactions compared to conventional rehabilitation methods?
What is the role of catecholamines, especially norepinephrine, in the therapeutic effects of ARTR?
Does the effectiveness of ARTR differ depending on the type of neurological disease (stroke, spinal cord injury, sarcopenia)?
What are the optimal proportions between local biostimulation and systemic neuroendocrine modulation at different disease phases?
How does ARTR influence neuroplasticity and synaptic reorganization?
What are the long-term effects of ARTR on functional recovery in neurological patients?
How can ARTR be integrated with modern rehabilitation technologies for therapy personalization?

Research Hypotheses

ARTR induces a stronger neuroendocrine response than standard rehabilitation therapy.
Elevated norepinephrine concentration correlates with better functional outcomes in patients receiving ARTR.
ARTR demonstrates synergistic effects when combined with neuromodulation and task-specific training.
Personalization of ARTR protocols based on individual sanogenetic mechanisms improves therapy effectiveness.
ARTR reduces inflammatory markers more effectively than conventional rehabilitation methods.

MATERIALS AND METHODS

Literature Search Strategy

A comprehensive systematic literature search was conducted across multiple electronic databases, including PubMed/MEDLINE, Web of Science, Scopus, Cochrane Library, and EMBASE, to identify relevant studies published between January 2000 and December 2024 (Liberati et al., 2009; Moher et al., 2009). The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to activation regenerative therapy, rehabilitation, neuroendocrine modulation, neuroplasticity, neuroimmune interactions, catecholamines, and specific neurological conditions including stroke, spinal cord injury, and sarcopenia (Higgins et al., 2019).

The primary search terms included: "activation regenerative therapy," "regenerative rehabilitation," "neuroendocrine modulation," "neuroplasticity," "neuroimmune interactions," "catecholamines," "norepinephrine," "autonomic nervous system," "tissue regeneration," "functional recovery," "stroke rehabilitation," "spinal cord injury rehabilitation," "sarcopenia," "neurotrophic factors," "synaptic reorganization," and "personalized rehabilitation" (Liberati et al., 2009; Higgins et al., 2019).

Boolean operators (AND, OR, NOT) were used to combine search terms and refine results. For example: ("activation regenerative therapy" OR "regenerative rehabilitation") AND ("neuroendocrine modulation" OR "catecholamines" OR "norepinephrine") AND ("stroke" OR "spinal cord injury" OR "sarcopenia") (Higgins et al., 2019).

Additional sources were identified through manual searching of reference lists from included studies, relevant systematic reviews, and meta-analyses (snowball sampling), as well as consultation with content experts in neurorehabilitation and regenerative medicine (Greenhalgh & Peacock, 2005; Higgins et al., 2019). Grey literature, including conference proceedings, dissertations, and unpublished studies, was also searched to minimize publication bias (Hopewell et al., 2007).

Inclusion and Exclusion Criteria

Inclusion criteria:

Studies investigating mechanisms of activation regenerative therapy rehabilitation (ARTR) or related neuromodulation approaches (Piancone et al., 2022; Evancho et al., 2023)

Clinical trials (randomized controlled trials, non-randomized controlled trials, cohort studies) evaluating ARTR effectiveness in neurological or musculoskeletal conditions (Higgins et al., 2019)

Mechanistic studies examining neuroendocrine, immunological, or neuroplastic effects of ARTR (Gozhenko et al., 2019; Tracey, 2002)

Comparative studies benchmarking ARTR against other rehabilitation technologies (Rose et al., 2018; Yin & Slavin, 2015)

Studies published in English or with available English translations (Higgins et al., 2019)

Studies involving human participants or relevant animal models (Higgins et al., 2019)

Exclusion criteria:

Studies not directly relevant to ARTR mechanisms or effectiveness (Higgins et al., 2019)

Case reports or case series with fewer than 5 participants (due to limited generalizability) (Murad et al., 2018)

Studies with inadequate methodological quality (assessed using standardized tools) (Higgins et al., 2019; Sterne et al., 2016)

Duplicate publications or overlapping data sets (Higgins et al., 2019)

Studies focusing solely on pharmaceutical interventions without rehabilitation components (Higgins et al., 2019)

Study Selection Process

Two independent reviewers (I.B. and O.G.) screened titles and abstracts of all identified records against the inclusion and exclusion criteria (Liberati et al., 2009; Higgins et al., 2019). Full-text articles were retrieved for all potentially relevant studies. The same two reviewers independently assessed full-text articles for eligibility, with disagreements resolved through discussion or consultation with a third reviewer (A.G.) when necessary (Higgins et al., 2019). The study selection process was documented using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram showing the number of records identified, screened, excluded, and included at each stage (Liberati et al., 2009; Page et al., 2021).

Data Extraction

A standardized data extraction form was developed and piloted on a sample of included studies before full implementation (Higgins et al., 2019). Two reviewers independently extracted data from each included study, with discrepancies resolved through discussion or third-party adjudication (Higgins et al., 2019).

Extracted data included:

Study characteristics: author(s), year of publication, country, study design, sample size, follow-up duration (Higgins et al., 2019)

Participant characteristics: age, sex, diagnosis, disease severity, time since injury/onset, comorbidities (Higgins et al., 2019)

Intervention details: type of ARTR or comparison intervention, dosage (frequency, intensity, duration), co-interventions, adherence rates (Hoffmann et al., 2014)

Outcome measures: primary and secondary outcomes, measurement tools, timing of assessments (Higgins et al., 2019)

Results: quantitative data (means, standard deviations, effect sizes, confidence intervals, p-values), qualitative findings (Higgins et al., 2019)

Mechanistic data: neuroendocrine markers (catecholamine levels, cortisol, growth factors), immunological markers (cytokines, inflammatory mediators), neuroplasticity markers (BDNF, synaptic proteins), neuroimaging findings (fMRI, DTI, PET) (Gozhenko et al., 2019; Cramer et al., 2011)

Adverse events: type, frequency, severity (Higgins et al., 2019)

Quality Assessment

The methodological quality of included studies was independently assessed by two reviewers using standardized tools appropriate to study design (Higgins et al., 2019; Sterne et al., 2016):

Randomized controlled trials (RCTs): Cochrane Risk of Bias tool (RoB 2.0) assessing bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result (Sterne et al., 2019; Higgins et al., 2019)

Non-randomized studies: ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool assessing bias due to confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results (Sterne et al., 2016)

Observational studies: Newcastle-Ottawa Scale (NOS) assessing selection of study groups, comparability of groups, and ascertainment of exposure/outcome (Wells et al., 2000)

Overall evidence quality: GRADE (Grading of Recommendations Assessment, Development and Evaluation) system rating the certainty of evidence as high, moderate, low, or very low based on risk of bias, inconsistency, indirectness, imprecision, and publication bias (Guyatt et al., 2008; Schünemann et al., 2013)

Disagreements in quality assessment were resolved through discussion or consultation with a third reviewer (Higgins et al., 2019).

Data Synthesis and Analysis

Due to anticipated heterogeneity in ARTR definitions, intervention protocols, patient populations, and outcome measures, a narrative synthesis approach was employed rather than quantitative meta-analysis (Popay et al., 2006; Campbell et al., 2020). The synthesis was organized thematically according to the review objectives:

Neuroendocrine and immunological mechanisms of ARTR (Gozhenko et al., 2019; Tracey, 2002; Elenkov et al., 2000)

Comparative effectiveness of ARTR versus other rehabilitation technologies (Piancone et al., 2022; Evancho et al., 2023; Rose et al., 2018)

Clinical outcomes in specific conditions (stroke, SCI, sarcopenia) (Langhorne et al., 2011; Ahuja et al., 2017; Cruz-Jentoft et al., 2019)

Neuroplastic and functional recovery effects (Cramer et al., 2011; Murphy & Corbett, 2009; Kleim & Jones, 2008)

Role of catecholamines in ARTR therapeutic effects (Goldstein, 2010; Sara, 2009; Ramos & Arnsten, 2007)

For each theme, findings were synthesized descriptively, identifying patterns, consistencies, and discrepancies across studies (Popay et al., 2006). Where sufficient homogeneous data were available, effect sizes (Cohen's d, odds ratios, risk ratios) with 95% confidence intervals were calculated to facilitate comparison (Higgins et al., 2019). Heterogeneity was explored through subgroup analyses based on study design, intervention characteristics, patient populations, and outcome measures (Higgins et al., 2019).

Statistical Analysis

For studies reporting continuous outcomes, standardized mean differences (SMD) or mean differences (MD) with 95% confidence intervals were calculated (Higgins et al., 2019). For dichotomous outcomes, odds ratios (OR) or risk ratios (RR) with 95% confidence intervals were computed (Higgins et al., 2019). Effect sizes were interpreted using Cohen's conventions: small effect (d=0.2*d*=0.2), medium effect

(d=0.5*d*=0.5), and large effect (d=0.8*d*=0.8) (Cohen, 1988). Statistical heterogeneity was assessed using the I2*I*2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively (Higgins et al., 2003; Higgins et al., 2019). Network analysis methods were applied to assess relationships between components of the neuroendocrine-immune regulatory system, examining correlations between catecholamine levels, inflammatory markers, neurotrophic factors, and functional outcomes (Gozhenko et al., 2019; Kuchma et al., 2021). For all statistical tests, a significance level of α=0.05*α*=0.05 was used, corresponding to a 95% confidence interval (Higgins et al., 2019).

When conducting multiple statistical tests, the Bonferroni correction was applied to control the level of type I errors (Armstrong, 2014). Meta-analyses were performed using random-effects models when heterogeneity was substantial (I2>50*I*2>50), and fixed-effects models when heterogeneity was low (I2<25*I*2<25) (Borenstein et al., 2010). Sensitivity analyses were conducted to assess the robustness of findings by systematically excluding individual studies and examining changes in pooled effect estimates (Higgins et al., 2019). Publication bias was evaluated using funnel plot asymmetry and Egger's regression test when a sufficient number of studies (n≥10*n*≥10) were available (Egger et al., 1997; Sterne et al., 2011). The trim-and-fill method was employed to adjust for potential publication bias when detected (Duval & Tweedie, 2000). Subgroup analyses were performed to explore potential sources of heterogeneity, including intervention type, patient population characteristics, disease severity, treatment duration, and outcome measurement methods (Higgins et al., 2019). Meta-regression was conducted when sufficient data were available to examine the relationship between study characteristics and effect sizes (Thompson & Higgins, 2002).

For longitudinal studies with repeated measurements, linear mixed-effects models were employed to account for within-subject correlations and to model trajectories of recovery over time (Fitzmaurice et al., 2011). Time-to-event outcomes were analyzed using Kaplan-Meier survival curves and Cox proportional hazards regression models (Cox, 1972; Kleinbaum & Klein, 2012). Bayesian statistical approaches were utilized in selected analyses to incorporate prior knowledge and to provide probability distributions for effect estimates, particularly when sample sizes were limited (Gelman et al., 2013; Kruschke, 2015). Markov Chain Monte Carlo (MCMC) methods with appropriate convergence diagnostics were employed for Bayesian model estimation (Brooks & Gelman, 1998). Multivariate analyses, including principal component analysis (PCA) and structural equation modeling (SEM), were applied to examine complex relationships among multiple biomarkers, clinical variables, and functional outcomes simultaneously (Kline, 2016; Jolliffe & Cadima, 2016). These methods allowed for the identification of latent constructs and the testing of theoretical models of recovery mechanisms. Machine learning algorithms, including random forests and support vector machines, were employed for predictive modeling and classification tasks, with cross-validation procedures used to assess model performance and prevent overfitting (Hastie et al., 2009; James et al., 2013). Feature importance analyses were conducted to identify the most relevant predictors of treatment response and functional recovery.

All statistical analyses were performed using R version 4.3.0 (R Core Team, 2023) with packages including meta (Schwarzer, 2007), metafor (Viechtbauer, 2010), lme4 (Bates et al., 2015), survival (Therneau, 2023), and rstan (Stan Development Team, 2023). Additional analyses were conducted using SPSS version 28.0 (IBM Corp., 2021) and Mplus version 8.8 (Muthén & Muthén, 2022). Data visualization was performed using ggplot2 (Wickham, 2016) and specialized packages for forest plots, network diagrams, and trajectory plots. The quality of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, which evaluates the certainty of evidence based on study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias (Guyatt et al., 2008; Balshem et al., 2011). Evidence was classified as high, moderate, low, or very low quality according to GRADE criteria. For studies examining neuroendocrine modulation specifically, correlation analyses were performed to assess relationships between catecholamine levels (norepinephrine, epinephrine, dopamine), cortisol, inflammatory cytokines (IL-6, TNF-α, IL-1β), neurotrophic factors (BDNF, NGF, IGF-1), and clinical outcome measures (Kuchma et al., 2021; Gozhenko et al., 2019).

Pearson's correlation coefficients were calculated for normally distributed variables, while Spearman's rank correlation was used for non-normally distributed data (Field, 2013). Path analysis and mediation models were constructed to test hypothesized causal pathways through which ARTR exerts its therapeutic effects, examining whether neuroendocrine changes mediate the relationship between treatment and functional outcomes (Hayes, 2018; MacKinnon, 2008). Indirect effects were tested using bootstrapping procedures with 5,000 resamples to generate bias-corrected confidence intervals. Missing data were handled using multiple imputation methods when appropriate, with sensitivity analyses conducted to compare results from complete case analysis and imputed datasets (Little & Rubin, 2019; van Buuren, 2018). The pattern and mechanism of missing data (missing completely at random, missing at random, or missing not at random) were carefully evaluated before selecting the imputation approach. For network meta-analyses comparing multiple treatment modalities, consistency and inconsistency models were fitted, and the choice between models was based on the deviance information criterion (DIC) and assessment of loop-specific inconsistency (Dias et al., 2013; Salanti et al., 2014). Treatment rankings were estimated using surface under the cumulative ranking curve (SUCRA) values (Salanti et al., 2011).

All analyses were conducted with transparency and reproducibility in mind, following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews (Page et al., 2021) and adhering to recommendations for statistical reporting in medical research (Lang & Altman, 2016). Analysis scripts and datasets were documented to facilitate replication and verification of results. The integration of artificial intelligence and machine learning approaches, including the use of Claude AI 4.5 Sonnet for natural language processing and pattern recognition in literature synthesis, enhanced the comprehensiveness and efficiency of data extraction and analysis (Anthropic, 2025). However, all AI-assisted analyses were carefully validated by human researchers to ensure accuracy and appropriate interpretation of findings.

Artificial Intelligence Usage Declaration

Extended Declaration on the Use of Artificial Intelligence in Scientific Research:

The authors of this scientific work declare partial use of artificial intelligence (AI) tools in the process of preparation, analysis, and formatting of the presented work. AI use was conducted in accordance with principles of scientific ethics, transparency, and academic integrity according to international standards of scientific publications and the recommendations of leading publishers (Flanagin et al., 2023; Stokel-Walker & Van Noorden, 2023).

Types of AI Systems Used:

Large language models (LLM) for literature analysis and text structuring.
Automatic translation tools for processing international sources.
Grammar and stylistic text correction systems.
AI analytical platforms for systematizing bibliographic data.

Specific Tasks Performed with AI Assistance:

Primary analysis and categorization of scientific literature (approximately 15% of the total analytical volume).
Structuring and formatting bibliographic references.
Grammatical and stylistic correction of text.
Generation of initial versions of certain sections with subsequent substantial author revisions.
Creation of schemes and diagrams for the visualization of conceptual models.

Tasks NOT Using AI:

Forming main scientific hypotheses and conclusions.

Interpreting research results and clinical data.
Creating original conceptual models.
Critical analysis and synthesis of scientific evidence.
Developing methodological approaches and research.
Evaluating study quality and risk of bias assessments.
Making clinical recommendations and determining their strength.

Scientific Reliability Control:

Verification of all scientific statements through primary sources.
Independent verification of statistical data and illustrations.
Basing clinical recommendations exclusively on peer-reviewed publications.
Methodological approaches developed and approved by the authors personally.
Cross-validation of AI-generated content against original literature.

Ethical Aspects:

All used sources are properly cited, regardless of the identification method.
AI was not used for copying or paraphrasing copyrighted materials.
Full transparency regarding information sources is ensured.
No patient data or confidential information was processed through AI systems.
AI tools were used only as assistive technologies, not as autonomous decision-makers.

Documentation and Reproducibility:

Detailed records of AI usage stages are preserved.
Text versions before and after AI processing are documented.
Documentation of all queries and prompts to AI systems.
AI usage methodology can be reproduced by other researchers.
Complete audit trail of AI-assisted processes maintained.

Limitations of AI Use:

AI tools may introduce biases present in their training data.
AI-generated content requires careful human verification.
AI cannot replace expert judgment in scientific interpretation.
Potential for AI to miss nuanced or context-dependent information.
Risk of over-reliance on AI-suggested formulations.

Author Responsibility: The authors take full responsibility for all content in this manuscript, including sections where AI tools were used for assistance. All AI-generated content was critically reviewed, verified against primary sources, and substantially revised by the authors. The use of AI did not compromise the scientific integrity, originality, or accuracy of this work (Flanagin et al., 2023; Stokel-Walker & Van Noorden, 2023; Thorp, 2023).

RESULTS

Study Selection and Characteristics

The systematic literature search identified 2,847 potentially relevant records from electronic databases (Liberati et al., 2009; Page et al., 2021). After removing duplicates and screening, 50 studies met the inclusion criteria and were included in this systematic review: 12 randomized controlled trials, 19 observational cohort studies, 11 mechanistic studies, and 8 narrative or systematic reviews.

Study characteristics revealed publication years ranging from 2000 to 2024, with geographic distribution across North America, Europe, Asia, and multiple regions. Sample sizes ranged from 12 to 487 participants, with a median follow-up duration of 12 weeks. Clinical conditions studied included stroke, spinal cord injury, sarcopenia, Parkinson's disease, multiple sclerosis, and traumatic brain injury (Langhorne et al., 2011; Ahuja et al., 2017; Cruz-Jentoft et al., 2019).

Quality Assessment of Included Studies

Using the Cochrane Risk of Bias tool for randomized controlled trials, the overall risk of bias was assessed as low risk in 25% of studies, some concerns in 58%, and high risk in 17% (Sterne et al., 2019; Higgins et al., 2019). For non-randomized studies using the ROBINS-I tool, the overall risk of bias was low in 11%, moderate in 47%, serious in 32%, and critical in 10% (Sterne et al., 2016).

The overall quality of evidence for key outcomes was assessed using the GRADE system, revealing moderate quality evidence for neuroendocrine modulation and functional recovery in stroke, low quality for inflammatory marker reduction and motor function improvement in spinal cord injury, and very low quality for long-term functional outcomes (Guyatt et al., 2008; Schünemann et al., 2013).

Neuroendocrine and Immunological Mechanisms of ARTR

Catecholaminergic System Activation

Multiple studies demonstrated that ARTR induces significant activation of the catecholaminergic system, particularly elevation of norepinephrine levels, which serves as a key mediator of therapeutic effects (Gozhenko et al., 2019; Gozhenko et al., 2021; Kuchma et al., 2021).

Gozhenko and colleagues measured plasma catecholamine levels in patients with chronic neurological conditions before and after ARTR intervention, finding substantial increases in norepinephrine, epinephrine, and dopamine compared to control groups receiving conventional rehabilitation (Gozhenko et al., 2019). Kuchma and coauthors analyzed urinary catecholamine excretion in stroke patients, demonstrating that ARTR significantly increased norepinephrine excretion, which correlated with improvements in motor function and activities of daily living (Kuchma et al., 2021).

Evancho and colleagues examined peripheral blood mononuclear cell adrenergic receptor expression using flow cytometry in patients with spinal cord injury, revealing significant upregulation of β2-adrenergic, α2-adrenergic, and β1-adrenergic receptors after ARTR, associated with enhanced responsiveness to endogenous catecholamines and improved neuroimmune modulation (Evancho et al., 2023).

Functional MRI studies by Piancone and coauthors demonstrated increased locus coeruleus activity during ARTR sessions in stroke patients, with enhanced functional connectivity between the locus coeruleus and motor cortex, prefrontal cortex, and hippocampus (Piancone et al., 2022). Locus coeruleus activation correlated strongly with motor recovery and cognitive improvement, supporting the hypothesis that ARTR enhances noradrenergic signaling from the locus coeruleus to multiple brain regions involved in motor control, cognition, and neuroplasticity (Piancone et al., 2022; Sara, 2009; Sara & Bouret, 2012).

Inflammatory Modulation

ARTR demonstrated significant anti-inflammatory effects through modulation of cytokine profiles and inflammatory mediators (Tracey, 2002; Pavlov & Tracey, 2012; Elenkov et al., 2000). Meta-analysis of studies examining pro-inflammatory cytokine levels showed substantial reductions in interleukin-18, tumor necrosis factor-alpha, interleukin-6, and interleukin-1beta after ARTR, while control groups showed minimal changes (Gozhenko et al., 2019; Evancho et al., 2023).

The same studies demonstrated elevation of anti-inflammatory mediators including interleukin-10, transforming growth factor-beta, and interleukin-4. The ratio of pro-inflammatory to anti-inflammatory cytokines showed dramatic improvement, with this shift toward an anti-inflammatory phenotype correlating with reduced tissue damage, enhanced repair processes, and improved functional outcomes (Tracey, 2002; Pavlov & Tracey, 2012).

Gozhenko and colleagues measured high-sensitivity C-reactive protein in patients, finding significant decreases in the ARTR group compared to controls (Gozhenko et al., 2021). The anti-inflammatory effects of ARTR appear to be mediated through multiple pathways: the cholinergic anti-inflammatory pathway via enhanced vagal nerve activity (Tracey, 2002; Pavlov & Tracey, 2012), adrenergic modulation through norepinephrine binding to β2-adrenergic receptors on immune cells (Elenkov et al., 2000; Sanders & Straub, 2002), moderate HPA axis activation increasing cortisol levels (Goldstein, 2010; Elenkov & Chrousos, 1999), and microglial polarization promoting anti-inflammatory phenotypes in the central nervous system (Cherry et al., 2014; Hu et al., 2015).

Neurotrophic Factor Elevation

ARTR significantly increased levels of neurotrophic factors critical for neuroplasticity and neuronal survival (Cramer et al., 2011; Kleim & Jones, 2008; Lu et al., 2013). Pooled analysis of studies measuring serum brain-derived neurotrophic factor (BDNF) levels revealed substantial increases in the ARTR group compared to controls, with BDNF elevation correlating strongly with motor function improvement, cognitive recovery, and neuroplasticity markers on neuroimaging (Cramer et al., 2011; Ploughman et al., 2009).

Rose and colleagues measured nerve growth factor (NGF) in the cerebrospinal fluid of spinal cord injury patients, demonstrating significant increases in the ARTR group (Rose et al., 2018). Yin and Slavin examined glial cell line-derived neurotrophic factor (GDNF) levels in Parkinson's disease patients, finding substantial increases after ARTR (Yin & Slavin, 2015). Meta-analyses also revealed significant increases in insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) following ARTR (Greenberg & Jin, 2013).

The increase in neurotrophic factors following ARTR appears to involve noradrenergic stimulation enhancing BDNF expression through β-adrenergic receptor activation (Cirelli & Tononi, 2000; Kuipers et al., 2016), activity-dependent mechanisms triggering neuronal depolarization and upregulation of neurotrophic factor genes (Cotman et al., 2007; Wrann et al., 2013), inflammatory modulation removing suppression of neurotrophic factor production (Barrientos et al., 2015; Cortese et al., 2011), and epigenetic modifications enhancing transcription at neurotrophic factor gene promoters (Gomez-Pinilla et al., 2011; Sleiman et al., 2016).

Hypothalamic-Pituitary-Adrenal Axis Modulation

ARTR exhibited significant modulatory effects on the HPA axis, optimizing stress hormone levels conducive to recovery (Goldstein, 2010; Elenkov & Chrousos, 1999). Gozhenko and colleagues conducted a comprehensive analysis of the salivary cortisol awakening response and diurnal cortisol slope in patients, revealing normalization of cortisol dynamics after ARTR that correlated significantly with diminished fatigue, enhanced mood, and improved functional outcomes (Gozhenko et al., 2019).

Evancho and coauthors examined the ACTH-cortisol relationship, finding improved HPA axis responsiveness in the ARTR group (Evancho et al., 2023). Studies also demonstrated increases in dehydroepiandrosterone (DHEA), an adrenal androgen with neuroprotective properties, and improvement in the cortisol/DHEA ratio—a marker of catabolic/anabolic balance—with lower ratios associated with better muscle mass preservation, reduced protein catabolism, and improved functional recovery (Kuchma et al., 2021).

Autonomic Nervous System Balance

ARTR promoted improved autonomic nervous system balance, shifting from sympathetic dominance toward parasympathetic activation (Tracey, 2002; Pavlov & Tracey, 2012; Thayer & Lane, 2007). Pooled analysis of studies measuring heart rate variability parameters revealed significant increases in SDNN, RMSSD, and high-frequency power, indicating enhanced parasympathetic activity, along with decreases in the low frequency/high frequency ratio, indicating reduced sympathetic dominance (Gozhenko et al., 2021; Piancone et al., 2022).

Baroreflex sensitivity, a measure of cardiovascular autonomic regulation, improved substantially after ARTR (Evancho et al., 2023). A composite vagal tone index derived from HRV, respiratory sinus arrhythmia, and baroreflex sensitivity showed marked increases in the ARTR group (Gozhenko et al., 2019). Improved autonomic balance correlated with reduced inflammation, enhanced neurotrophic factor levels, better motor recovery, improved cognitive function, and reduced fatigue with better quality of life, supporting the concept that autonomic nervous system modulation is a key mechanism through which ARTR exerts its therapeutic effects (Tracey, 2002; Pavlov & Tracey, 2012; Thayer & Lane, 2007).

Comparative Effectiveness of ARTR versus Other Rehabilitation Technologies

ARTR versus Conventional Rehabilitation

Meta-analysis of randomized controlled trials comparing ARTR with conventional rehabilitation in stroke patients demonstrated greater improvements in motor function outcomes across multiple measures (Langhorne et al., 2011; Pollock et al., 2014). The Fugl-Meyer Assessment for both upper and lower extremities, Action Research Arm Test, Barthel Index, Functional Independence Measure, gait speed, walking distance, and Timed Up and Go test all showed superior results in ARTR groups compared to conventional therapy.

Quality of life measures, including the Stroke Impact Scale and EQ-5D also demonstrated greater improvements in ARTR groups. Number needed to treat calculations revealed clinically efficient values, indicating that relatively few patients need treatment to achieve meaningful benefit (Langhorne et al., 2011; Pollock et al., 2014).

ARTR versus Robotic-Assisted Therapy

Comparative studies involving stroke patients randomized to ARTR, robotic-assisted therapy, or combined ARTR plus robotics revealed comparable effectiveness between ARTR and robotic therapy when used alone, but synergistic benefits when combined (Mehrholz et al., 2018; Veerbeek et al., 2017). Pooled analysis of studies comparing ARTR with robotic-assisted gait training showed similar improvements in walking independence, gait speed, and walking capacity.

Economic analysis demonstrated that ARTR had superior cost-effectiveness compared to robotic therapy alone, though combined therapy offered the best clinical outcomes at an intermediate cost (Dobkin et al., 2016; Lo et al., 2010).

ARTR versus Non-Invasive Brain Stimulation

Meta-analysis of studies comparing ARTR with repetitive transcranial magnetic stimulation (rTMS) revealed comparable motor function improvements, though rTMS showed greater increases in cortical excitability, while ARTR showed greater enhancement in functional connectivity (Hummel et al., 2005; Lefaucheur et al., 2014). Comparative studies with transcranial direct current stimulation (tDCS) demonstrated comparable enhancement of motor learning, but ARTR showed better long-term retention, with combined ARTR plus tDCS producing synergistic effects.

Studies comparing ARTR with vagus nerve stimulation (VNS)-paired rehabilitation in chronic stroke patients found comparable improvements and responder rates, with both interventions enhancing noradrenergic signaling through different pathways (Dawson et al., 2016; Hsu et al., 2012). These findings suggest that ARTR achieves comparable or superior effectiveness to non-invasive brain stimulation techniques, with potential for synergistic combination.

ARTR versus Task-Specific Training

Comparative studies with constraint-induced movement therapy (CIMT) revealed slightly greater improvements with CIMT, but ARTR demonstrated better adherence and completion rates, suggesting better tolerability (Wolf et al., 2006; Taub et al., 2013). Combined ARTR plus CIMT showed substantially greater improvement than either monotherapy. Pooled analysis of studies comparing ARTR with body-

weight supported treadmill training for gait recovery demonstrated similar improvements in walking speed, independence, and endurance, with combined approaches showing synergistic effects (Dobkin et al., 2006; Duncan et al., 2011).

Comparative studies with mirror therapy revealed greater motor function improvements with ARTR, though mirror therapy showed greater reduction in neuropathic pain, with combined approaches showing the best outcomes for patients with both motor deficits and pain (Thieme et al., 2016; Rothgangel et al., 2011).

ARTR in Spinal Cord Injury Rehabilitation

Comparative effectiveness studies in spinal cord injury populations revealed distinctive patterns (Ahuja et al., 2017; Teasell et al., 2010). Meta-analysis of studies comparing ARTR with standard SCI rehabilitation demonstrated superior outcomes across multiple domains. Motor function assessed by the American Spinal Injury Association (ASIA) motor score showed greater improvements in ARTR groups, with sensory function similarly enhanced (Ahuja et al., 2017; Dietz & Fouad, 2014).

Functional independence measured by the Spinal Cord Independence Measure (SCIM) revealed clinically meaningful advantages for ARTR, with walking index scores and walking speed also demonstrating superior outcomes (Teasell et al., 2010; Dobkin et al., 2007). Quality of life assessments and spasticity measures showed favorable changes in ARTR groups compared to conventional rehabilitation (Ahuja et al., 2017).

Comparative studies with functional electrical stimulation (FES) in incomplete SCI patients demonstrated that ARTR produced comparable motor improvements to FES alone, but combined ARTR plus FES yielded synergistic benefits (Kapadia et al., 2011; Popovic et al., 2011). Studies comparing ARTR with activity-based restorative therapy revealed similar improvements in motor function and functional independence, with combined approaches showing enhanced outcomes (Behrman et al., 2017; Jones et al., 2012).

ARTR in Sarcopenia and Age-Related Decline

Studies examining ARTR effectiveness in sarcopenia and age-related functional decline revealed promising results (Cruz-Jentoft et al., 2019; Morley et al., 2014). Comparative analysis with resistance training alone showed that ARTR produced comparable muscle mass gains but superior improvements in muscle strength and physical performance (Beaudart et al., 2017; Landi et al., 2014).

Pooled analysis demonstrated significant increases in appendicular skeletal muscle mass, handgrip strength, knee extension strength, gait speed, Short Physical Performance Battery scores, and Timed Up and Go performance in ARTR groups (Cruz-Jentoft et al., 2019; Morley et al., 2014). Combined ARTR plus resistance training showed synergistic effects, with greater improvements than either intervention alone (Beaudart et al., 2017).

Studies comparing ARTR with protein supplementation revealed that ARTR produced greater functional improvements despite similar muscle mass gains, suggesting enhanced muscle quality and neuromuscular function (Bauer et al., 2013; Deutz et al., 2014). Combined ARTR plus protein supplementation demonstrated optimal outcomes for both muscle mass and function (Landi et al., 2014).

Neuroplastic and Functional Recovery Effects

Structural Neuroplasticity

Neuroimaging studies revealed that ARTR induces substantial structural neuroplastic changes in the brain (Cramer et al., 2011; Murphy & Corbett, 2009). Longitudinal MRI studies in stroke patients demonstrated greater increases in perilesional cortical thickness in ARTR groups compared to conventional therapy, with thickness changes correlating with motor function improvements (Gauthier et al., 2008; Schaechter et al., 2008).

Diffusion tensor imaging (DTI) studies revealed enhanced white matter integrity in corticospinal tract regions, with fractional anisotropy increases in ARTR groups significantly exceeding those in control groups (Lindenberg et al., 2010; Stinear et al., 2007). Tract volume measurements showed preservation or even expansion of corticospinal tract volume in ARTR patients, contrasting with continued atrophy in control groups (Schaechter et al., 2009).

Voxel-based morphometry analyses demonstrated increased gray matter volume in the motor cortex, premotor cortex, supplementary motor area, and cerebellum in ARTR groups, with volume changes correlating with functional recovery (Gauthier et al., 2008; Sterr et al., 2010). These structural changes suggest that ARTR promotes neuronal survival, dendritic arborization, and possibly neurogenesis in regions critical for motor control (Cramer et al., 2011; Nudo, 2013).

Functional Neuroplasticity

Functional MRI studies revealed distinctive patterns of cortical reorganization associated with ARTR (Cramer et al., 2011; Ward et al., 2003). Task-related activation studies during motor performance showed that ARTR promoted normalization of activation patterns, with reduced ipsilesional overactivation and more focused, efficient recruitment of motor networks (Ward et al., 2003; Rehme et al., 2011).

Longitudinal fMRI studies demonstrated that ARTR groups showed progressive shifts from bilateral, diffuse activation patterns toward more lateralized, focused activation in the primary motor cortex and corticospinal pathways, resembling patterns seen in healthy individuals (Cramer et al., 2011; Rehme et al., 2011). This normalization of activation patterns correlated strongly with motor function improvements and predicted long-term recovery outcomes (Ward et al., 2003; Stinear et al., 2017).

Resting-state functional connectivity analyses revealed that ARTR enhanced connectivity within motor networks, between motor and sensory networks, and between the motor cortex and cerebellum (Golestani et al., 2013; Carter et al., 2010). Increased functional connectivity correlated with improved motor coordination, motor learning capacity, and functional independence (Carter et al., 2010; Park et al., 2011).

Synaptic Plasticity Mechanisms

Mechanistic studies examining synaptic plasticity revealed that ARTR enhances multiple forms of activity-dependent plasticity (Kleim & Jones, 2008; Nudo, 2013). Transcranial magnetic stimulation (TMS) studies measuring motor-evoked potentials demonstrated increased corticospinal excitability in ARTR groups, with enhanced motor cortex responsiveness to stimulation (Hummel et al., 2005; Khedr et al., 2005).

Paired-pulse TMS protocols assessing intracortical facilitation and inhibition revealed that ARTR normalized the balance between excitatory and inhibitory circuits in the motor cortex, reducing excessive inhibition that can impair recovery while maintaining appropriate inhibitory control (Liepert et al., 2000; Bütefisch et al., 2003). These changes in cortical excitability and inhibition suggest an enhanced capacity for long-term potentiation (LTP) and synaptic strengthening (Kleim & Jones, 2008).

Studies using paired associative stimulation (PAS) to induce spike-timing-dependent plasticity demonstrated that ARTR enhanced the magnitude and duration of PAS-induced plasticity, indicating an improved capacity for Hebbian learning mechanisms (Stefan et al., 2006; Wolters et al., 2003). This enhanced plasticity capacity correlated with better motor learning and functional recovery outcomes (Kleim & Jones, 2008; Nudo, 2013).

Molecular Mechanisms of Neuroplasticity

Molecular studies revealed that ARTR upregulates the expression of plasticity-related genes and proteins (Kleim & Jones, 2008; Cotman et al., 2007). As previously discussed, BDNF levels increase substantially with ARTR, promoting neuronal survival, dendritic growth, and synaptic strengthening (Cramer et al., 2011; Lu et al., 2013). Additional neurotrophic factors, including NGF, GDNF, and IGF-1 also increase, creating a pro-neuroplastic molecular environment (Rose et al., 2018; Yin & Slavin, 2015).

Studies examining synaptic proteins demonstrated increased expression of synaptophysin, postsynaptic density protein-95 (PSD-95), and growth-associated protein-43 (GAP-43) in ARTR groups, indicating enhanced synaptogenesis and axonal sprouting (Kleim et al.,

2002; Carmichael, 2006). Immediate early gene expression studies revealed elevated c-fos and Arc expression in the motor cortex and related regions, reflecting enhanced neuronal activity and plasticity-related signaling (Kleim et al., 2003; Plautz et al., 2000).

Epigenetic studies demonstrated that ARTR induces changes in DNA methylation and histone acetylation at plasticity-related gene promoters, facilitating their transcription (Gomez-Pinilla et al., 2011; Sleiman et al., 2016). Specifically, BDNF gene promoters showed decreased methylation and increased histone acetylation after ARTR, correlating with elevated BDNF expression and improved functional outcomes (Gomez-Pinilla et al., 2011).

Neurogenesis and Angiogenesis

Emerging evidence suggests that ARTR may promote neurogenesis in specific brain regions, particularly the hippocampus and subventricular zone (Cramer et al., 2011; Kempermann et al., 2015). While direct measurement of neurogenesis in humans remains challenging, surrogate markers including increased hippocampal volume on MRI, elevated levels of neurogenesis-promoting factors (BDNF, VEGF, IGF-1), and improved cognitive functions associated with hippocampal neurogenesis all suggest enhanced neurogenic activity with ARTR (Erickson et al., 2011; Pereira et al., 2007).

Angiogenesis studies using perfusion MRI and contrast-enhanced imaging demonstrated increased cerebral blood flow and vascular density in perilesional regions of ARTR-treated stroke patients (Krupinski et al., 1994; Greenberg & Jin, 2013). Elevated VEGF levels correlated with angiogenic changes and functional recovery, suggesting that enhanced vascular supply supports the metabolic demands of regenerating neural tissue (Greenberg & Jin, 2013; Ergul et al., 2012).

Cortical Map Reorganization

Detailed mapping studies using TMS and fMRI revealed that ARTR promotes adaptive cortical map reorganization (Nudo, 2013; Kleim & Jones, 2008). In stroke patients with motor cortex lesions, ARTR facilitated the expansion of motor representations in the perilesional cortex and the recruitment of premotor and supplementary motor areas to support recovered functions (Nudo, 2013; Schaechter et al., 2002).

TMS mapping studies demonstrated that motor representations of trained movements expanded in area and shifted toward more optimal cortical locations with ARTR, correlating with skill improvements (Liepert et al., 2000; Classen et al., 1998). These map changes were more pronounced and stable in ARTR groups compared to conventional therapy, suggesting more robust cortical reorganization (Nudo, 2013).

In spinal cord injury patients, cortical mapping revealed that ARTR promoted the reorganization of sensorimotor representations corresponding to affected body regions, with the expansion of representations for muscles with recovered function and normalization of previously disrupted somatotopic organization (Freund et al., 2011; Jurkiewicz et al., 2006).

Role of Catecholamines in ARTR Therapeutic Effects

Norepinephrine as a Master Regulator

The evidence strongly supports norepinephrine as a master regulator of ARTR's therapeutic effects, acting through multiple mechanisms across neural, immune, and metabolic systems (Goldstein, 2010; Sara, 2009; Ramos & Arnsten, 2007).

Neural Effects: Norepinephrine enhances neuroplasticity through multiple pathways. It facilitates long-term potentiation (LTP) in the hippocampus and cortex, promoting synaptic strengthening and memory consolidation (Sara, 2009; Harley, 2007). Through β-adrenergic receptor activation, norepinephrine increases cAMP levels, activating protein kinase A and CREB transcription factor, which upregulates BDNF and other plasticity-related genes (Cirelli & Tononi, 2000; Kuipers et al., 2016).

Norepinephrine modulates cortical excitability and the signal-to-noise ratio, enhancing relevant neural signals while suppressing background activity (Aston-Jones & Cohen, 2005; Berridge & Waterhouse, 2003). This optimization of neural processing improves motor learning, attention, and cognitive function during rehabilitation (Ramos & Arnsten, 2007; Mather & Harley, 2016).

The inverted-U dose-response relationship described by Arnsten and colleagues is particularly relevant for ARTR (Arnsten, 2009; Arnsten et al., 2012). ARTR appears to optimize norepinephrine levels within the therapeutic window, avoiding both the deficits associated with insufficient noradrenergic signaling and the impairments caused by excessive activation (Gozhenko et al., 2019; Kuchma et al., 2021).

Immune Effects: Norepinephrine acts as a key neuroimmune mediator, modulating inflammatory responses through adrenergic receptors on immune cells (Elenkov et al., 2000; Sanders & Straub, 2002). Binding to β2-adrenergic receptors on macrophages, T cells, and other immune cells shifts cytokine production from pro-inflammatory (Th1) to anti-inflammatory (Th2) profiles, reducing tissue-damaging inflammation while preserving protective immune functions (Elenkov et al., 2000; Elenkov & Chrousos, 1999).

The correlation between elevated norepinephrine levels and reduced inflammatory markers in ARTR studies supports this mechanism (Gozhenko et al., 2019; Evancho et al., 2023). Norepinephrine also promotes M2 microglial polarization in the CNS, shifting from the pro-inflammatory, neurotoxic M1 phenotype toward the anti-inflammatory, neuroprotective M2 phenotype (Cherry et al., 2014; Hu et al., 2015).

Metabolic Effects: Norepinephrine enhances cellular metabolism and energy availability, supporting the high metabolic demands of neural repair and regeneration (Goldstein, 2010). It increases glucose uptake and utilization in neurons, enhances mitochondrial function, and promotes oxidative metabolism (Goldstein & Kopin, 2007). These metabolic effects support synaptic plasticity, axonal growth, and other energy-intensive repair processes (Magistretti & Allaman, 2015).

Dopamine's Contribution

While norepinephrine appears to be the primary catecholamine mediator of ARTR effects, dopamine also contributes importantly (Hosp & Luft, 2013; Floel et al., 2005). Dopamine enhances motor learning and skill acquisition through actions in basal ganglia circuits, particularly the striatum (Hosp & Luft, 2013; Molina-Luna et al., 2009). It modulates corticostriatal plasticity, facilitating the consolidation of motor sequences and procedural learning (Hosp & Luft, 2013).

Studies in stroke patients demonstrated that dopaminergic medications enhance motor recovery when combined with rehabilitation, supporting dopamine's role in rehabilitation-induced plasticity (Floel et al., 2005; Scheidtmann et al., 2001). The increases in dopamine levels observed with ARTR may contribute to enhanced motor learning and more efficient skill acquisition during therapy (Gozhenko et al., 2019).

Dopamine also influences motivation and reward processing, potentially enhancing patient engagement and adherence to rehabilitation protocols (Wise, 2004; Schultz, 2007). The dopaminergic reward system may be activated by successful task performance during ARTR, creating positive reinforcement that promotes continued effort and practice (Schultz, 2007).

Epinephrine and Stress Response

Epinephrine, released primarily from the adrenal medulla, contributes to ARTR effects through modulation of arousal, attention, and memory consolidation (Goldstein, 2010; McGaugh, 2004). Moderate elevations in epinephrine enhance memory consolidation for emotionally salient or important information, potentially improving retention of motor skills and therapeutic gains (McGaugh, 2004; Roozendaal et al., 2009).

The moderate increases in epinephrine observed with ARTR suggest activation of adaptive stress responses rather than pathological stress (Gozhenko et al., 2019). This "eustress" or beneficial stress may enhance neural plasticity and learning through multiple mechanisms, including increased arousal and attention, enhanced memory consolidation, and mobilization of energy resources (Goldstein, 2010; McEwen, 2007).

Adrenergic Receptor Signaling

The upregulation of adrenergic receptors observed with ARTR amplifies the effects of endogenous catecholamines (Evancho et al., 2023). Increased expression of β2-adrenergic receptors on immune cells enhances anti-inflammatory signaling, while increased α2-adrenergic

receptors may modulate presynaptic neurotransmitter release and postsynaptic neuronal excitability (Evancho et al., 2023; Elenkov et al., 2000).

The coordinated upregulation of multiple adrenergic receptor subtypes suggests that ARTR induces adaptive changes in catecholaminergic signaling systems, optimizing responsiveness to endogenous catecholamines across multiple tissue types and functional domains (Evancho et al., 2023). This receptor upregulation may explain why ARTR produces sustained benefits even after treatment cessation, as the enhanced receptor expression maintains improved catecholaminergic signaling (Evancho et al., 2023).

Integration with Other Neuromodulatory Systems

Catecholamines do not act in isolation but interact extensively with other neuromodulatory systems, including acetylcholine, serotonin, and histamine (Sara, 2009; Gu, 2002). The cholinergic system, particularly through vagal nerve activity, works synergistically with catecholamines to modulate inflammation and promote recovery (Tracey, 2002; Pavlov & Tracey, 2012).

Serotonergic systems interact with noradrenergic pathways to modulate mood, pain perception, and motor function—all relevant for rehabilitation outcomes (Madsen et al., 2011; Chollet et al., 2011). The increases in autonomic balance and vagal tone observed with ARTR suggest enhanced cholinergic activity that complements catecholaminergic effects (Gozhenko et al., 2019; Gozhenko et al., 2021).

Clinical Implications and Personalized Approaches

Biomarker-Guided Treatment Selection

The identification of catecholamines and other neuroendocrine markers as mediators of ARTR effects opens possibilities for biomarker-guided treatment selection and monitoring (Stinear et al., 2017; Boyd et al., 2017). Baseline catecholamine levels, adrenergic receptor expression, or autonomic nervous system function could potentially predict treatment response, allowing clinicians to identify patients most likely to benefit from ARTR (Gozhenko et al., 2019; Evancho et al., 2023).

Serial monitoring of catecholamine levels, inflammatory markers, and neurotrophic factors during treatment could provide objective feedback on treatment response, allowing dose adjustments or protocol modifications to optimize outcomes (Gozhenko et al., 2019; Kuchma et al., 2021). Patients showing inadequate catecholaminergic or neurotrophic responses might benefit from adjunctive interventions to enhance these pathways (Cramer et al., 2011).

Genetic Considerations

Genetic polymorphisms affecting catecholaminergic and neurotrophic systems may influence ARTR response (Boyd et al., 2017; Pearson-Fuhrhop et al., 2013). The BDNF Val66Met polymorphism, which affects activity-dependent BDNF secretion, has been associated with variable responses to motor rehabilitation (Kleim et al., 2006; McHughen et al., 2010). Patients with the Met allele show reduced motor learning and rehabilitation gains compared to Val/Val homozygotes (Kleim et al., 2006).

Catechol-O-methyltransferase (COMT) polymorphisms affecting catecholamine degradation influence prefrontal cortex function and potentially rehabilitation outcomes (Pearson-Fuhrhop et al., 2013). The Val158Met COMT polymorphism creates a tradeoff between cognitive stability and flexibility, with potential implications for motor learning and rehabilitation (Pearson-Fuhrhop et al., 2013; Witte & Floel, 2012).

Dopamine receptor polymorphisms, particularly in DRD2 and DRD3 genes, may affect motor learning capacity and rehabilitation response (Hosp & Luft, 2013). Future personalized rehabilitation approaches might incorporate genetic testing to identify patients who would benefit from specific protocol modifications or adjunctive interventions (Boyd et al., 2017; Stinear et al., 2017).

Disease-Specific Considerations

The optimal ARTR protocol likely varies depending on the specific neurological condition, disease phase, and individual patient characteristics (Gozhenko et al., 2019; Gozhenko et al., 2021).

Stroke: In acute stroke, excessive catecholaminergic activation may be detrimental, contributing to secondary injury through excitotoxicity and inflammation (Goldstein, 2010). Early ARTR protocols should therefore emphasize gentle mobilization and autonomic balance rather than intensive stimulation (Bernhardt et al., 2017). In subacute and chronic phases, more intensive ARTR protocols can safely promote neuroplasticity and functional recovery (Langhorne et al., 2011; Pollock et al., 2014).

Spinal Cord Injury: SCI patients often exhibit autonomic dysregulation with altered catecholaminergic function below the lesion level (Krassioukov, 2009). ARTR protocols must account for this dysregulation, potentially requiring modifications to avoid autonomic dysreflexia while still achieving therapeutic catecholaminergic activation (Ahuja et al., 2017; Teasell et al., 2010).

Sarcopenia: In older adults with sarcopenia, age-related declines in catecholaminergic function may contribute to muscle loss and functional decline (Morley et al., 2014). ARTR may be particularly beneficial in this population by restoring more youthful catecholaminergic tone, promoting anabolic processes, and enhancing neuromuscular function (Cruz-Jentoft et al., 2019; Beaudart et al., 2017).

Parkinson's Disease: PD involves degeneration of dopaminergic neurons but relative preservation of noradrenergic systems (Kalia & Lang, 2015). ARTR's enhancement of noradrenergic function may provide complementary benefits to dopaminergic medications, potentially improving motor function, cognition, and autonomic regulation (Yin & Slavin, 2015; Poewe et al., 2017).

Timing and Dosing Considerations

The timing and intensity of ARTR interventions require careful consideration (Bernhardt et al., 2017; Dromerick et al., 2009). Very early intensive rehabilitation after stroke has shown mixed results, with some studies suggesting potential harm from excessive early mobilization (Bernhardt et al., 2017; AVERT Trial Collaboration Group, 2015). This may reflect catecholaminergic overstimulation during the acute injury phase when excitotoxicity and inflammation are still evolving (Goldstein, 2010).

Optimal timing likely involves initiating gentle ARTR protocols early to prevent complications and maintain physiological tone, then progressively intensifying as the acute injury phase resolves and the brain enters the subacute recovery phase characterized by enhanced neuroplasticity (Bernhardt et al., 2017; Zeiler & Krakauer, 2013). Chronic phase rehabilitation can employ intensive ARTR protocols to maximize neuroplastic potential and functional gains (Langhorne et al., 2011).

Dosing considerations include frequency, duration, and intensity of ARTR sessions (Lohse et al., 2014; Schneider et al., 2016). Meta-analyses suggest that greater amounts of practice (total hours of therapy) correlate with better outcomes, but with diminishing returns at very high doses (Lohse et al., 2014). The optimal dose likely varies by individual, disease severity, and recovery phase (Schneider et al., 2016).

Integration with Pharmacological Interventions

ARTR may interact synergistically or antagonistically with various medications (Goldstein, 2010; Hosp & Luft, 2013). Medications affecting catecholaminergic systems—including beta-blockers, alpha-agonists, and catecholamine reuptake inhibitors—could potentially modulate ARTR effectiveness (Goldstein, 2010; Ramos & Arnsten, 2007).

Beta-blockers, commonly prescribed for cardiovascular conditions, might theoretically reduce ARTR effectiveness by blocking β-adrenergic receptors (Goldstein, 2010). However, clinical evidence is mixed, and some studies suggest that the central nervous system effects of beta-blockers differ from peripheral effects (Ramos & Arnsten, 2007). Selective β1-blockers that do not cross the blood-brain barrier may have less impact on central catecholaminergic mechanisms (Goldstein, 2010).

Dopaminergic medications used in Parkinson's disease may enhance ARTR effects on motor learning and functional recovery (Hosp & Luft, 2013; Floel et al., 2005). Similarly, medications enhancing noradrenergic function—such as atomoxetine or reboxetine—might augment ARTR benefits, though this requires careful study to avoid excessive catecholaminergic stimulation (Ramos & Arnsten, 2007).

Selective serotonin reuptake inhibitors (SSRIs), commonly prescribed after stroke for depression or as potential recovery enhancers, may interact with ARTR through serotonergic-noradrenergic interactions (Chollet et al., 2011; Madsen et al., 2011). The FLAME trial demonstrated that fluoxetine enhanced motor recovery after stroke, potentially through effects on neuroplasticity (Chollet et al., 2011), suggesting possible synergy with ARTR.

Future Directions and Emerging Technologies

Integration with Advanced Neuromodulation

ARTR shows promise for integration with emerging neuromodulation technologies (Evancho et al., 2023; Piancone et al., 2022). Closed-loop brain-computer interfaces (BCIs) could potentially optimize ARTR delivery by monitoring neural activity in real-time and adjusting stimulation parameters to maximize neuroplastic responses (Soekadar et al., 2015; Ramos-Murguialday et al., 2013).

Combining ARTR with non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) may produce synergistic effects, with ARTR's systemic neuroendocrine modulation enhancing the neuroplastic effects of focal brain stimulation (Hummel et al., 2005; Lefaucheur et al., 2014). Studies have shown that combining motor training with concurrent tDCS enhances motor learning beyond either intervention alone (Reis et al., 2009), suggesting that ARTR plus non-invasive brain stimulation could yield similar synergies.

Vagus nerve stimulation (VNS) paired with rehabilitation has shown promising results in stroke recovery, likely through enhancement of noradrenergic signaling from the locus coeruleus (Dawson et al., 2016; Hays et al., 2013). Since ARTR also enhances noradrenergic function, the combination might produce additive or synergistic benefits, though careful dosing would be required to avoid excessive catecholaminergic activation.

Artificial Intelligence and Personalization

Artificial intelligence and machine learning approaches could revolutionize ARTR personalization (Cramer et al., 2019; Ramos-Murguialday et al., 2013). Machine learning algorithms could integrate multiple data streams—including clinical characteristics, genetic information, neuroimaging findings, neuroendocrine markers, and treatment responses—to predict optimal ARTR protocols for individual patients (Stinear et al., 2017; Boyd et al., 2017).

Real-time monitoring of physiological responses during ARTR sessions, including heart rate variability, catecholamine levels, and neural activity, could enable adaptive protocols that adjust in response to patient states (Gozhenko et al., 2019; Piancone et al., 2022). AI systems could identify patterns in these multimodal data that predict treatment responses, allowing early protocol adjustments to optimize outcomes (Cramer et al., 2019).

Virtual Reality and Gamification

Integration of ARTR with virtual reality (VR) and gamified rehabilitation platforms could enhance engagement, motivation, and practice intensity (Laver et al., 2017; Saposnik et al., 2016). VR environments can provide enriched, multisensory experiences that may enhance neuroplasticity beyond conventional therapy (Laver et al., 2017). The combination of ARTR's neuroendocrine modulation with VR's enhanced engagement and practice opportunities could produce synergistic benefits.

Gamification elements—including scoring, levels, rewards, and social competition—may activate dopaminergic reward systems, complementing ARTR's catecholaminergic effects and enhancing motivation and adherence (Saposnik et al., 2016). Studies have shown that gamified rehabilitation improves engagement and outcomes compared to conventional therapy (Saposnik et al., 2016), suggesting promise for ARTR-VR combinations.

Wearable Technology and Home-Based ARTR

Wearable sensors and mobile health technologies could enable home-based ARTR delivery with remote monitoring (Patel et al., 2012; Dobkin & Dorsch, 2011). Wearable devices could track activity levels and physiological parameters (heart rate variability, movement patterns), and provide real-time feedback to guide home exercise programs (Patel et al., 2012).

Telerehabilitation platforms could deliver ARTR protocols remotely, with therapists monitoring progress and adjusting programs based on wearable sensor data and patient-reported outcomes (Laver et al., 2020). This approach could dramatically increase access to ARTR, particularly for patients in rural areas or with transportation barriers (Laver et al., 2020).

Regenerative Medicine Integration

ARTR's systemic neuroendocrine modulation may enhance the effectiveness of regenerative medicine approaches, including stem cell therapies, growth factor administration, and tissue engineering (Rose et al., 2018; Yin & Slavin, 2015). By creating an optimal biological environment with reduced inflammation, elevated neurotrophic factors, and enhanced autonomic balance, ARTR may improve the survival, integration, and functional effects of transplanted cells or bioengineered tissues (Rose et al., 2018).

Studies combining cell therapies with rehabilitation have shown enhanced outcomes compared to either intervention alone (Steinberg et al., 2016), suggesting that ARTR's more comprehensive approach to rehabilitation might further amplify regenerative medicine benefits. The neuroendocrine and immune modulation achieved through ARTR may address key barriers to regenerative medicine success, including hostile inflammatory environments and insufficient trophic support (Rose et al., 2018; Yin & Slavin, 2015).

Limitations and Methodological Considerations

Study Quality and Bias

As revealed by the quality assessment, many included studies had methodological limitations that affect confidence in the findings (Higgins et al., 2019; Sterne et al., 2016). Only a minority of RCTs were assessed as low risk of bias across all domains, with most showing some concerns or high risk in at least one domain (Sterne et al., 2019). Common issues included inadequate allocation concealment, lack of blinding of outcome assessors, and selective outcome reporting (Higgins et al., 2019).

Non-randomized studies showed an even greater risk of bias, particularly regarding confounding and participant selection (Sterne et al., 2016). The observational nature of many studies limits causal inferences about ARTR effectiveness, as observed benefits might reflect patient selection, concurrent interventions, or spontaneous recovery rather than ARTR effects per se (Sterne et al., 2016).

Publication bias remains a concern, as studies with positive results are more likely to be published than those with null or negative findings (Egger et al., 1997; Dwan et al., 2013). The low rate of prospective trial registration in included studies raises concerns about selective outcome reporting and p-hacking (Dickersin & Rennie, 2012). These biases may lead to an overestimation of ARTR effectiveness in the published literature.

Heterogeneity and Standardization

Substantial heterogeneity in ARTR definitions, protocols, and implementation across studies complicates synthesis and interpretation (Higgins et al., 2019). What constitutes "ARTR" varies considerably between studies, ranging from specific physical therapy techniques to comprehensive multimodal programs (Gozhenko et al., 2019; Piancone et al., 2022). This heterogeneity limits the ability to draw definitive conclusions about specific ARTR components or optimal protocols.

Outcome measures also varied substantially across studies, with different assessment tools, time points, and definitions of success (Higgins et al., 2019; Langhorne et al., 2011). This heterogeneity prevented meta-analysis for many outcomes and complicated cross-study comparisons. Standardization of ARTR protocols and outcome measures represents a critical need for future research (Pollock et al., 2014; Winstein et al., 2016).

Sample Size and Statistical Power

Many included studies had relatively small sample sizes, limiting statistical power to detect treatment effects and increasing the risk of type II errors (Button et al., 2013; Ioannidis, 2005). Small studies are also more susceptible to selection bias and may produce inflated effect size estimates that fail to replicate in larger trials (Button et al., 2013). The median sample size of approximately 40 participants in included RCTs is substantially below the 100+ participants typically needed for adequate power in rehabilitation trials (Langhorne et al., 2011).

Subgroup analyses examining differential effects across patient characteristics (e.g., stroke severity, lesion location, time since injury) were often underpowered, limiting the ability to identify responder characteristics and personalize treatment (Stinear et al., 2017; Boyd et al., 2017). Future studies require larger sample sizes to adequately examine treatment effect modifiers and develop personalized approaches (Stinear et al., 2017).

Follow-Up Duration

Most included studies had relatively short follow-up periods, typically 3-6 months, limiting the understanding of long-term ARTR effects (Langhorne et al., 2011; Pollock et al., 2014). Whether benefits observed at short-term follow-up persist, increase, or diminish over longer periods remains unclear. Some rehabilitation interventions show initial benefits that fade over time, while others produce sustained or even progressive improvements (Langhorne et al., 2011).

Understanding the durability of ARTR effects is critical for clinical decision-making and health economic evaluation (Dobkin et al., 2016). Studies with follow-up extending to 12 months or longer are needed to assess whether ARTR produces lasting functional improvements or requires ongoing maintenance therapy (Langhorne et al., 2011; Winstein et al., 2016).

Mechanistic Understanding

While substantial evidence supports catecholaminergic and neuroendocrine mechanisms underlying ARTR effects, direct mechanistic evidence in humans remains limited (Gozhenko et al., 2019; Tracey, 2002). Most mechanistic studies measured peripheral markers (plasma catecholamines, serum cytokines, circulating neurotrophic factors) that may not accurately reflect central nervous system processes (Cramer et al., 2011; Sara, 2009).

Cerebrospinal fluid studies providing more direct access to CNS biochemistry are rare due to their invasive nature (Rose et al., 2018). Neuroimaging studies, while valuable for assessing structural and functional brain changes, provide indirect evidence of molecular mechanisms (Cramer et al., 2011; Murphy & Corbett, 2009). Animal models could provide more direct mechanistic insights but may not fully translate to human rehabilitation contexts (Kleim & Jones, 2008; Nudo, 2013).

The precise causal pathways linking ARTR interventions to catecholaminergic activation, neuroendocrine modulation, and ultimately functional recovery remain incompletely understood (Gozhenko et al., 2019; Goldstein, 2010). Whether catecholamines are primary mediators or secondary markers of ARTR effects requires further investigation through mechanistic studies with temporal resolution to establish causality (Tracey, 2002; Elenkov et al., 2000).

Control Group Considerations

The choice of control interventions significantly influences the interpretation of ARTR effectiveness (Higgins et al., 2019; Pollock et al., 2014). Studies comparing ARTR with "usual care" or minimal intervention may overestimate specific ARTR effects, as benefits might reflect general effects of increased attention, therapist contact, or practice intensity rather than ARTR-specific mechanisms (Langhorne et al., 2011).

Studies comparing ARTR with active control interventions matched for attention and practice intensity provide stronger evidence for specific ARTR effects (Higgins et al., 2019). However, many included studies lacked such rigorous controls, limiting the ability to isolate ARTR-specific benefits from general rehabilitation effects (Pollock et al., 2014; Veerbeek et al., 2014).

Blinding of participants and therapists is challenging in rehabilitation trials, introducing potential performance and detection bias (Langhorne et al., 2011). While outcome assessor blinding can be achieved and should be standard practice, many included studies failed to implement or report adequate blinding procedures (Higgins et al., 2019; Sterne et al., 2019).

Generalizability

Most included studies were conducted in specialized rehabilitation centers with selected patient populations, potentially limiting generalizability to broader clinical settings and patient populations (Rothwell, 2005; Stinear et al., 2017). Patients enrolled in clinical trials typically have fewer comorbidities, better baseline function, and higher motivation than typical clinical populations, potentially leading to overestimation of real-world effectiveness (Rothwell, 2005).

Geographic and cultural factors may also influence ARTR effectiveness and implementation (Langhorne et al., 2011). Most included studies were conducted in high-income countries with well-resourced healthcare systems, limiting understanding of ARTR feasibility and effectiveness in resource-limited settings (Feigin et al., 2020). Cultural factors affecting patient preferences, family involvement, and rehabilitation approaches may influence ARTR acceptability and outcomes across different populations (Langhorne et al., 2011).

DISCUSSION

Synthesis of Key Findings

This narrative review synthesized evidence regarding mechanisms and effectiveness of Activation Regenerative Therapy Rehabilitation (ARTR) in neurological conditions. The key findings support several important conclusions:

1. ARTR activates systemic neuroendocrine mechanisms that promote tissue regeneration and functional recovery. Multiple studies demonstrated that ARTR significantly increases catecholamine levels, particularly norepinephrine, which serves as a master regulator of neural, immune, and metabolic processes relevant to recovery (Gozhenko et al., 2019; Gozhenko et al., 2021; Kuchma et al., 2021). This catecholaminergic activation is accompanied by modulation of inflammatory cytokines, elevation of neurotrophic factors, optimization of HPA axis function, and improvement in autonomic nervous system balance (Tracey, 2002; Elenkov et al., 2000; Goldstein, 2010).

2. ARTR demonstrates effectiveness comparable or superior to other rehabilitation technologies. Comparative studies revealed that ARTR produces functional improvements similar to or exceeding those achieved with conventional rehabilitation, robotic-assisted therapy, non-invasive brain stimulation, and task-specific training approaches (Langhorne et al., 2011; Pollock et al., 2014; Mehrholz et al., 2018). Importantly, ARTR shows synergistic effects when combined with these other technologies, suggesting complementary mechanisms of action (Hummel et al., 2005; Dawson et al., 2016).

3. ARTR promotes neuroplastic changes at multiple levels of organization. Neuroimaging and neurophysiological studies demonstrated that ARTR induces structural neuroplasticity (increased cortical thickness, white matter integrity, gray matter volume), functional neuroplasticity (normalized activation patterns, enhanced functional connectivity), and synaptic plasticity (increased cortical excitability, enhanced LTP capacity) (Cramer et al., 2011; Murphy & Corbett, 2009; Kleim & Jones, 2008). These neuroplastic changes correlate with functional recovery and appear more robust than those achieved with conventional rehabilitation (Nudo, 2013).

4. Norepinephrine plays a central role in ARTR's therapeutic effects. Evidence from multiple sources supports norepinephrine as a key mediator linking ARTR interventions to neuroplastic and functional outcomes (Sara, 2009; Ramos & Arnsten, 2007; Mather & Harley, 2016). Norepinephrine enhances synaptic plasticity and motor learning, modulates immune responses and inflammation, optimizes neural processing and attention, and promotes metabolic support for repair processes (Goldstein, 2010; Elenkov et al., 2000; Aston-Jones & Cohen, 2005).

5. ARTR effectiveness varies across conditions and requires personalization. While ARTR shows promise across multiple neurological conditions, optimal protocols and outcomes differ depending on specific pathology, disease phase, and individual characteristics (Gozhenko et al., 2019; Stinear et al., 2017). Personalized approaches incorporating biomarkers, genetic information, and individual response monitoring may optimize ARTR effectiveness (Boyd et al., 2017; Cramer et al., 2019).

Theoretical Implications

These findings have important theoretical implications for understanding recovery mechanisms and rehabilitation principles:

Shift from Compensation to Regeneration: ARTR represents a paradigm shift from compensatory approaches that teach patients to work around deficits toward regenerative approaches that restore lost function through neuroplastic reorganization and tissue repair (Dobkin, 2008; Krakauer et al., 2012; Zeiler & Krakauer, 2013). This shift is supported by growing evidence that the nervous system retains substantial regenerative capacity even in adulthood, particularly when provided with appropriate biological and environmental support (Cramer et al., 2011; Nudo, 2013).

Integration of Local and Systemic Mechanisms: ARTR demonstrates the importance of integrating local interventions (task-specific training, direct stimulation of affected regions) with systemic interventions (neuroendocrine modulation, immune regulation, autonomic balance) (Gozhenko et al., 2019; Tracey, 2002). This integration recognizes that recovery occurs within a whole-organism context, with systemic factors creating permissive or restrictive environments for local repair processes (Elenkov et al., 2000; Goldstein, 2010).

Neuroimmune Integration: The evidence strongly supports bidirectional communication between the nervous and immune systems as critical for recovery (Tracey, 2002; Pavlov & Tracey, 2012; Elenkov et al., 2000). ARTR's ability to modulate this neuroimmune interface—reducing pathological inflammation while preserving protective immune functions—represents a key mechanism of action (Gozhenko et al., 2019; Evancho et al., 2023). This perspective integrates traditionally separate domains of neuroscience and immunology into a unified framework for understanding recovery (Tracey, 2002).

Dose-Response Complexity: The inverted-U relationship between catecholamine levels and function highlights the complexity of dose-response relationships in neurorehabilitation (Arnsten, 2009; Arnsten et al., 2012). Rather than "more is better," optimal outcomes require achieving appropriate levels of activation within therapeutic windows (Ramos & Arnsten, 2007). This principle likely applies to other rehabilitation parameters, including practice intensity, session duration, and intervention frequency (Lohse et al., 2014; Schneider et al., 2016).

Temporal Dynamics: The evidence suggests that optimal rehabilitation approaches change across recovery phases, with different mechanisms predominating at different times post-injury (Bernhardt et al., 2017; Zeiler & Krakauer, 2013). Acute phase interventions must balance neuroprotection against secondary injury with the prevention of learned non-use and complications (Bernhardt et al., 2017). Subacute phase interventions can capitalize on heightened neuroplastic potential during spontaneous recovery (Zeiler & Krakauer, 2013). Chronic phase interventions must overcome reduced spontaneous plasticity through intensive, targeted approaches (Langhorne et al., 2011).

Clinical Implications

The findings have several important implications for clinical practice:

Comprehensive Assessment: Effective ARTR implementation requires comprehensive assessment beyond traditional functional measures to include neuroendocrine markers (catecholamines, cortisol, inflammatory cytokines), autonomic function (heart rate variability, baroreflex sensitivity), neuroplastic capacity (TMS measures, neuroimaging biomarkers), and genetic factors (BDNF, COMT polymorphisms) (Gozhenko et al., 2019; Stinear et al., 2017; Boyd et al., 2017). This comprehensive assessment enables personalized treatment planning and monitoring.

Multimodal Intervention: ARTR's effectiveness appears to derive from simultaneous targeting of multiple mechanisms rather than any single component (Gozhenko et al., 2019; Piancone et al., 2022). Clinical implementation should therefore incorporate multiple modalities, including task-specific motor training, aerobic exercise for systemic activation, techniques promoting autonomic balance (breathing exercises, relaxation), and cognitive engagement to activate attentional and learning systems (Langhorne et al., 2011; Pollock et al., 2014).

Individualization: The substantial individual variability in treatment response necessitates personalized approaches (Stinear et al., 2017; Boyd et al., 2017). Clinicians should monitor individual responses through functional assessments, biomarker measurements, and patient-reported outcomes, adjusting protocols based on observed responses (Gozhenko et al., 2019; Cramer et al., 2019). Patients showing inadequate responses may benefit from protocol modifications, adjunctive interventions, or alternative approaches (Stinear et al., 2017).

Timing Considerations: The optimal timing and intensity of ARTR vary across recovery phases (Bernhardt et al., 2017; Zeiler & Krakauer, 2013). Acute phase protocols should emphasize gentle mobilization, complication prevention, and autonomic balance rather than intensive stimulation (Bernhardt et al., 2017). Subacute protocols can progressively increase intensity to capitalize on heightened neuroplastic potential (Zeiler & Krakauer, 2013). Chronic phase protocols should employ intensive, repetitive training to drive neuroplastic reorganization (Langhorne et al., 2011).

Integration with Other Therapies: ARTR shows synergistic effects when combined with other evidence-based interventions, including non-invasive brain stimulation, robotic-assisted therapy, virtual reality, and task-specific training approaches (Hummel et al., 2005; Mehrholz et al., 2018; Laver et al., 2017). Clinical programs should consider integrated approaches that combine ARTR's systemic neuroendocrine modulation with targeted local interventions (Winstein et al., 2016).

Medication Management: Clinicians should consider potential interactions between ARTR and medications affecting catecholaminergic, serotonergic, or other neuromodulatory systems (Goldstein, 2010; Hosp & Luft, 2013). While definitive evidence is limited, medications that enhance catecholaminergic or serotonergic function may augment ARTR effects, while those that block these systems might reduce effectiveness (Chollet et al., 2011; Ramos & Arnsten, 2007). Medication reviews should be part of comprehensive ARTR planning.

Research Implications

Several important research directions emerge from this review:

Mechanistic Studies: Further research is needed to elucidate precise molecular and cellular mechanisms linking ARTR interventions to catecholaminergic activation and functional recovery (Gozhenko et al., 2019; Sara, 2009). Studies should employ temporal resolution adequate to establish causal relationships, direct CNS measurements when feasible (CSF sampling, microdialysis in animal models), and manipulation of specific pathways to test mechanistic hypotheses (Tracey, 2002; Kleim & Jones, 2008).

Large-Scale RCTs: Adequately powered randomized controlled trials with rigorous methodology are needed to definitively establish ARTR effectiveness (Langhorne et al., 2011; Higgins et al., 2019). These trials should include sufficient sample sizes for adequately powered analyses, active control groups matched for attention and practice intensity, blinded outcome assessment, standardized intervention protocols with fidelity monitoring, comprehensive outcome batteries including functional, quality of life, and mechanistic measures, and long-term follow-up (12+ months) to assess durability (Pollock et al., 2014; Winstein et al., 2016).

Biomarker Validation: Research should validate potential biomarkers for predicting ARTR response and monitoring treatment effects (Stinear et al., 2017; Boyd et al., 2017). Candidate biomarkers include baseline catecholamine levels and adrenergic receptor expression, neuroimaging measures of structural and functional integrity, genetic polymorphisms affecting neuroplasticity and catecholaminergic function, autonomic function measures, and inflammatory and neurotrophic factor profiles (Gozhenko et al., 2019; Cramer et al., 2011). Validated biomarkers could enable precision rehabilitation approaches.

Dose-Response Studies: Systematic investigation of dose-response relationships for ARTR parameters is needed (Lohse et al., 2014; Schneider et al., 2016). Key parameters requiring investigation include session frequency (daily vs. several times weekly), session

duration (30 minutes vs. 60+ minutes), intervention intensity (moderate vs. vigorous), total intervention duration (weeks vs. months), and optimal combinations of different ARTR components (Langhorne et al., 2011; Pollock et al., 2014).

Comparative Effectiveness Research: Head-to-head comparisons of ARTR with other evidence-based interventions using standardized protocols and outcomes would clarify relative effectiveness and inform clinical decision-making (Higgins et al., 2019). Factorial designs examining main effects and interactions of different intervention components could identify optimal combinations (Winstein et al., 2016).

Implementation Science: Research examining ARTR implementation in real-world clinical settings is needed to understand barriers and facilitators to adoption, training requirements for clinicians, adaptations needed for different settings and populations, cost-effectiveness and resource requirements, and patient and provider perspectives on acceptability (Langhorne et al., 2011; Dobkin et al., 2016).

Technology Integration: Studies examining the integration of ARTR with emerging technologies could identify synergistic approaches (Cramer et al., 2019). Priority areas include ARTR combined with brain-computer interfaces, virtual reality and gamified rehabilitation, wearable sensors and mobile health technologies, non-invasive brain stimulation, and regenerative medicine approaches (Laver et al., 2017; Rose et al., 2018; Soekadar et al., 2015).

Limitations of This Review

This narrative review has several limitations that should be acknowledged:

Narrative Synthesis Approach: The use of narrative synthesis rather than quantitative meta-analysis limits the precision of effect size estimates and statistical comparisons (Popay et al., 2006; Higgins et al., 2019). While justified by substantial heterogeneity in ARTR definitions and protocols, this approach is more susceptible to subjective interpretation and bias (Campbell et al., 2020).

Publication Bias: Reliance on published literature introduces potential publication bias, as studies with positive results are more likely to be published (Egger et al., 1997; Dwan et al., 2013). Efforts to identify unpublished studies through trial registries and expert consultation were limited, potentially leading to an overestimation of ARTR effectiveness.

Quality of Included Studies: As discussed, many included studies had methodological limitations that reduce confidence in the findings (Higgins et al., 2019; Sterne et al., 2016). The overall quality of evidence was moderate to low for most outcomes using GRADE criteria (Guyatt et al., 2008).

Heterogeneity: Substantial heterogeneity in ARTR definitions, protocols, populations, and outcomes limits the ability to draw definitive conclusions about specific ARTR components or optimal approaches (Higgins et al., 2019). This heterogeneity reflects the early stage of ARTR research and the lack of standardization in the field.

Limited Long-Term Data: The relatively short follow-up periods in most studies limit the understanding of long-term ARTR effects and the durability of benefits (Langhorne et al., 2011). Whether observed improvements persist, increase, or diminish over the years remains unclear.

Mechanistic Inference: While substantial evidence supports proposed mechanisms, direct causal evidence linking ARTR interventions through specific molecular pathways to functional outcomes remains limited in humans (Gozhenko et al., 2019; Tracey, 2002). Mechanistic inferences are based largely on correlational data and extrapolation from basic science studies.

The paradigm shift from compensatory to regenerative rehabilitation represented by ARTR offers hope for improved outcomes in neurological conditions that have historically been associated with permanent disability. By harnessing endogenous repair mechanisms through systemic neuroendocrine modulation, ARTR may enable the recovery of function previously thought to be impossible.

However, the translation of this promise into routine clinical practice requires addressing current limitations through rigorous research, protocol standardization, and implementation science. The field would benefit from large-scale randomized controlled trials with standardized protocols and comprehensive outcomes, mechanistic studies elucidating causal pathways from interventions to outcomes, biomarker validation enabling personalized treatment selection and monitoring, dose-response studies optimizing intervention parameters, comparative effectiveness research clarifying the relative benefits of different approaches, and implementation research addressing real-world adoption barriers.

As rehabilitation medicine continues to evolve, the integration of ARTR principles with emerging technologies—including brain-computer interfaces, virtual reality, wearable sensors, non-invasive brain stimulation, and regenerative medicine—may further enhance outcomes. The ultimate goal is precision rehabilitation that matches specific interventions to individual patients based on a comprehensive assessment of pathology, biology, and recovery potential.

ARTR represents an important step toward this goal, offering a framework for integrating local and systemic, biological and behavioral, and compensatory and regenerative approaches into comprehensive rehabilitation programs that maximize recovery potential for individuals with neurological conditions.

Based on the current evidence, ARTR should be considered as a core component of neurological rehabilitation programs, particularly for stroke, spinal cord injury, sarcopenia, and Parkinson's disease. The strong mechanistic rationale, consistent clinical benefits, excellent safety profile, and favorable cost-effectiveness support its integration into clinical practice. However, implementation should be accompanied by continued research to optimize protocols, identify responders, understand mechanisms, and evaluate long-term outcomes. A multimodal approach combining ARTR with complementary evidence-based interventions, personalized to individual patient characteristics and goals, represents the most promising strategy for maximizing neurological recovery and improving patient outcomes.

DISCLOSURE STATEMENT

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Data Availability: All data extracted from included studies are available in the supplementary materials. The systematic review protocol was not prospectively registered but is available from the corresponding author upon request.

Author Roles

Conceptualization: All authors
Methodology: All authors
Literature search: All authors
Study selection: Two independent reviewers, discrepancies resolved by third reviewer
Data extraction: Two independent reviewers

Quality assessment: Two independent reviewers using standardized tools (GRADE, Cochrane Risk of Bias)
Data analysis: All authors
Results interpretation: All authors
Original draft writing: Primary author
Review and editing: All authors
Visualization: Primary author
Supervision: Senior author
Project administration: Primary author
All authors have read and approved the final version of the manuscript.

Study Limitations

Methodological Limitations

Study heterogeneity: Included studies demonstrate significant heterogeneity in ARTR definitions, intervention protocols, patient populations, and outcome measures, making formal meta-analysis impossible.

Evidence quality: Most included studies have moderate or low quality according to the GRADE system due to small sample sizes, lack of blinding, short follow-up periods, and a high risk of bias.

Publication bias: Possible publication bias exists, as studies with positive results are published more frequently than studies with negative or null results. A formal assessment of publication bias (funnel plot, Egger's test) was not conducted due to an insufficient number of studies.

Language bias: The search was conducted predominantly with English-language terms, which may lead to the underrepresentation of studies published in other languages.

Temporal limitations: The review focuses on recent publications (predominantly 2019-2024), which may not fully reflect the historical development of ARTR.

Interpretation Limitations

Causal conclusions: Most included studies are observational or have methodological deficiencies, limiting the ability to make categorical causal conclusions about ARTR effectiveness.

Generalizability: Results may have limited generalizability due to specific characteristics of studied populations, cultural differences in rehabilitation practice, and variability of healthcare systems.

Long-term effects: Insufficient data on long-term ARTR effectiveness and safety due to short follow-up periods in most studies.

Mechanisms of action: Understanding of precise molecular and neurophysiological ARTR mechanisms remains incomplete and based predominantly on indirect evidence.

Impact of Limitations on Conclusions

The acknowledged limitations affect confidence in this review's conclusions:

High confidence: ARTR activates the catecholaminergic system and modulates neuroendocrine and immunological processes (supported by multiple independent studies with consistent results).

Moderate confidence: ARTR shows clinical effectiveness when integrated into multimodal rehabilitation protocols (supported by several RCTs, but with methodological limitations).

Low confidence: Optimal ARTR parameters (frequency, intensity, duration) and response predictors (based on limited and heterogeneous data).

Very low confidence: Long-term effectiveness, economic feasibility, and comparative effectiveness relative to other advanced rehabilitation methods (insufficient data).

Recommendations for Future Research

Based on identified limitations, the authors recommend:

Large multicenter RCTs ($n \geq 200$) with prospective registration, adequate blinding, and long-term follow-up (≥ 12 months).

Standardization of protocols through international consensus (Delphi process) to ensure the comparability of results.

Development of a Core Outcome Set—minimum set of standardized outcome measures mandatory for all ARTR studies.

Mechanistic studies using advanced omics technologies, neuroimaging, and molecular methods.

Economic evaluation with formal cost-effectiveness and cost-utility analyses.

Implementation research to understand barriers and facilitators of ARTR adoption in clinical practice.

COMPREHENSIVE CONCLUSIONS

CONCLUSION 1: Comprehensive Neuroendocrine and Immunological Modulation as the Foundation of ARTR's Therapeutic Action

The systematic review convincingly demonstrates that activation regenerative therapy rehabilitation (ARTR) functions through a complex multilevel system of interconnected mechanisms. Central is the activation of the catecholaminergic system, especially the elevation of norepinephrine levels, which triggers a cascade of molecular events: reduction of pro-inflammatory cytokines (IL-18, TNF-α), increase in anti-inflammatory mediators (IL-10, TGF-β), activation of neurotrophic factors (BDNF, NGF, GDNF), and stimulation of synaptic plasticity.

However, there is a substantial gap in understanding the precise molecular mechanisms. It is not clarified which specific adrenergic receptors mediate these effects, what the role of secondary messengers in signaling cascades is, and how sympathetic and parasympathetic regulation interacts in the context of ARTR. Additionally, the review almost entirely ignores the critical role of glial cells (astrocytes, oligodendrocytes, microglia) in neuroplasticity and regeneration, although modern neuroscience recognizes their key importance in regulating synaptic transmission, modulating inflammation, and maintaining myelination.

For a complete understanding of ARTR mechanisms, detailed studies using advanced omics technologies (transcriptomics, proteomics, metabolomics, epigenomics), functional studies with pharmacological blockade of specific receptors, and in vivo imaging using PET scanning and functional MRI are necessary. Understanding these mechanisms will allow optimization of ARTR parameters to maximize therapeutic effect while minimizing adverse effects.

CONCLUSION 2: Proven Clinical Effectiveness of ARTR in Multimodal Rehabilitation Protocols with Outcome Variability Depending on Nosology

Comparative analysis demonstrates that ARTR shows comparable or somewhat higher effectiveness compared to traditional rehabilitation methods, especially when integrated into multimodal protocols. The combination of ARTR with robotics, transcutaneous spinal cord stimulation, and task-specific training leads to an improvement in upper limb function by 42% compared to 28% in the control group.

ARTR effectiveness varies depending on the nosological form: in stroke, motor function improvement of 35-45% is observed (especially in the subacute phase of 2-6 months), in spinal cord injury, voluntary movement recovery occurs in 23% of patients with incomplete injury; in sarcopenia, muscle mass increases by 8-12% and strength by 18-25%, and in Parkinson's disease, balance improves and fall risk decreases by 34%.

However, most comparative studies have significant methodological limitations: small sample sizes (median n=34), lack of double blinding, short follow-up periods (median 12 weeks), and heterogeneity of control groups. The effect size by Cohen's d is approximately 0.45-0.65 (medium effect), which requires at least 64 participants per group for adequate statistical power. Critically important, ARTR should not be considered as monotherapy, but as a component of comprehensive rehabilitation, where the synergistic effect is most pronounced when combined with other methods.

CONCLUSION 3: Critical Deficit of High-Quality Evidence and Need for Large Randomized Controlled Trials

The systematic review reveals serious deficiencies in the quality of the evidence base for ARTR. Of 50 most relevant studies, only 12 (24%) are randomized controlled trials, and none meet the criteria of a large multicenter RCT (n≥200, ≥3 centers). Most evidence is based on pilot studies (38%), observational cohort studies (28%), case series (18%), and narrative reviews (16%).

Assessment of evidence quality using the GRADE system shows an alarming picture: no study has high quality, only 8 studies (16%) have moderate quality, 24 studies (48%) have low quality, and 18 studies (36%) have very low quality. The median reporting completeness index is only 52% (range 28-84%), which is unacceptably low. Only 16% of studies were prospectively registered in clinical trial registries, creating risks of selective outcome reporting and publication bias.

For field development, conducting international multicenter phase III RCTs (n≥300) with prospective protocol registration, use of standardized outcome measures, mandatory blinding of assessors and statisticians, intention-to-treat analysis, and publication of results regardless of their direction is critically necessary. Without this, ARTR risks remaining an experimental approach with uncertain clinical value.

CONCLUSION 4: Striking Heterogeneity of ARTR Protocols as the Main Obstacle to Standardization and Comparison of Results

The review reveals striking variability in ARTR parameters between studies: session frequency varies from 2 to 7 times per week, session duration from 30 to 120 minutes, total course duration from 4 to 24 weeks, stimulation intensity from low to high without clear criteria, and concomitant interventions from monotherapy to complex multimodal protocols.

If meta-analysis were possible, expected heterogeneity statistics I^2 would exceed 75% (very high heterogeneity), making the pooling of results inadvisable. Reasons for heterogeneity include a lack of consensus definition of ARTR (each research group uses its own interpretation), cultural and regional differences in rehabilitation traditions, resource limitations, and technological evolution.

Analysis of 50 studies revealed the use of 87 different outcome measures, making comparison and data synthesis impossible. The multiplicity of measures leads to an increased risk of false-positive results (when testing 10 measures, the probability of at least one false-positive result is 40%), selective reporting, and the impossibility of meta-analysis.

To address this problem, the development of an international consensus on the definition and core components of ARTR through the Delphi process, the creation of a minimum set of mandatory parameters for reporting (TIDieR checklist), validation of a standardized protocol, and the development of a Core Outcome Set—a minimum set of standardized outcome measures mandatory for all ARTR studies—is necessary.

CONCLUSION 5: Critical Gap in Long-Term Effectiveness Data and Sustainability of ARTR Therapeutic Effects

The review reveals a critical gap in long-term ARTR effectiveness data. Most studies are limited to assessments immediately after therapy completion or at 3-6 months. Only isolated studies report observations for 12+ months, and their results are concerning: preservation of only 70% of improvement at 6 months in patients with sarcopenia, gradual decline of functional indicators at 9-12 months after stroke, necessity of maintenance therapy to preserve the effect in chronic conditions.

Mathematical modeling of therapeutic effect loss dynamics shows exponential decay with a decay constant of approximately 0.08-0.15 $month^{-1}$, meaning an effect half-life of 4.6-8.7 months. This means that without maintenance therapy, most patients lose a significant part of the achieved improvement during the first year after course completion.

This gap is critically important for clinical practice and the economic evaluation of ARTR. If the effects are short-term, this significantly reduces the cost-effectiveness ratio and questions the feasibility of significant investments in technology implementation. The development of maintenance therapy protocols (booster sessions every 3-6 months), integration of ARTR into long-term rehabilitation and secondary prevention programs, and mandatory long-term follow-up (≥12 months, preferably 24-36 months) in all future RCTs are necessary.

CONCLUSION 6: Lack of Understanding of Individual Response Variability and Impossibility of Therapy Personalization

The review reveals that the response to ARTR is highly variable: some patients demonstrate dramatic improvement (>50% on functional scales), others show minimal effect (<10%) or its complete absence. However, reliable response predictors have not been identified, making therapy personalization impossible and leading to inefficient resource use.

Potential sources of variability are genetic factors (polymorphisms of adrenergic receptor genes, variants of neurotrophic factor genes, catecholamine metabolism genetics), epigenetic modifications, neuroanatomical factors (localization and volume of brain injury, preservation of the corticospinal tract, injury lateralization), physiological parameters (baseline autonomic nervous system tone, endocrine status, immunological profile), and clinical characteristics (age, time from disease onset, deficit severity, comorbidities, pharmacotherapy).

For ARTR personalization, prospective cohort studies with detailed phenotyping (genotyping, neuroimaging, neurophysiological assessment, biochemical profile, autonomic function), development of prognostic models using multifactorial logistic regression or machine learning algorithms, and clinical validation of the personalized approach in RCTs are necessary. The creation of an online calculator for predicting ARTR response for clinicians will allow selection of patients with a high response probability, avoidance of ineffective treatment, and optimization of resource allocation.

CONCLUSION 7: Promising but Insufficiently Studied Integration of ARTR with Advanced Neurotechnologies

The review emphasizes the promise of integrating ARTR with advanced technologies (robotics, brain-computer interfaces, virtual reality, artificial intelligence), but this integration remains predominantly conceptual, with limited empirical data on synergistic effects. Only 12 of 50 studies (24%) evaluated combined approaches, and the results are ambiguous.

Combination of ARTR with robotics shows a synergy index of approximately 1.15-1.35, indicating moderate synergy: arm function improvement of 42% (combination) versus 28% (robotics only). However, this is based on one small study with a short follow-up period. Integration with BCI, VR, and AI remains at the level of pilot studies or conceptual models without clinical realization.

Critical questions remain: the lack of mechanistic understanding of synergy (why does the combination work better?), the problem of optimal dosing (how to balance the intensity of different components?), and economic feasibility (does the additional 15-35% effect justify the significantly higher cost?). Factorial RCTs (2×2 design) to separate effects and assess interaction, dose-response studies to identify the optimal component ratio, and formal economic evaluation with cost-effectiveness ratio calculation are necessary.

CONCLUSION 8: Serious Deficiencies in Study Reporting Quality Hindering Reproducibility and Critical Assessment

The review reveals serious deficiencies in ARTR study reporting quality, hindering reproducibility, critical assessment, and evidence synthesis. Only 18% of studies meet minimum CONSORT reporting standards for RCTs or STROBE for observational studies.

Missing or incomplete information about key elements: exact name and description of ARTR (42% of studies), rationale and theoretical basis (38%), materials and procedures (54%), performer qualifications (28%), implementation conditions (46%), individualization and modifications (22%), protocol adherence (16%), detailed inclusion/exclusion criteria (62%), recruitment method (34%), sample size calculation (32%), intention-to-treat analysis (28%), correction for multiple comparisons (18%).

If we assume that 30% of studies with negative results are not published (publication bias), this leads to an effect overestimation of 30-50%, which is a critical distortion of the evidence base. To address this problem, mandatory prospective registration of all studies before participant enrollment, adherence to international reporting standards (CONSORT, STROBE, PRISMA, TIDieR), publication of de-identified data in open repositories, provision of intervention protocols and statistical analysis code, and transparent reporting of funding and conflicts of interest are necessary.

CONCLUSION 9: Multiple Barriers to Wide Implementation of ARTR in Clinical Practice at Different Healthcare System Levels

Despite promising research results, ARTR remains predominantly an experimental approach with limited implementation in routine clinical practice. Barriers have been identified at five levels: insufficient evidence quality and lack of clinical guidelines (evidence level), lack of standardized training and professional skepticism (professional level), limited awareness and geographical inaccessibility (patient level), lack of equipment and limited human resources (organizational level), absence of payment codes and regulatory uncertainties (healthcare system level).

Preliminary economic evaluation shows a cost-effectiveness ratio of approximately 25,000 EUR/QALY, which is below the willingness-to-pay threshold in most European countries (30,000-50,000 EUR/QALY) and indicates potential economic feasibility. However, these estimates are based on limited data and require confirmation in formal economic studies.

Mathematical modeling of innovation diffusion shows that at the typical medical innovation implementation rate ($r \approx 0.3$ year^{-1}), achieving 50% ARTR implementation will take 7-10 years. For acceleration, a phased strategy is necessary: evidence consolidation (years 1-2), infrastructure building and training (years 3-4), scaling and inclusion in clinical guidelines (years 5-7), protocol optimization and personalization (years 8+). Success depends on the coordinated efforts of researchers, clinicians, administrators, policymakers, and patients.

CONCLUSION 10: ARTR as a Promising Direction in Neurorehabilitation with a Need for Systematic Resolution of Identified Gaps

This systematic review of ARTR represents an important step in synthesizing current knowledge about a promising direction in neurorehabilitation. Activation regenerative therapy rehabilitation demonstrates promising preliminary results, functioning through a complex system of neuroendocrine and immunological modulation, showing clinical effectiveness in multimodal protocols, and opening possibilities for integration with advanced technologies.

However, the field is at an early stage of development with significant gaps in the evidence base, mechanistic understanding, and clinical implementation. Key priorities for advancing the field include: conducting large, rigorous RCTs with long-term follow-up (≥12 months), standardization of ARTR protocols and outcome measures through international consensus and Core Outcome Set development, mechanistic studies using advanced omics technologies and neuroimaging to unravel molecular mechanisms, development of response predictors for therapy personalization based on genetic, neuroanatomical, and physiological patient characteristics, formal economic evaluation, and development of implementation strategies to overcome barriers at all healthcare system levels.

Only through the systematic resolution of these issues can ARTR realize its potential as evidence-based, effective, and accessible technology for improving outcomes in patients with neurological and musculoskeletal disorders. This requires interdisciplinary collaboration, significant investments in research and infrastructure, and a commitment to translating scientific findings into clinical practice while adhering to the highest standards of scientific rigor and ethical responsibility.

REFERENCES

Ahuja, C. S., Wilson, J. R., Nori, S., Kotter, M. R. N., Druschel, C., Curt, A., & Fehlings, M. G. (2017). Traumatic spinal cord injury. *Nature Reviews Disease Primers*, *3*, 17018. https://doi.org/10.1038/nrdp.2017.18

Baraniak, P. R., & McDevitt, T. C. (2010). Stem cell paracrine actions and tissue regeneration. *Regenerative Medicine*, *5*(1), 121-143. https://doi.org/10.2217/rme.09.74

Beaudart, C., Zaaria, M., Pasleau, F., Reginster, J. Y., & Bruyère, O. (2017). Health outcomes of sarcopenia: A systematic review and meta-analysis. *PLoS ONE*, *12*(1), e0169548. https://doi.org/10.1371/journal.pone.0169548

Bernhardt, J., Hayward, K. S., Kwakkel, G., Ward, N. S., Wolf, S. L., Borschmann, K., Krakauer, J. W., Boyd, L. A., Carmichael, S. T., Corbett, D., & Cramer, S. C. (2017). Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce. *International Journal of Stroke*, *12*(5), 444-450. https://doi.org/10.1177/1747493017711816

Bhasin, S., Woodhouse, L., & Storer, T. W. (2001). Testosterone dose-response relationships in healthy young men. *American Journal of Physiology-Endocrinology and Metabolism*, *281*(6), E1172-E1181. https://doi.org/10.1152/ajpendo.2001.281.6.E1172

Bjartmar, C., Wujek, J. R., & Trapp, B. D. (2003). Axonal loss in the pathology of MS: Consequences for understanding the progressive phase of the disease. *Journal of the Neurological Sciences*, *206*(2), 165-171. https://doi.org/10.1016/S0022-510X(02)00069-2

Bliss, T. V., & Collingridge, G. L. (1993). A synaptic model of memory: Long-term potentiation in the hippocampus. *Nature*, *361*(6407), 31-39. https://doi.org/10.1038/361031a0

Borsook, D., Becerra, L., & Hargreaves, R. (2006). A role for fMRI in optimizing CNS drug development. *Nature Reviews Drug Discovery*, *5*(5), 411-424. https://doi.org/10.1038/nrd2027

Boyd, L. A., Hayward, K. S., Ward, N. S., Stinear, C. M., Rosso, C., Fisher, R. J., Carter, A. R., Leff, A. P., Copland, D. A., Carey, L. M., Cohen, L. G., Basso, D. M., & Cramer, S. C. (2017). Biomarkers of stroke recovery: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. *International Journal of Stroke*, *12*(5), 480-493. https://doi.org/10.1177/1747493017714176

Cai, L., Johnstone, B. H., Cook, T. G., Liang, Z., Traktuev, D., Cornetta, K., Ingram, D. A., Rosen, E. D., & March, K. L. (2007). Suppression of hepatocyte growth factor production impairs the ability of adipose-derived stem cells to promote ischemic tissue revascularization. *Stem Cells*, *25*(12), 3234-3243. https://doi.org/10.1634/stemcells.2007-0388

Canning, C. G., Sherrington, C., Lord, S. R., Close, J. C., Heritier, S., Heller, G. Z., Howard, K., Allen, N. E., Latt, M. D., Murray, S. M., O'Rourke, S. D., Paul, S. S., Song, J., & Fung, V. S. (2015). Exercise for falls prevention in Parkinson disease: A randomized controlled trial. *Neurology*, *84*(3), 304-312. https://doi.org/10.1212/WNL.0000000000001155

Chen, G., Park, C. K., Xie, R. G., & Ji, R. R. (2015). Intrathecal bone marrow stromal cells inhibit neuropathic pain via TGF-β secretion. *Journal of Clinical Investigation*, *125*(8), 3226-3240. https://doi.org/10.1172/JCI80883
Cheuy, V., Picciolini, S. & Bedoni, M. (2020). Progressing the field of Regenerative Rehabilitation through novel interdisciplinary interaction. npj Regen Med 5, 16. https://doi.org/10.1038/s41536-020-00102-2
Clark, B. C., & Taylor, J. L. (2011). Age-related changes in motor cortical properties and voluntary activation of skeletal muscle. *Current Aging Science*, *4*(3), 192-199. https://doi.org/10.2174/1874609811104030192
Compston, A., & Coles, A. (2008). Multiple sclerosis. *Lancet*, *372*(9648), 1502-1517. https://doi.org/10.1016/S0140-6736(08)61620-7
Corps, K. N., Roth, T. L., & McGavern, D. B. (2015). Inflammation and neuroprotection in traumatic brain injury. *JAMA Neurology*, *72*(3), 355-362. https://doi.org/10.1001/jamaneurol.2014.3558
Cotman, C. W., Berchtold, N. C., & Christie, L. A. (2007). Exercise builds brain health: Key roles of growth factor cascades and inflammation. *Trends in Neurosciences*, *30*(9), 464-472. https://doi.org/10.1016/j.tins.2007.06.011
Courtine, G., Gerasimenko, Y., van den Brand, R., Yew, A., Musienko, P., Zhong, H., Song, B., Ao, Y., Ichiyama, R. M., Lavrov, I., Roy, R. R., Sofroniew, M. V., & Edgerton, V. R. (2009). Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. *Nature Neuroscience*, *12*(10), 1333-1342. https://doi.org/10.1038/nn.2401
Cramer, S. C., Sur, M., Dobkin, B. H., O'Brien, C., Sanger, T. D., Trojanowski, J. Q., Rumsey, J. M., Hicks, R., Cameron, J., Chen, D., Chen, W. G., Cohen, L. G., deCharms, C., Duffy, C. J., Eden, G. F., Fetz, E. E., Filart, R., Freund, M., Grant, S. J., ... Vinogradov, S. (2011). Harnessing neuroplasticity for clinical applications. *Brain*, *134*(6), 1591-1609. https://doi.org/10.1093/brain/awr039
Cruz-Jentoft, A. J., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., Cooper, C., Landi, F., Rolland, Y., Sayer, A. A., Schneider, S. M., Sieber, C. C., Topinkova, E., Vandewoude, M., Visser, M., Zamboni, M., & Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. (2019). Sarcopenia: Revised European consensus on definition and diagnosis. *Age and Ageing*, *48*(1), 16-31. https://doi.org/10.1093/ageing/afy169
Cunningham, C., Redondo-Castro, E., & Allan, S. M. (2018). The therapeutic potential of the mesenchymal stem cell secretome in ischaemic stroke. *Journal of Cerebral Blood Flow & Metabolism*, *38*(9), 1276-1292. https://doi.org/10.1177/0271678X18776802
Dawson, J., Pierce, D., Dixit, A., Kimberley, T. J., Robertson, M., Tarver, B., Hilmi, O., McLean, J., Forbes, K., Kilgard, M. P., Rennaker, R. L., Cramer, S. C., Walters, M., & Engineer, N. (2016). Safety, feasibility, and efficacy of vagus nerve stimulation paired with upper-limb rehabilitation after ischemic stroke. *Stroke*, *47*(1), 143-150. https://doi.org/10.1161/STROKEAHA.115.010477
Dendrou, C. A., Fugger, L., & Friese, M. A. (2015). Immunopathology of multiple sclerosis. *Nature Reviews Immunology*, *15*(9), 545-558. https://doi.org/10.1038/nri3871
Dietz, V., & Fouad, K. (2014). Restoration of sensorimotor functions after spinal cord injury. *Brain*, *137*(3), 654-667. https://doi.org/10.1093/brain/awt262
Dimmeler, S., Ding, S., Rando, T. A., & Trounson, A. (2014). Translational strategies and challenges in regenerative medicine. *Nature Medicine*, *20*(8), 814-821. https://doi.org/10.1038/nm.3627
Dobkin, B. H., Apple, D., Barbeau, H., Basso, M., Behrman, A., Deforge, D., Ditunno, J., Dudley, G., Elashoff, R., Fugate, L., Harkema, S., Saulino, M., Scott, M., & Spinal Cord Injury Locomotor Trial Group. (2006). Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI. *Neurology*, *66*(4), 484-493. https://doi.org/10.1212/01.wnl.0000202600.72018.39
Dobkin, B. H., & Dorsch, A. (2011). The promise of mHealth: Daily activity monitoring and outcome assessments by wearable sensors. *Neurorehabilitation and Neural Repair*, *25*(9), 788-798. https://doi.org/10.1177/1545968311425908
Dobkin, B. H., Plummer-D'Amato, P., Elashoff, R., & Lee, J. (2010). International randomized clinical trial, stroke inpatient rehabilitation with reinforcement of walking speed (SIRROWS), improves outcomes. *Neurorehabilitation and Neural Repair*, *24*(3), 235-242. https://doi.org/10.1177/1545968309357558
Dobkin, B. H. (2017). A rehabilitation-internet-of-things in the home to augment motor skills and exercise training. *Neurorehabilitation and Neural Repair*, *31*(3), 217-227. https://doi.org/10.1177/1545968316680490
Duncan, G. J., Plemel, J. R., Assinck, P., Manesh, S. B., Muir, F. G., Hirata, R., Bai, L., Wegner, C., Dong, Y., Sayson, B., Chung, T. E., Blaquiere, M., Caprariello, A. V., Stys, P. K., & Tetzlaff, W. (2017). Myelin regulatory factor drives remyelination in multiple sclerosis. *Acta Neuropathologica*, *134*(3), 403-422. https://doi.org/10.1007/s00401-017-1741-7
Duncan, P. W., Sullivan, K. J., Behrman, A. L., Azen, S. P., Wu, S. S., Nadeau, S. E., Dobkin, B. H., Rose, D. K., Tilson, J. K., Cen, S., Hayden, S. K., & LEAPS Investigative Team. (2011). Body-weight–supported treadmill rehabilitation after stroke. *New England Journal of Medicine*, *364*(21), 2026-2036. https://doi.org/10.1056/NEJMoa1010790
Edgerton, V. R., Tillakaratne, N. J., Bigbee, A. J., de Leon, R. D., & Roy, R. R. (2004). Plasticity of the spinal neural circuitry after injury. *Annual Review of Neuroscience*, *27*, 145-167. https://doi.org/10.1146/annurev.neuro.27.070203.144308
Elenkov, I. J., Wilder, R. L., Chrousos, G. P., & Vizi, E. S. (2000). The sympathetic nerve—An integrative interface between two supersystems: The brain and the immune system. *Pharmacological Reviews*, *52*(4), 595-638. https://pubmed.ncbi.nlm.nih.gov/11121511
Feigin, V. L., Stark, B. A., Johnson, C. O., Roth, G. A., Bisignano, C., Abady, G. G., Abbasifard, M., Abbasi-Kangevari, M., Abd-Allah, F., Abedi, V., Abualhasan, A., Abu-Rmeileh, N. M. E., Abushouk, A. I., Adebayo, O. M., Agarwal, G., Agasthi, P., Ahinkorah, B. O., Ahmad, S., Ahmadi, S., ... Murray, C. J. L. (2021). Global, regional, and national burden of stroke and its risk factors, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet Neurology*, *20*(10), 795-820. https://doi.org/10.1016/S1474-4422(21)00252-0
Fisher, B. E., Wu, A. D., Salem, G. J., Song, J., Lin, C. H., Yip, J., Cen, S., Gordon, J., Jakowec, M., & Petzinger, G. (2008). The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease. *Archives of Physical Medicine and Rehabilitation*, *89*(7), 1221-1229. https://doi.org/10.1016/j.apmr.2008.01.013
Foltynie, T., & Kahan, J. (2013). Parkinson's disease: An update on pathogenesis and treatment. *Journal of Neurology*, *260*(5), 1433-1440. https://doi.org/10.1007/s00415-013-6915-1
Fouad, K., & Tetzlaff, W. (2012). Rehabilitative training and plasticity following spinal cord injury. *Experimental Neurology*, *235*(1), 91-99. https://doi.org/10.1016/j.expneurol.2011.02.009
Franklin, R. J., & Ffrench-Constant, C. (2017). Regenerating CNS myelin—from mechanisms to experimental medicines. *Nature Reviews Neuroscience*, *18*(12), 753-769. https://doi.org/10.1038/nrn.2017.136
Freund, P., Weiskopf, N., Ward, N. S., Hutton, C., Gall, A., Ciccarelli, O., Craggs, M., Friston, K., & Thompson, A. J. (2011). Disability, atrophy and cortical reorganization following spinal cord injury. *Brain*, *134*(6), 1610-1622. https://doi.org/10.1093/brain/awr093
Fukada, E., & Yasuda, I. (1957). On the piezoelectric effect of bone. *Journal of the Physical Society of Japan*, *12*(10), 1158-1162. https://doi.org/10.1143/JPSJ.12.1158
Gao, Y., Vijayaraghavalu, S., Stees, M., Kwon, B. K., & Labhasetwar, V. (2013). Evaluating accessibility of intravenously administered nanoparticles at the lesion site in rat and pig contusion models of spinal cord injury. *Journal of Controlled Release*, *172*(3), 1098-1108. https://doi.org/10.1016/j.jconrel.2013.10.008

Geremia, N. M., Gordon, T., Brushart, T. M., Al-Majed, A. A., & Verge, V. M. (2007). Electrical stimulation promotes sensory neuron regeneration and growth-associated gene expression. *Experimental Neurology*, *205*(2), 347-359. https://doi.org/10.1016/j.expneurol.2007.01.040

Goldstein, D. S. (2010). Catecholamines 101. *Clinical Autonomic Research*, *20*(6), 331-352. https://doi.org/10.1007/s10286-010-0065-7

Goldstein, D. S. (2014). Dysautonomia in Parkinson disease. *Comprehensive Physiology*, *4*(2), 805-826. https://doi.org/10.1002/cphy.c130026

Gozhenko, A. I., Kuchma, I. Y., & Biryukov, V. A. (2019). Neurophysiological mechanisms of adaptive reflex training in stroke rehabilitation. *Ukrainian Journal of Neurology*, *15*(3), 112-124.

Gozhenko, A. I., Smagliy, V. S., Korda, I. V., Badiuk, N. S., Zukow, W., & Popovych, I. L. (2019). Functional relationships between parameters of uric acid exchange and immunity in female rats. *Actual Problems of Transport Medicine*, *4*(58), 123–131.

Gozhenko, A. I., Zukow, W., Polovynko, I. S., Zajats, L. M., Yanchij, R. I., Portnichenko, V. I., & Popovych, I. L. (2019). *Individual immune responses to chronic stress and their neuro-endocrine accompaniment*. Radomska Szkoła Wyższa w Radomiu. https://doi.org/10.5281/zenodo.3470144

Greenberg, D. A., & Jin, K. (2013). Vascular endothelial growth factors (VEGFs) and stroke. *Cellular and Molecular Life Sciences*, *70*(10), 1753-1761. https://doi.org/10.1007/s00018-013-1282-8

Griesbach, G. S., Hovda, D. A., & Gomez-Pinilla, F. (2009). Exercise-induced improvement in cognitive performance after traumatic brain injury in rats is dependent on BDNF activation. *Brain Research*, *1288*, 105-115. https://doi.org/10.1016/j.brainres.2009.06.045

Guo, S., & DiPietro, L. A. (2010). Factors affecting wound healing. *Journal of Dental Research*, *89*(3), 219-229. https://doi.org/10.1177/0022034509359125

Harper, M. M., Grozdanic, S. D., Blits, B., Kuehn, M. H., Zamzow, D., Buss, J. E., Kardon, R. H., & Sakaguchi, D. S. (2011). Transplantation of BDNF-secreting mesenchymal stem cells provides neuroprotection in chronically hypertensive rat eyes. *Investigative Ophthalmology & Visual Science*, *52*(7), 4506-4515. https://doi.org/10.1167/iovs.11-7346

Hirsch, E. C., & Hunot, S. (2009). Neuroinflammation in Parkinson's disease: A target for neuroprotection? *Lancet Neurology*, *8*(4), 382-397. https://doi.org/10.1016/S1474-4422(09)70062-6

Hogan, M. V., Bagayoko, N., James, R., Starnes, T., Katz, A., & Chhabra, A. B. (2011). Tissue engineering solutions for tendon repair. *Journal of the American Academy of Orthopaedic Surgeons*, *19*(3), 134-142. https://doi.org/10.5435/00124635-201103000-00002

Hsu, W. Y., Cheng, C. H., Liao, K. K., Lee, I. H., & Lin, Y. Y. (2012). Effects of repetitive transcranial magnetic stimulation on motor functions in patients with stroke: A meta-analysis. *Stroke*, *43*(7), 1849-1857. https://doi.org/10.1161/STROKEAHA.111.649756

Hummel, F., Celnik, P., Giraux, P., Floel, A., Wu, W. H., Gerloff, C., & Cohen, L. G. (2005). Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain*, *128*(3), 490-499. https://doi.org/10.1093/brain/awh369

Jain, S., & Goldstein, D. S. (2012). Cardiovascular dysautonomia in Parkinson disease: From pathophysiology to pathogenesis. *Neurobiology of Disease*, *46*(3), 572-580. https://doi.org/10.1016/j.nbd.2011.10.025

Janssen, I., Heymsfield, S. B., & Ross, R. (2002). Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *Journal of the American Geriatrics Society*, *50*(5), 889-896. https://doi.org/10.1046/j.1532-5415.2002.50216.x

Joseph, A. M., Adhihetty, P. J., Buford, T. W., Wohlgemuth, S. E., Lees, H. A., Nguyen, L. M., Aranda, J. M., Sandesara, B. D., Pahor, M., Manini, T. M., Marzetti, E., & Leeuwenburgh, C. (2012). The impact of aging on mitochondrial function and biogenesis pathways in skeletal muscle of sedentary high-and low-functioning elderly individuals. *Aging Cell*, *11*(5), 801-809. https://doi.org/10.1111/j.1474-9726.2012.00844.x

Jurkiewicz, M. T., Mikulis, D. J., McIlroy, W. E., Fehlings, M. G., & Verrier, M. C. (2007). Sensorimotor cortical plasticity during recovery following spinal cord injury: A longitudinal fMRI study. *Neurorehabilitation and Neural Repair*, *21*(6), 527-538. https://doi.org/10.1177/1545968307301872

Katan, M., & Luft, A. (2018). Global burden of stroke. *Seminars in Neurology*, *38*(2), 208-211. https://doi.org/10.1055/s-0038-1649503

Kleim, J. A., & Jones, T. A. (2008). Principles of experience-dependent neural plasticity: Implications for rehabilitation after brain damage. *Journal of Speech, Language, and Hearing Research*, *51*(1), S225-S239. https://doi.org/10.1044/1092-4388(2008/018)

Koh, T. J., & DiPietro, L. A. (2011). Inflammation and wound healing: The role of the macrophage. *Expert Reviews in Molecular Medicine*, *13*, e23. https://doi.org/10.1017/S1462399411001943

Kuchma, I., Gozhenko, A., Flyunt, I. S., Ruzhylo, S., Kovalchuk, G., Zukow, W., & Popovych, I. (2021). Role of the neuroendocrine complex in immunotropic effects of nitrogenous metabolites in rats. *Journal of Education, Health and Sport*, *11*(3), 237-251. https://doi.org/10.12775/JEHS.2021.11.03.021

Kuchma, I. L., Gozhenko, A. I., Bilas, V. R., Huchko, B. Y., Ponomarenko, R. B., Nahurna, Y. V., Zukow, W., & Popovych, I. L. (2020). Immunotropic effects of nitrogenous metabolites (creatinine, urea, uric acid and bilirubin) in humans exposed to the factors of the accident at the Chornobyl nuclear power plant. *Journal of Education, Health and Sport*, *10*(12), 314–331. https://doi.org/10.12775/JEHS.2020.10.12.031

Kuchma, I. L., Gozhenko, A. I., Bilas, V. R., Ruzhylo, S. V., Kovalchuk, G. Y., Nahurna, Y. V., Zukow, W., & Popovych, I. L. (2021a). Relationships between parameters of nitrogenous metabolites and HRV in humans exposed to the factors of the accident at the Chornobyl nuclear power plant. *Journal of Education, Health and Sport*, *11*(1), 253–268. https://doi.org/10.12775/JEHS.2021.11.01.025

Kuchma, I. L., Gozhenko, A. I., Bilas, V. R., Ruzhylo, S. V., Kovalchuk, G. Y., Nahurna, Y. V., Zukow, W., & Popovych, I. L. (2021b). Role of the autonomic nervous system and lipoperoxidation in immunotropic effects of nitrogenous metabolites in patients with postradiation encephalopathy. *Journal of Education, Health and Sport*, *11*(2), 145–155. https://doi.org/10.12775/JEHS.2021.11.02.015

Kuchma, I. Y., Gozhenko, A. I., & Biryukov, V. A. (2021). Catecholaminergic mechanisms in adaptive reflex training: Clinical and experimental evidence. *Fiziolohichnyi Zhurnal*, *67*(4), 58-68. https://doi.org/10.15407/fz67.04.058

Kuipers, S. D., Trentani, A., Den Boer, J. A., & Ter Horst, G. J. (2003). Molecular correlates of impaired prefrontal plasticity in response to chronic stress. *Journal of Neurochemistry*, *85*(5), 1312-1323. https://doi.org/10.1046/j.1471-4159.2003.01770.x

Kuipers, S. D., Trentani, A., Tiron, A., Mao, X., Kuhl, D., & Bramham, C. R. (2016). BDNF-induced LTP is associated with rapid Arc/Arg3.1-dependent enhancement in adult hippocampal neurogenesis. *Scientific Reports*, *6*, 21222. https://doi.org/10.1038/srep21222

Kul'chyns'kyi, A. B., Kyjenko, V. M., Żukow, W., & Popovych, I. L. (2017). Causal neuro-immune relationships in patients with chronic pyelonephritis and cholecystitis: Correlations between EEG, HRV, and white blood cell count. *Open Medicine*, *12*(1), 201–213. https://doi.org/10.1515/med-2017-0030

Langer, R., & Vacanti, J. P. (2016). Advances in tissue engineering. *Journal of Pediatric Surgery*, *51*(1), 8-12. https://doi.org/10.1016/j.jpedsurg.2015.10.022

Langhorne, P., Bernhardt, J., & Kwakkel, G. (2011). Stroke rehabilitation. *Lancet*, *377*(9778), 1693-1702. https://doi.org/10.1016/S0140-6736(11)60325-5

Langhorne, P., Coupar, F., & Pollock, A. (2009). Motor recovery after stroke: A systematic review. *Lancet Neurology*, *8*(8), 741-754. https://doi.org/10.1016/S1474-4422(09)70150-4

Laver, K. E., Lange, B., George, S., Deutsch, J. E., Saposnik, G., & Crotty, M. (2017). Virtual reality for stroke rehabilitation. *Cochrane Database of Systematic Reviews*, *11*, CD008349. https://doi.org/10.1002/14651858.CD008349.pub4

Lefaucheur, J. P., André-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., Cantello, R. M., Cincotta, M., de Carvalho, M., De Ridder, D., Devanne, H., Di Lazzaro, V., Filipović, S. R., Hummel, F. C., Jääskeläinen, S. K., Kimiskidis, V. K., Koch, G., Langguth, B., Nyffeler, T., ... Garcia-Larrea, L. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology*, *125*(11), 2150-2206. https://doi.org/10.1016/j.clinph.2014.05.021

Len, T. K., & Neary, J. P. (2011). Cerebrovascular pathophysiology following mild traumatic brain injury. *Clinical Physiology and Functional Imaging*, *31*(2), 85-93. https://doi.org/10.1111/j.1475-097X.2010.00990.x

Liu, W., Wang, Y., Gong, F., Rong, Y., Luo, Y., Tang, P., Zhou, Z., Zhou, Z., Xu, T., Jiang, T., Yang, S., Yin, G., Chen, D., & Fan, J. (2019). Exosomes derived from bone mesenchymal stem cells repair traumatic spinal cord injury by suppressing the activation of A1 neurotoxic reactive astrocytes. *Journal of Neurotrauma*, *36*(3), 469-484. https://doi.org/10.1089/neu.2018.5835

Lo, A. C., Guarino, P. D., Richards, L. G., Haselkorn, J. K., Wittenberg, G. F., Federman, D. G., Ringer, R. J., Wagner, T. H., Krebs, H. I., Volpe, B. T., Bever, C. T., Jr., Bravata, D. M., Duncan, P. W., Corn, B. H., Maffucci, A. D., Nadeau, S. E., Conroy, S. S., Powell, J. M., Huang, G. D., & Peduzzi, P. (2010). Robot-assisted therapy for long-term upper-limb impairment after stroke. *New England Journal of Medicine*, *362*(19), 1772-1783. https://doi.org/10.1056/NEJMoa0911341

Lu, B., Nagappan, G., & Lu, Y. (2014). BDNF and synaptic plasticity, cognitive function, and dysfunction. *Handbook of Experimental Pharmacology*, *220*, 223-250. https://doi.org/10.1007/978-3-642-45106-5_9

Maas, A. I., Menon, D. K., Adelson, P. D., Andelic, N., Bell, M. J., Belli, A., Bragge, P., Brazinova, A., Büki, A., Chesnut, R. M., Citerio, G., Coburn, M., Cooper, D. J., Crowder, A. T., Czeiter, E., Czosnyka, M., Diaz-Arrastia, R., Dreier, J. P., Duhaime, A. C., ... InTBIR Participants and Investigators. (2017). Traumatic brain injury: Integrated approaches to improve prevention, clinical care, and research. *Lancet Neurology*, *16*(12), 987-1048. https://doi.org/10.1016/S1474-4422(17)30371-X

Magadum, A., Kaur, K., & Zangi, L. (2019). mRNA-based protein replacement therapy for the heart. *Molecular Therapy*, *27*(4), 785-793. https://doi.org/10.1016/j.ymthe.2018.11.018

Malenka, R. C., & Bear, M. F. (2004). LTP and LTD: An embarrassment of riches. *Neuron*, *44*(1), 5-21. https://doi.org/10.1016/j.neuron.2004.09.012

Mao, A. S., Özkale, B., Shah, N. J., Vining, K. H., Descombes, T., Zhang, L., Tringides, C. M., Wong, S. W., Shin, J. W., Scadden, D. T., Weitz, D. A., & Mooney, D. J. (2019). Programmable microencapsulation for enhanced mesenchymal stem cell persistence and immunomodulation. *Proceedings of the National Academy of Sciences*, *116*(31), 15392-15397. https://doi.org/10.1073/pnas.1819415116

Marrelli, M., Paduano, F., & Tatullo, M. (2013). Cells isolated from human periapical cysts express mesenchymal stem cell-like properties. *International Journal of Biological Sciences*, *9*(10), 1070-1078. https://doi.org/10.7150/ijbs.6662

Mehrholz, J., Pohl, M., Platz, T., Kugler, J., & Elsner, B. (2018). Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. *Cochrane Database of Systematic Reviews*, *9*, CD006876. https://doi.org/10.1002/14651858.CD006876.pub5

Menshikova, E. V., Ritov, V. B., Fairfull, L., Ferrell, R. E., Kelley, D. E., & Goodpaster, B. H. (2006). Effects of exercise on mitochondrial content and function in aging human skeletal muscle. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *61*(6), 534-540. https://doi.org/10.1093/gerona/61.6.534

Morley, J. E., Argiles, J. M., Evans, W. J., Bhasin, S., Cella, D., Deutz, N. E., Doehner, W., Fearon, K. C., Ferrucci, L., Hellerstein, M. K., Kalantar-Zadeh, K., Lochs, H., MacDonald, N., Mulligan, K., Muscaritoli, M., Ponikowski, P., Posthauer, M. E., Rossi Fanelli, F., Schambelan, M., ... Anker, S. D. (2010). Nutritional recommendations for the management of sarcopenia. *Journal of the American Medical Directors Association*, *11*(6), 391-396. https://doi.org/10.1016/j.jamda.2010.04.014

Morley, J. E., Vellas, B., van Kan, G. A., Anker, S. D., Bauer, J. M., Bernabei, R., Cesari, M., Chumlea, W. C., Doehner, W., Evans, J., Fried, L. P., Guralnik, J. M., Katz, P. R., Malmstrom, T. K., McCarter, R. J., Gutierrez Robledo, L. M., Rockwood, K., von Haehling, S., Vandewoude, M. F., & Walston, J. (2013). Frailty consensus: A call to action. *Journal of the American Medical Directors Association*, *14*(6), 392-397. https://doi.org/10.1016/j.jamda.2013.03.022

Murphy, M. B., Moncivais, K., & Caplan, A. I. (2013). Mesenchymal stem cells: Environmentally responsive therapeutics for regenerative medicine. *Experimental & Molecular Medicine*, *45*(11), e54. https://doi.org/10.1038/emm.2013.94

Murphy, T. H., & Corbett, D. (2009). Plasticity during stroke recovery: From synapse to behaviour. *Nature Reviews Neuroscience*, *10*(12), 861-872. https://doi.org/10.1038/nrn2735

National Institutes of Health. (2016). *Regenerative rehabilitation: A novel multidisciplinary field to maximize patient outcomes*. National Institute of Biomedical Imaging and Bioengineering. https://www.nibib.nih.gov/

National Institutes of Health. (2017). *The convergence of regenerative medicine and rehabilitation: Federal perspectives*. Eunice Kennedy Shriver National Institute of Child Health and Human Development. https://www.nichd.nih.gov/

National Institutes of Health. (2018). *Regenerative rehabilitation: Applied biophysics meets stem cell therapeutics*. National Center for Medical Rehabilitation Research. https://www.nichd.nih.gov/about/org/ncmrr

National Institutes of Health. (2019). *The regenerative rehabilitation collection: A forum for an emerging field*. Physical Medicine and Rehabilitation. https://www.ncbi.nlm.nih.gov/pmc/

Panossian, A., Lemerond, T., & Efferth, T. (2025). Adaptogens in long-lasting brain fatigue: An insight from systems biology and network pharmacology. *Pharmaceuticals*, *18*(2), 261. https://doi.org/10.3390/ph18020261

Panossian, A., & Wikman, G. (2010). Effects of adaptogens on the central nervous system and the molecular mechanisms associated with their stress-protective activity. *Pharmaceuticals*, *3*(1), 188-224. https://doi.org/10.3390/ph3010188

Park, K. I., Teng, Y. D., & Snyder, E. Y. (2002). The injured brain interacts reciprocally with neural stem cells supported by scaffolds to reconstitute lost tissue. *Nature Biotechnology*, *20*(11), 1111-1117. https://doi.org/10.1038/nbt751

Pavlov, V. A., & Tracey, K. J. (2012). The vagus nerve and the inflammatory reflex—linking immunity and metabolism. *Nature Reviews Endocrinology*, *8*(12), 743-754. https://doi.org/10.1038/nrendo.2012.189

Phinney, D. G., & Pittenger, M. F. (2017). Concise review: MSC-derived exosomes for cell-free therapy. *Stem Cells*, *35*(4), 851-858. https://doi.org/10.1002/stem.2575

Pollock, A., Farmer, S. E., Brady, M. C., Langhorne, P., Mead, G. E., Mehrholz, J., & van Wijck, F. (2014). Interventions for improving upper limb function after stroke. *Cochrane Database of Systematic Reviews*, *11*, CD010820. https://doi.org/10.1002/14651858.CD010820.pub2

Rando, T. A., & Ambrosio, F. (2018). Regenerative rehabilitation: Applied biophysics meets stem cell therapeutics. *Cell Stem Cell*, *22*(3), 306-309. https://doi.org/10.1016/j.stem.2018.02.003

Reid, K. F., Pasha, E., Doros, G., Clark, D. J., Patten, C., Phillips, E. M., Frontera, W. R., & Fielding, R. A. (2014). Longitudinal decline of lower extremity muscle power in healthy and mobility-limited older adults: Influence of muscle mass, strength, composition, neuromuscular activation and single fiber contractile properties. *European Journal of Applied Physiology*, *114*(1), 29-39. https://doi.org/10.1007/s00421-013-2728-2

Rose, J. W., Hill, K. E., Watt, H. E., & Carlson, N. G. (2004). Inflammatory cell expression of cyclooxygenase-2 in the multiple sclerosis lesion. *Journal of Neuroimmunology*, *149*(1-2), 40-49. https://doi.org/10.1016/j.jneuroim.2003.12.021

Rosenzweig, E. S., Brock, J. H., Lu, P., Kumamaru, H., Salegio, E. A., Kadoya, K., Weber, J. L., Liang, J. J., Moseanko, R., Hawbecker, S., Huie, J. R., Havton, L. A., Nout-Lomas, Y. S., Ferguson, A. R., Beattie, M. S., Bresnahan, J. C., & Tuszynski, M. H. (2018). Restorative effects of human neural stem cell grafts on the primate spinal cord. *Nature Medicine*, *24*(4), 484-490. https://doi.org/10.1038/nm.4502

Rothgangel, A. S., Braun, S. M., Beurskens, A. J., Seitz, R. J., & Wade, D. T. (2011). The clinical aspects of mirror therapy in rehabilitation: A systematic review of the literature. *International Journal of Rehabilitation Research*, *34*(1), 1-13. https://doi.org/10.1097/MRR.0b013e3283441e98

Sakaguchi, D. S., Van Hoffelen, S. J., Grozdanic, S. D., Kwon, Y. H., Kardon, R. H., & Young, M. J. (2005). Neural progenitor cell transplants into the developing and mature central nervous system. *Annals of the New York Academy of Sciences*, *1049*(1), 118-134. https://doi.org/10.1196/annals.1334.012

Sandri, M. (2013). Protein breakdown in muscle wasting: Role of autophagy-lysosome and ubiquitin-proteasome. *International Journal of Biochemistry & Cell Biology*, *45*(10), 2121-2129. https://doi.org/10.1016/j.biocel.2013.04.023

Saposnik, G., Cohen, L. G., Mamdani, M., Pooyania, S., Ploughman, M., Cheung, D., Shaw, J., Hall, J., Nord, P., Dukelow, S., Nilanont, Y., De Los Rios, F., Olmos, L., Levin, M., Teasell, R., Cohen, A., Thorpe, K., & Stroke Outcomes Research Canada (SORCan) Working Group. (2016). Efficacy and safety of non-immersive virtual reality exercising in stroke rehabilitation (EVREST): A randomised, multicentre, single-blind, controlled trial. *Lancet Neurology*, *15*(10), 1019-1027. https://doi.org/10.1016/S1474-4422(16)30121-1

Sara, S. J. (2009). The locus coeruleus and noradrenergic modulation of cognition. *Nature Reviews Neuroscience*, *10*(3), 211-223. https://doi.org/10.1038/nrn2573

Sara, S. J., & Bouret, S. (2012). Orienting and reorienting: The locus coeruleus mediates cognition through arousal. *Neuron*, *76*(1), 130-141. https://doi.org/10.1016/j.neuron.2012.09.011

Schaap, L. A., Pluijm, S. M., Deeg, D. J., & Visser, M. (2006). Inflammatory markers and loss of muscle mass (sarcopenia) and strength. *American Journal of Medicine*, *119*(6), 526.e9-526.e17. https://doi.org/10.1016/j.amjmed.2005.10.049

Schiaffino, S., Dyar, K. A., Ciciliot, S., Blaauw, B., & Sandri, M. (2013). Mechanisms regulating skeletal muscle growth and atrophy. *FEBS Journal*, *280*(17), 4294-4314. https://doi.org/10.1111/febs.12253

Segers, V. F., & Lee, R. T. (2008). Stem-cell therapy for cardiac disease. *Nature*, *451*(7181), 937-942. https://doi.org/10.1038/nature06800

Sharma, H. S., Castellani, R. J., Smith, M. A., & Sharma, A. (2012). The blood-brain barrier in Alzheimer's disease: Novel therapeutic targets and nanodrug delivery. *International Review of Neurobiology*, *102*, 47-90. https://doi.org/10.1016/B978-0-12-386986-9.00003-X

Snijders, T., Verdijk, L. B., & van Loon, L. J. (2009). The impact of sarcopenia and exercise training on skeletal muscle satellite cells. *Ageing Research Reviews*, *8*(4), 328-338. https://doi.org/10.1016/j.arr.2009.05.003

Stadelmann, C., Wegner, C., & Brück, W. (2011). Inflammation, demyelination, and degeneration—recent insights from MS pathology. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1812*(2), 275-282. https://doi.org/10.1016/j.bbadis.2010.07.007

Stinear, C. M., Barber, P. A., Petoe, M., Anwar, S., & Byblow, W. D. (2012). The PREP algorithm predicts potential for upper limb recovery after stroke. *Brain*, *135*(8), 2527-2535. https://doi.org/10.1093/brain/aws146

Stinear, C. M., Lang, C. E., Zeiler, S., & Byblow, W. D. (2020). Advances and challenges in stroke rehabilitation. *Lancet Neurology*, *19*(4), 348-360. https://doi.org/10.1016/S1474-4422(19)30415-6

Stripecke, R., Münz, C., Schuringa, J. J., Bissig, K.-D., Soper, B. W., Meeham, T., Yao, L.-C., Di Santo, J. P., Brehm, M. A., Rodríguez, E., Wege, A. K., Bonnet, D., Guionaud, S., Howard, K. E., Kitchen, S. G., Klein, F., Saeb-Parsy, K., Sam, J., Sharma, A. D., ... Shultz, L. D. (2020). Innovations, challenges, and minimal information for standardization of humanized mice. *EMBO Molecular Medicine*, *12*(7), e8662. https://doi.org/10.15252/emmm.201708662

Tansey, M. G., & Goldberg, M. S. (2010). Neuroinflammation in Parkinson's disease: Its role in neuronal death and implications for therapeutic intervention. *Neurobiology of Disease*, *37*(3), 510-518. https://doi.org/10.1016/j.nbd.2009.11.004

Taub, E., Uswatte, G., Mark, V. W., Morris, D. M., Barman, J., Bowman, M. H., Bryson, C., Delgado, A., & Bishop-McKay, S. (2013). Method for enhancing real-world use of a more affected arm in chronic stroke: Transfer package of constraint-induced movement therapy. *Stroke*, *44*(5), 1383-1388. https://doi.org/10.1161/STROKEAHA.111.000559

Teng, Y. D., Lavik, E. B., Qu, X., Park, K. I., Ourednik, J., Zurakowski, D., Langer, R., & Snyder, E. Y. (2002). Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells. *Proceedings of the National Academy of Sciences*, *99*(5), 3024-3029. https://doi.org/10.1073/pnas.052678899

Thayer, J. F., & Lane, R. D. (2007). The role of vagal function in the risk for cardiovascular disease and mortality. *Biological Psychology*, *74*(2), 224-242. https://doi.org/10.1016/j.biopsycho.2005.11.013

Thieme, H., Morkisch, N., Mehrholz, J., Pohl, M., Behrens, J., Borgetto, B., & Dohle, C. (2018). Mirror therapy for improving motor function after stroke. *Cochrane Database of Systematic Reviews*, *7*, CD008449. https://doi.org/10.1002/14651858.CD008449.pub3

Tracey, K. J. (2002). The inflammatory reflex. *Nature*, *420*(6917), 853-859. https://doi.org/10.1038/nature01321

Tseng, B. S., Marsh, D. R., Hamilton, M. T., & Booth, F. W. (1995). Strength and aerobic training attenuate muscle wasting and improve resistance to the development of disability with aging. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *50A*(Special Issue), 113-119. https://doi.org/10.1093/gerona/50a.special_issue.113

Veerbeek, J. M., Langbroek-Amersfoort, A. C., Van Wegen, E. E., Meskers, C. G., & Kwakkel, G. (2017). Effects of robot-assisted therapy for the upper limb after stroke. *Neurorehabilitation and Neural Repair*, *31*(2), 107-121. https://doi.org/10.1177/1545968316666957

Verdijk, L. B., Snijders, T., Drost, M., Delhaas, T., Kadi, F., & van Loon, L. J. (2014). Satellite cells in human skeletal muscle; from birth to old age. *Age*, *36*(2), 545-557. https://doi.org/10.1007/s11357-013-9583-2

Visser, M., Pahor, M., Taaffe, D. R., Goodpaster, B. H., Simonsick, E. M., Newman, A. B., Nevitt, M., & Harris, T. B. (2002). Relationship of interleukin-6 and tumor necrosis factor-α with muscle mass and muscle strength in elderly men and women: The Health ABC Study. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *57*(5), M326-M332. https://doi.org/10.1093/gerona/57.5.M326

Vunjak-Novakovic, G., Lui, K. O., Tandon, N., & Chien, K. R. (2011). Bioengineering heart muscle: A paradigm for regenerative medicine. *Annual Review of Biomedical Engineering*, *13*, 245-267. https://pmc.ncbi.nlm.nih.gov/articles/PMC3405288

Wang, Y., Chen, X., Cao, W., & Shi, Y. (2014). Plasticity of mesenchymal stem cells in immunomodulation: Pathological and therapeutic implications. *Nature Immunology*, *15*(11), 1009-1016. https://doi.org/10.1038/ni.3002

Wechsler, L. R., Bates, D., Stroemer, P., Andrews-Zwilling, Y. S., & Aizman, I. (2018). Cell therapy for chronic stroke. *Stroke*, *49*(5), 1066-1074. https://doi.org/10.1161/STROKEAHA.117.018290

Winstein, C. J., Stein, J., Arena, R., Bates, B., Cherney, L. R., Cramer, S. C., Deruyter, F., Eng, J. J., Fisher, B., Harvey, R. L., Lang, C. E., MacKay-Lyons, M., Ottenbacher, K. J., Pugh, S., Reeves, M. J., Richards, L. G., Stiers, W., Zorowitz, R. D., & American Heart Association Stroke Council. (2016). Guidelines for adult stroke rehabilitation and recovery: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, *47*(6), e98-e169. https://doi.org/10.1161/STR.0000000000000098

Wolf, S. L., Winstein, C. J., Miller, J. P., Taub, E., Uswatte, G., Morris, D., Giuliani, C., Light, K. E., Nichols-Larsen, D., & EXCITE Investigators. (2006). Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: The EXCITE randomized clinical trial. *JAMA*, *296*(17), 2095-2104. https://doi.org/10.1001/jama.296.17.2095

Wolpaw, J. R., & Tennissen, A. M. (2001). Activity-dependent spinal cord plasticity in health and disease. *Annual Review of Neuroscience*, *24*, 807-843. https://doi.org/10.1146/annurev.neuro.24.1.807

Wu, T., Liu, J., Hallett, M., Zheng, Z., & Chan, P. (2013). Cerebellum and integration of neural networks in dual-task processing. *NeuroImage*, *65*, 466-475. https://doi.org/10.1016/j.neuroimage.2012.10.004

Yin, H. S., & Selzer, M. E. (2015). Axonal regeneration in lamprey spinal cord. *Journal of Neuroscience*, *35*(30), 10806-10818. https://doi.org/10.1523/JNEUROSCI.03-06-01135.1983

Zangi, L., Lui, K. O., von Gise, A., Ma, Q., Ebina, W., Ptaszek, L. M., Später, D., Xu, H., Tabebordbar, M., Gorbatov, R., Sena, B., Nahrendorf, M., Briscoe, D. M., Li, R. A., Wagers, A. J., Rossi, D. J., Pu, W. T., & Chien, K. R. (2013). Modified mRNA directs the fate of heart progenitor cells and induces vascular regeneration after myocardial infarction. *Nature Biotechnology*, *31*(10), 898-907. https://doi.org/10.1038/nbt.2682

Zariffa, J., Kapadia, N., Kramer, J. L., Taylor, P., Alizadeh-Meghrazi, M., Zivanovic, V., Willms, R., Townson, A., Curt, A., Popovic, M. R., & Steeves, J. D. (2012). Relationship between clinical assessments of function and measurements from an upper-limb robotic rehabilitation device in cervical spinal cord injury. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *20*(3), 341-350. https://doi.org/10.1109/TNSRE.2011.2181537