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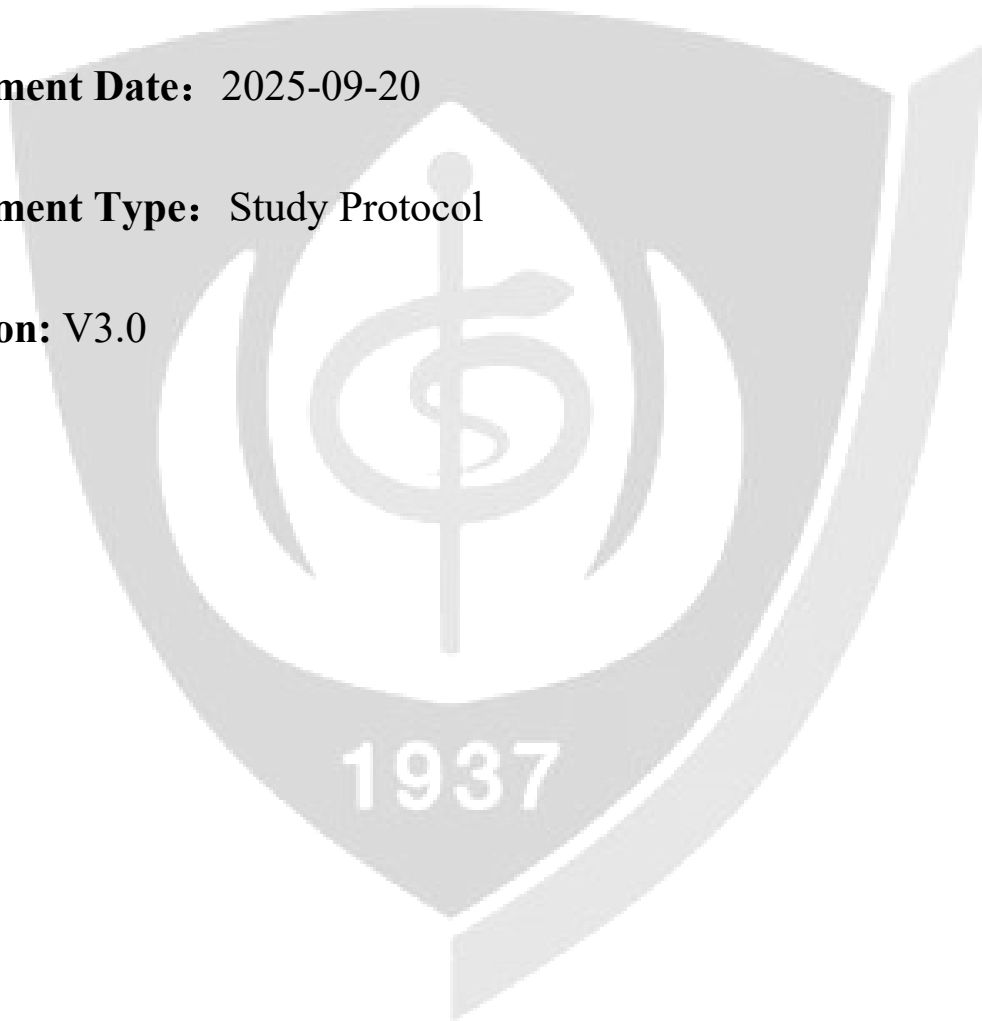
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Investigator-Initiated Interventional Clinical Study Protocol

Safety and Efficacy of High-Channel Implanted Brain-Computer Interface in Promoting Motor Function Improvement in Patients with Tetraplegia

University

Study Site: Zhongshan Hospital, Fudan

Principal Investigator: Jing Ding

Sponsor: Zhongshan Hospital, Fudan University

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Investigator's Statement

I will faithfully perform the duties of an investigator in accordance with the Good Clinical Practice (GCP) regulations of the People's Republic of China and will personally conduct or directly supervise this clinical study.

I have read and approved this protocol and affirm its scientific and ethical soundness. I will carry out the responsibilities specified by applicable laws and regulations of China, the Declaration of Helsinki, Chinese GCP, and this protocol, and will initiate the study only after obtaining approvals from the Academic Committee and the Institutional Review Board (IRB)/Ethics Committee (EC). Unless measures are required to protect the safety, rights, and interests of participants, I will keep this protocol confidential.

Study Site: Zhongshan Hospital, Fudan University

Principal Investigator: Jing Ding

Date: 2025-09-20

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Protocol Synopsis

Title	Safety and Efficacy of a High-Channel Implanted Brain-Computer Interface (BCI) in Promoting Motor Function Improvement in Patients with Tetraplegia
Objective	To explore the safety and efficacy of a high-channel implanted Brain-Computer Interface (BCI) for motor function impairment in patients with tetraplegia
Endpoints	<p>Primary Endpoint</p> <ul style="list-style-type: none">Grasping success rate: the proportion of successfully completed pre-specified grasp tasks (including basic and functional grasp). <p>Secondary Endpoints</p> <ul style="list-style-type: none">Coverage of object types for grasp: range of objects accurately grasped (e.g., cup, mobile phone, paper).Accuracy of BCI command recognition: correctness of translating brain signals into grasp commands.

	<ul style="list-style-type: none"> • Grasp latency: time interval from the emergence of grasp intent to execution. • Manual Muscle Testing (MMT). • Modified Ashworth Scale (MAS) for spasticity. • 3-meter walk time. • Motion-capture gait analysis: step width, stride length, step height, cadence, and gait speed. • Plantar pressure values. • Limb muscle volume. • Visual Analog Scale (VAS). • SHIM / SCS–W. • ICIQ-SF score for urinary retention. • Bowel function assessment scale. • 128-channel electroencephalography (EEG). • Electromyography (EMG) and somatosensory evoked potentials (SEP). • Brain functional magnetic resonance imaging (fMRI). <p>Safety Endpoint</p> <ul style="list-style-type: none"> • Incidence of adverse events (AEs).
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Overall Design	<p>This is an open-label, single-arm clinical study conducted at a designated clinical trial institution. The study comprises a 3-month main study period, a 3-month extension period, and a 3-month follow-up period. Main study period: screening/baseline, preoperative preparation, surgery, upper-limb rehabilitation tuning, and pneumatic hand-function training (3 months). Before surgery, brain and spinal imaging will determine electrode implantation sites. After implantation of high-channel electrodes, combined rehabilitation begins; a motor-intent decoding model is built to recognize intent in real time and drive a pneumatic hand to perform grasp tasks. Extension period: precise evaluation of upper-limb grasp function and monitoring/adjustment of signal stability; implantation of a spinal epidural test electrode; closed-loop rehabilitation training in which signals from the implanted intracranial electrodes modulate epidural electrical stimulation (EES) for limb rehabilitation.</p>
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	Follow-up period: explantation of intracranial electrodes and implantation of long-term epidural electrodes; closed-loop limb rehabilitation guided by scalp EEG with remote guidance.
Sample Size	10 participants
Study Arms	Single arm; no randomization or control group (all participants receive the investigational intervention)
Inclusion/Exclusion criteria	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Age 18–65 years (no sex restriction). • Clinically diagnosed quadriplegic motor dysfunction secondary to brainstem or spinal cord injury. • ≥ 6 months since brainstem or spinal cord injury with clinical stability (spinal shock resolved; no obvious recovery or deterioration of sensory/motor function). • MMT: bilateral upper limbs \leq Grade 2; bilateral lower limbs \leq Grade 3. • MMSE ≥ 20.

	<p>Exclusion criteria</p> <ul style="list-style-type: none"> • Pregnancy. • Substance abuse or alcoholism. • Comorbidities limiting limb movement: fractures (progressive/deformity-inducing), hip dysplasia or other hip range-limiting disorders, diabetic foot, severe osteoporosis, limb joint contractures/deformities, spasticity, hospitalization for autonomic dysreflexia within the past 3 months, etc. • Neurological diseases/injuries: traumatic brain injury, epilepsy, neurodegenerative disease or neuropathy, severe anxiety/depression, suicidal ideation. • Surgical contraindications: infectious diseases; unstable angina; severe arrhythmias or other cardiac diseases; immune disorders or major organ disease; coagulopathy/bleeding tendency; ankylosing spondylitis; malignancy; spinal instability; spinal canal stenosis.
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	<ul style="list-style-type: none"> • Body mass index (BMI) ≥ 30.0 kg/m². • Depressive disorder (HAMD > 17). • Inability to comply with study procedures.
Intervention	<p>Main study period: intracranial electrode implantation; postoperative decoding of brain signals to drive an external continuous passive motion device for upper-limb grasp training.</p> <p>Extension period: implantation of a spinal epidural test electrode; closed-loop rehabilitation in which signals from implanted intracranial electrodes modulate EES. Follow-up period: closed-loop EES-based functional training guided by scalp EEG and follow-up observations.</p>
Withdrawal Criteria	<ul style="list-style-type: none"> • Participant unwilling or unable to continue. • Intolerable adverse event or serious adverse event (SAE) posing health/safety risk; investigator judges risk outweighs benefit. • Personal request by participant or family; upon investigator's assessment that withdrawal will not adversely affect the participant.

	<ul style="list-style-type: none"> • Poor compliance with study procedures.
Statistical Analysis Plan	<ul style="list-style-type: none"> • Exploratory pilot; sample size not formally calculated. • Demographics, medical history, primary and secondary endpoints will be analyzed. Two-sided tests; $P < 0.05$ denotes statistical significance. • Normality testing first. Continuous data: mean\pmSD, or median and range; categorical data: frequency and percentage. • Pre-/post- comparisons of primary and secondary outcomes: paired-sample tests, linear mixed-effects models, or non-parametric tests as appropriate.

Abbreviations

Brainstem Injury, BI

Spinal Cord Injury, SCI

Brain–Spine Interface, BSI

Brain-Machine Interface, BCI

Epidural electrical stimulation, EES

Magnetoencephalography, MEG

Electrocorticogram, ECoG

Electroencephalography, EEG

Computed Tomography, CT

Magnetic Resonance Imaging, MRI

Functional Magnetic Resonance Imaging, fMRI

Functional electrical stimulation, FES

Event-related desynchronization, ERD

American Spinal Injury Association, ASIA



1. Research Background

Tetraplegia is a common manifestation of neurological disorders and can occur across all age groups. As the hub connecting the brain and spinal cord, the brainstem contains numerous vital nuclei and ascending and descending tracts. Damage to the brainstem often results in severe consequences such as respiratory and circulatory failure and disturbances of consciousness; among these, injury to the pyramidal tracts causes bilateral limb paralysis. The spinal cord is the “main highway” transmitting motor signals to the limbs. Following cervical spinal cord injury, sensory and motor function in both the upper and lower limbs is easily impaired, leading to tetraplegia. Such injuries severely compromise patients’ quality of life, causing loss of independence and imposing a heavy burden on families and society^[1]. With the rising incidence of trauma such as traffic accidents and falls from height, as well as the increasing prevalence of cerebrovascular disease, cases of brainstem and spinal cord injury are on the rise. Research on the mechanisms by which these injuries cause tetraplegia is therefore becoming increasingly important. Developing rehabilitation strategies for this type of tetraplegia to enhance limb functional recovery and improve quality of life is also a major task of current medical research.

1.1 Pathophysiological Mechanisms and Clinical Challenges

The brainstem, the life center of the human body, houses the respiratory center, circulatory center, and dense regions of neural conduction tracts. When infarction or hemorrhage occurs, occlusion or rupture of the vertebrobasilar system leads to acute ischemia and hypoxia of the midbrain, pons, and medulla oblongata, triggering neuronal apoptosis and axonal injury. Bilateral corticobulbar tract damage may result in dysarthria, aphasia, or complete loss of speech; injury to the reticular formation disrupts respiratory regulation, often necessitating long-term ventilatory support. For example, a large infarction at the base of the pons can cause locked-in syndrome, leaving the patient only vertical eye movement while completely losing voluntary speech and limb movement. Cervical spinal cord injury is mainly caused by external forces resulting in contusion, compression, or transection of the spinal cord parenchyma. Injury to segments C1–C4 leads to complete tetraplegia, whereas injury to C5–C8 results in tetraplegia with partial upper-limb function retained. Neuroanatomical studies show that the corticospinal tract, as the core pathway for motor command transmission, undergoes axonal disruption and demyelination after cervical spinal cord injury, preventing motor commands issued by the brain from reaching effectors. This physical interruption of neural signal transmission deprives patients of voluntary limb movement and increases the burden on families and society^[2].

1.2 Limitations of Conventional Therapies

Current clinical interventions exhibit significant limitations in improving neurological deficits. Pharmacologically, recombinant tissue-type plasminogen activator (rt-PA) can be used for thrombolysis in acute brainstem infarction but only within 4.5 hours of onset and carries the risk of serious complications such as intracranial hemorrhage. Neuroprotective agents such as edaravone have shown potential for neural repair in animal studies, but phase III clinical trials have yet to achieve breakthrough results. In rehabilitation therapy, physical training combined with robotic-assisted exercises may delay muscle atrophy but cannot restore voluntary motor

function of paralyzed limbs. In addition, although research on neural regeneration after spinal cord injury has made progress in areas such as stem cell transplantation and biomaterial scaffolds, clinical application remains far off^[3].

1.3 Transformative Potential of Brain–Computer Interface Technology and Progress in China and Abroad

Brain–Computer Interface (BCI) technology—an interdisciplinary frontier integrating neuroscience, biomedical engineering, and artificial intelligence—is reshaping the paradigm of neural function restoration. Invasive BCI, by virtue of its unique advantages in signal acquisition, precisely implants microelectrode arrays (MEA) into the motor cortex, premotor cortex, or sensory cortex to directly capture the action potentials of single neurons or local neuronal ensembles. Compared with non-invasive electroencephalography (EEG), this “close-contact” approach improves the signal-to-noise ratio by two to three orders of magnitude and achieves millisecond-level temporal resolution, enabling precise decoding of neural activity patterns underlying intention generation, motor planning, and execution, thereby providing unprecedented technical support for neural function replacement^[4].

In recent years, numerous milestone studies worldwide have validated the clinical feasibility and application potential of invasive BCI. At Stanford University, the “neuroprosthetic program” implanted 96-channel electrode arrays into the motor cortex of paralyzed patients and innovatively used deep learning algorithms to decode neural signals in real time, successfully achieving precise three-dimensional control of a robotic arm for grasping tasks. This system not only simulates the complex movement trajectories of a natural arm but also adjusts grip strength according to the patient’s subtle intentions, allowing independent performance of daily activities such as eating and drinking. After three months of training, patients’ control accuracy improved from 68% at baseline to 89%, with some even able to write simple letters using the robotic arm. Notably, long-term follow-up revealed that after one year of BCI use, patients exhibited significant neuroplasticity in the motor cortex, manifested as expanded activation areas and increased signal strength. Brown University’s BrainGate system targets communication needs of aphasic patients by capturing neural signals from language-related brain regions and combining them with speech synthesis and natural language processing to achieve “thought-to-text” at 15 words per minute. In a clinical experiment, a patient with complete aphasia due to brainstem hemorrhage successfully sent the electronic message “I want water” to family members in the fourth week after electrode implantation, marking a breakthrough in invasive BCI for speech restoration^[5,6]. Subsequent research optimized signal processing algorithms to increase typing speed to 22 words per minute and developed emotional prosody matching for synthesized speech, making it more personalized. Brown and MIT researchers have also combined BCI with virtual reality (VR) to create virtual conversation scenarios for language rehabilitation, with preliminary results showing a 30% improvement in communication willingness and accuracy compared with traditional training. The invasive BCI field has also drawn wide attention from industry. Neuralink, founded by Elon Musk, developed a “sewing machine” implantation technique using flexible filament electrodes only 5 μm in diameter, greatly reducing brain tissue damage compared with traditional rigid electrodes. Its core N1 sensor uses a robotic system to implant over a thousand electrode filaments into the cortex, covering approximately 1,024 neurons in a single procedure

for high-density signal acquisition. In a 2020 demonstration, pigs implanted with Neuralink devices controlled a game controller via brain signals, illustrating real-time signal processing and motor decoding potential. Later studies applied the technology to primates, enabling monkeys to control a computer cursor by thought to perform drawing and gaming tasks with stable signals for months^[7,8]. Although Neuralink has yet to conduct large-scale human clinical trials, its innovations in electrode materials, minimally invasive implantation, and wireless transmission—especially its concept of a “whole-brain interface” using high-density arrays for comprehensive monitoring—hold potential for treating severe neurological diseases such as Alzheimer’s and Parkinson’s disease.

China has likewise achieved breakthroughs in invasive BCI. The “Tianjixin” system developed by Tsinghua University’s BCI and Neural Regulation Laboratory combines multimodal neural signal processing with neuromorphic computing. Using self-developed flexible microelectrode arrays, the team achieved long-term stable recording of neuronal activity in the monkey cortex and built a real-time decoding algorithm based on spiking neural networks. In animal models of spinal cord injury with motor deficits, monkeys implanted with Tianjixin controlled a robotic arm to feed themselves with training, achieving <50-ms control latency—significantly superior to traditional algorithms. Notably, the flexible electrodes use a bionic structure mimicking nanoscale synaptic protrusions to improve electrode–neuron coupling efficiency by 40% and reduce glial encapsulation. The team also developed a proprietary wireless implantable neural signal acquisition chip integrating 256 channels at one-third the power consumption of conventional devices, supporting miniaturization and clinical translation of invasive BCI^[9].

In clinical translation, Tsinghua University and Tiantan Hospital launched the “BrainTalker” project, completing the first human trial. A patient with tetraplegia due to cervical spinal cord injury was implanted with the second-generation BCI system, which captured motor cortical signals in real time to drive an exoskeleton robot for standing and walking. Over six months of training, the patient not only independently controlled the exoskeleton to perform complex actions such as stair climbing but also mitigated lower-limb muscle atrophy. Functional MRI (fMRI) showed increased connectivity between sensory and motor cortices during BCI use, indicating positive neural function reconstruction. In partnership with domestic medical companies, Tsinghua has also developed a closed-loop BCI rehabilitation system that feeds exoskeleton motion information back to the sensory cortex as electrical stimulation, forming a complete “intention–execution–feedback” loop that markedly improves motor control precision and rehabilitation outcomes.

For patients with brainstem or cervical spinal cord injury, invasive BCI can build a “digital compensatory channel” bypassing damaged neural pathways. In speech restoration, the Broca’s area, Wernicke’s area, and motor cortex regions associated with articulatory muscles generate specific neural activity patterns during attempted expression. Invasive electrodes can capture these high-frequency, high-resolution signals and, via combined convolutional (CNN) and recurrent (RNN) neural networks, convert them into speech commands to drive external speech synthesis devices, thus restoring communication. Recent studies have begun exploring multimodal BCI by integrating facial electromyography with brain signals to improve naturalness and fluency of synthesized speech. For example, an MIT team developed a hybrid BCI system capturing both EEG and facial micro-expression data to increase emotional expression accuracy of synthesized speech by 37%. Building on this, Tsinghua introduced an

emotion-recognition module analyzing emotional features in neural signals to automatically match corresponding emotional prosody, greatly enhancing communication authenticity.

In motor function restoration, invasive BCI combined with exoskeleton robots and functional electrical stimulation (FES) shows immense potential. For tetraplegic patients, electrodes implanted in the motor cortex can capture motor intention signals in real time, decode them, and drive an exoskeleton robot to stand or walk, or directly stimulate paralyzed muscles through FES to restore voluntary limb movement. In a clinical study at Case Western Reserve University, six cervical spinal cord injury patients used BCI-controlled exoskeletons to perform standing training three times a week for over 20 minutes per session. In a Tsinghua–Tiantan Hospital trial, a spinal cord injury patient trained with the Tianjixin system successfully stood independently and walked short distances via brain-controlled exoskeleton after four weeks, verifying the technology’s safety and efficacy in humans. Moreover, closed-loop BCI systems use real-time feedback to return external device motion information as neural signals to the sensory cortex, forming a complete “intention generation–action execution–sensory feedback” loop that promotes cortical plasticity and provides sustained drive for long-term neural recovery^[10]. Recent studies show that after six months of closed-loop BCI training, some patients develop new neural connections in the motor cortex, offering renewed hope for neural function repair.

Technological innovations extend beyond signal processing to materials science and engineering, laying a solid foundation for clinical application of invasive BCI. New flexible electrode materials—such as ultrathin parylene-based electrodes and carbon nanotube composites—substantially reduce physical damage and immune rejection compared with conventional implants. Harvard University developed flexible electrodes only 5 μm thick that seamlessly adhere to brain tissue without significant inflammatory response in two-year animal experiments. Tsinghua achieved breakthroughs in electrode surface modification by coating electrodes with biomimetic hydrogel to lower interface impedance by 60% and inhibit glial scarring. Tsinghua has also developed biodegradable microelectrode materials that gradually degrade and are absorbed after completing signal acquisition, eliminating long-term implantation risks. Neuralink’s flexible filament electrodes likewise innovate in materials, using platinum–iridium alloy filaments with polyimide insulation to ensure both signal conduction and biocompatibility for long-term stable recording.

Breakthroughs in wireless power supply and data transmission have enabled implanted devices to operate stably without external cables, greatly improving convenience and quality of life. For example, a wireless BCI system developed by Caltech uses magnetic resonance coupling for energy transfer up to 10 cm and achieves 10-Mbps data transmission. Tsinghua’s new wireless protocol lowers transmission power consumption by 40% while preserving signal integrity, supporting long-term implantation. Neuralink has proposed an integrated, wireless, miniaturized solution in which the N1 sensor combines signal acquisition, amplification, and digitization in a coin-sized device with Bluetooth data transmission and all-day battery life, greatly enhancing portability and usability. Concurrently, continued optimization of neural signal encoding and decoding algorithms—especially the introduction of generative adversarial networks (GANs) and reinforcement learning—has dramatically improved decoding accuracy and real-time performance, pushing invasive BCI toward clinical translation. DeepMind’s reinforcement learning algorithm reduces motor control error by 42% in simulated

environments, while Tsinghua's attention-based decoding algorithm improves accuracy by 28% in multitasking scenarios, significantly boosting system utility^[11]. Tsinghua has also proposed an adaptive learning framework that dynamically adjusts decoding parameters to patients' neural signal characteristics, increasing cross-individual adaptation efficiency by 50% and providing a new solution for personalized BCI applications^[12].

Our research team has previously performed high-throughput electrode implantation surgery in two rhesus monkeys. Neither short-term (12 days) nor long-term (183 days) implantation produced obvious scar proliferation or angiogenesis on the brain surface, indicating no significant effect on brain safety in large animals. During high-throughput electrode implantation, both monkeys used the BCI to control external devices such as a mouse for web browsing and gaming.

1.4 Necessity and Societal Value of the Study

In the field of neurological injury, patients with brainstem and cervical spinal cord injury face multiple survival challenges, and their urgent medical needs have become a major social issue. In addition to profound deficits in physiological functions such as limb motor and sensory function, this population experiences long-term psychological trauma and social isolation. According to the latest statistics from the International Spinal Cord Injury Database, the prevalence of depression among patients with tetraplegia reaches 40%, significantly higher than in the general population.

Developing an invasive Brain-Computer Interface (BCI) system tailored to patients with brainstem and cervical spinal cord injury has substantial practical significance and far-reaching societal value. At the individual level, such a system can help patients overcome physiological limitations and markedly enhance independence in daily living, including autonomous wheelchair control, operation of smart devices, and performance of routine activities, thereby reducing the long-term caregiving burden on families and society. At the societal level, this technology helps re-establish a communication bridge with the outside world, reshape social roles, facilitate participation in social activities and return to work, promote the social inclusion of people with disabilities, and foster a fairer, more accessible environment. From a technological development perspective, brainstem/cervical cord injury involves complex neural pathways and physiological mechanisms; overcoming the challenges of BCI applications in these conditions will catalyze cross-disciplinary innovation. These advances will not only benefit patients with brainstem/cervical cord injury but also provide a generalizable technological platform for other neurological disorders (e.g., neurodegenerative diseases, amyotrophic lateral sclerosis), bringing new therapeutic concepts and solutions to neuromedicine and driving leapfrog development in neural repair and regenerative medicine.

Accordingly, the significance of this study lies in:

- 1) Providing a new therapeutic avenue: Offering patients with tetraplegia an innovative treatment modality that directly reads motor intention signals from the brain via BCI, bypasses damaged neural pathways, and converts signals into motor commands to drive a hand continuous passive motion device and electrical stimulation, thereby helping restore motor function and offering hope to patients with limited benefit from conventional rehabilitation.
- 2) Establishing technical safety: Determining the safety of a high-channel implanted BCI in

human use, including surgical risks, the impact of long-term implantation on brain tissue, and the potential for infection or immune reactions, thus laying a foundation for broader clinical application.

- 3) Promoting neural remodeling: Based on neuroplasticity, BCI-assisted motor training may facilitate reorganization of neural circuits and strengthen relevant connections, contributing to recovery of intrinsic neural function, improving limb motor ability over the long term, and potentially reducing dependence on external devices for some patients.
- 4) Improving quality of life: Enabling patients with tetraplegia to regain certain motor abilities—such as volitional grasping and ambulation—thereby enhancing independence in daily activities, alleviating family caregiving burden, and improving participation in social life, dignity, and well-being.
- 5) Alleviating socio-economic burden: Given the considerable medical resources and household expenditures required for long-term rehabilitation and care, effective improvement in motor function could shorten rehabilitation courses, reduce long-term care needs, and lower economic burdens on families and society, freeing medical resources for other patients.
- 6) Advancing BCI technology: Addressing a series of challenges in high-channel signal acquisition, processing, and decoding will promote progress in signal fidelity, transmission speed, and stability, and drive optimization and upgrading of related hardware and algorithms.
- 7) Fostering cross-disciplinary integration: This research spans neuroscience, medicine, bioengineering, and computer science, fostering communication and collaboration across disciplines, providing new ideas and methods for related fields, and advancing the broader life sciences and technology ecosystem.

1.5 Risks and Benefits of the Study

The known and potential risks and benefits to participants are as follows.

Known Risks: Surgical procedures for implantation of intracranial electrodes and spinal epidural electrodes carry certain risks, including:

- 1) Risks of intracranial electrode implantation:
 - Hemorrhage and hematoma: Intraoperative vascular injury may cause intracranial hemorrhage or hematoma formation, potentially compressing adjacent brain tissue and resulting in neurological deficits (e.g., limb weakness, speech disturbance, altered consciousness), and in severe cases, life-threatening events.
 - Infection: As with any invasive surgery, there is a risk of infection at the incision, intracranially, or at the electrode site. Intracranial infection is a serious complication that may lead to meningitis or brain abscess, causing fever, headache, vomiting, seizures, and further brain injury.
 - Neurological injury: Implantation may directly damage surrounding neural tissue, with symptoms varying by location of injury (e.g., sensory abnormalities, motor deficits, visual or auditory impairment).
 - Cerebrospinal fluid (CSF) leak: Dural injury may lead to CSF leakage, causing intracranial hypotension syndrome (headache, dizziness, nausea, vomiting) and increasing infection risk.

- Seizures: Surgical stimulation of brain tissue and the presence of electrodes may precipitate seizures, with frequency and severity varying across individuals and potentially affecting quality of life and rehabilitation.
- Electrode migration or malfunction: Postoperative electrode displacement may impair accurate targeting and therapeutic efficacy. Hardware failure (e.g., open/short circuits) may necessitate revision surgery for repair or replacement. (

2) Risks of epidural electrode implantation:

- Hemorrhage: Injury to epidural vessels can cause epidural hematoma which, if unrecognized or untreated, may compress the spinal cord or nerve roots and lead to neurological dysfunction (e.g., numbness, weakness, urinary/fecal incontinence).
- Infection: Similar to intracranial implantation, infection may occur at the incision or spread to the epidural space, causing epidural abscess; without timely treatment, this may lead to myelitis and neurological impairment.
- Neurological injury: Unintentional injury to the spinal cord, nerve roots, or peripheral nerves during implantation can result in sensory and motor dysfunction (e.g., pain, numbness, muscle weakness).
- CSF leak: Dural injury may cause CSF leakage with symptoms of intracranial hypotension and increased infection risk.
- Electrode-related issues: Epidural electrodes may migrate, extrude, or malfunction, reducing therapeutic effect; migration can misdirect stimulation, extrusion may require re-implantation, and malfunction may necessitate replacement.
- Pain and discomfort: Postoperative pain or discomfort at the implantation site may occur due to surgical trauma or local stimulation and can affect rehabilitation and quality of life, requiring appropriate management.

Potential Risks: Primarily related to brain-signal decoding and the rehabilitation process:

1) Risks related to brain-signal decoding:

- Signal interference: BCI devices rely on precise neural signal acquisition and decoding. Endogenous bioelectric signals are weak and susceptible to electromagnetic interference from external electronic devices (e.g., mobile phones, computers) and to circuit noise within the device, potentially degrading signal quality, impairing interpretation, and affecting device performance.
- Device malfunction: Brain-spine interface equipment comprises complex electronic systems that may experience hardware failures (e.g., electrode fracture, circuit short) or software issues (e.g., algorithmic errors, system crashes). Such failures may interrupt function and, in rare cases, pose incidental risks (e.g., unexpected shutdown due to depleted implant battery).
- Decoding errors: Current neural decoding technologies are still evolving and may not fully and accurately interpret complex neural patterns. Decoding errors may lead to incorrect execution of user commands (e.g., imprecise prosthetic movements, erroneous BCI responses), affecting usability and user experience.

2) Risks during rehabilitation:

- Physical injury: Improper training may cause musculoskeletal injury; individuals with cardiovascular disease or frailty may face cardiac risks; inappropriate training in

neurological disease may aggravate deficits and pain.

- Infection: Inadequate wound care increases infection risk; bedridden or low-activity individuals are more prone to respiratory infections.
- Psychological issues: Rehabilitation difficulty may induce anxiety or depression; unmet expectations may cause frustration.
- Other: Risks such as falls.

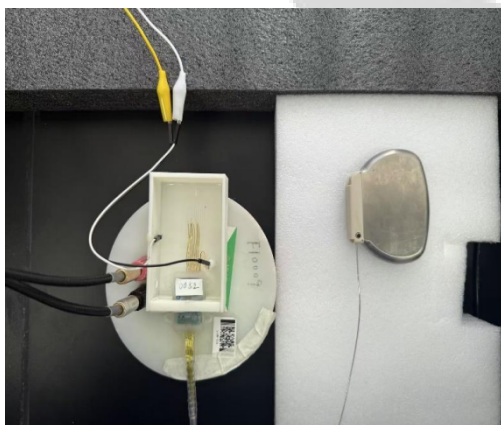
Known Benefits: By decoding participant intentions, neural function restoration and substitution may be achieved with assistance from external devices:

- 1) Upper-limb motor improvement: Capturing motor commands from the brain to control a hand continuous passive motion device and electrical stimulation to achieve volitional actions such as grasping.
- 2) Lower-limb motor improvement: Stimulating and training muscles to prevent atrophy and enhance strength and endurance, thereby improving independence in daily living; decoding motor intentions may support assisted volitional activities with external devices, such as standing and walking.

Potential Benefits: Participants in this study may be prioritized for access to future clinical trials, products, and therapeutic technologies based on this platform. In terms of sensory function, feeding back limb sensory signals to the brain may help restore perception of limb position, touch, and pain, and may modulate neural function to alleviate neuropathic pain. Regarding autonomic function, modulation of the autonomic nervous system may help restore bladder and bowel control and improve urinary and fecal incontinence; it may also stabilize cardiovascular function (blood pressure and heart rate), reducing cardiovascular risk. In psychological and social domains, restoration of motor and sensory function and improved independence may enhance self-confidence and self-esteem, reduce psychological burden, and facilitate social integration while mitigating discrimination and bias.

1.6 Infrastructure and Personnel Allocation

Infrastructure: The following basic equipment support is currently available:



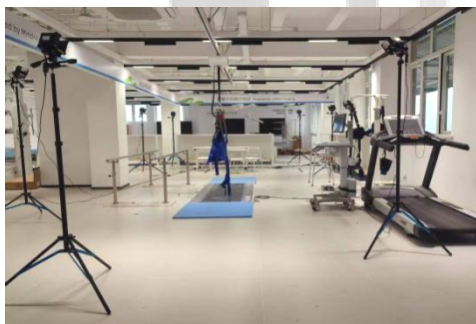
High-throughput implantable brain activity recording system



Wireless electroencephalography (EEG) acquisition device



Magnetic resonance imaging (MRI) equipment



Suspension system apparatus

Personnel Allocation: This study involves multidisciplinary collaboration among the Departments of Rehabilitation, Neurology, and Neurosurgery at Fudan University Zhongshan Hospital. The Lingang Laboratory provides technical support for the high-throughput implantable brain activity recording system.

1.7 Research Plan

Based on the above, this study is an open-label, single-arm clinical trial conducted at a designated clinical trial institution. The overall study comprises a 3-month main study period, a 3-month extension period, and a 3-month follow-up period: Main study period (3 months): screening/baseline, preoperative preparation, surgery, upper-limb rehabilitation tuning, and pneumatic hand-function training. Before surgery, brain and spinal imaging will be performed to determine electrode implantation sites; subsequently, high-channel electrodes will be

implanted. After surgery, combined rehabilitation training will begin, a motor-intent decoding model will be constructed, and motor intent will be recognized in real time to drive a pneumatic hand to perform grasping actions. Extension period (3 months): precise evaluation of upper-limb grasp function, monitoring and adjustment of signal stability, implantation of spinal epidural test electrodes, and closed-loop rehabilitation training in which signals from implanted intracranial electrodes modulate epidural electrical stimulation (EES) for limb rehabilitation. Follow-up period (3 months): explantation of intracranial electrodes and implantation of long-term spinal epidural electrodes, followed by limb rehabilitation training based on scalp EEG signals and remote guidance training.

2. Study Objectives

2.1 Safety

To explore the safety of rehabilitation therapy based on a high-channel implanted Brain–Computer Interface (BCI) in patients with tetraplegia.

2.2 Feasibility of the Therapeutic Process

To explore the feasibility of the rehabilitation process using a high-channel implanted BCI in patients with tetraplegia.

2.3 Tolerability

To explore the tolerability of rehabilitation therapy based on a high-channel implanted BCI in patients with tetraplegia.

2.4 Selectivity of Epidural Electrical Stimulation for Lower-Limb

Muscle Activation in Participants with Paraplegia

To investigate the ability of epidural electrical stimulation (EES) to selectively activate limb muscles in participants with paraplegia.

2.5 Efficacy

To explore the efficacy of a high-channel implanted BCI in improving motor function in patients with tetraplegia.

3. Study Overview

3.1 Overall Study Design and Plan

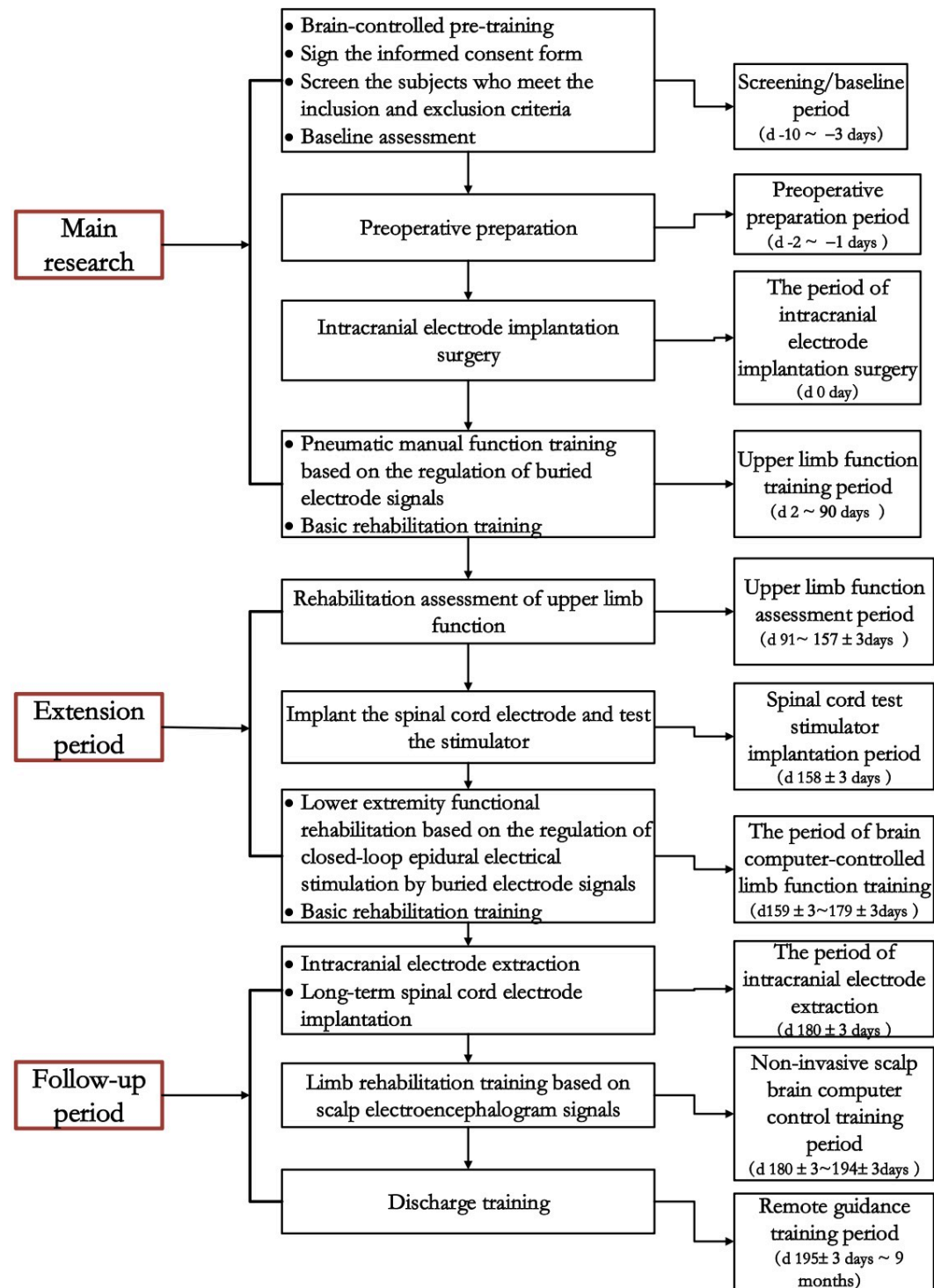
This study is an open-label, single-arm clinical trial conducted at a designated clinical trial institution. The overall study comprises a 3-month main study period, a 3-month extension period, and a 3-month follow-up period: Main study period (3 months): screening/baseline, preoperative preparation, surgery, upper-limb rehabilitation tuning, and pneumatic hand-function training. Before surgery, brain and spinal imaging will be performed to determine electrode implantation sites; subsequently, high-channel electrodes will be implanted. After surgery, combined rehabilitation training will begin, a motor-intent decoding model will be constructed, and motor intent will be recognized in real time to drive a pneumatic hand to perform grasping actions. Extension period (3 months): precise evaluation of upper-limb functional efficacy, monitoring and adjustment of signal stability, implantation of spinal epidural test electrodes, and closed-loop rehabilitation training in which signals from implanted intracranial electrodes modulate EES for limb rehabilitation. Follow-up period (3 months): explantation of intracranial electrodes and implantation of long-term epidural electrodes, followed by limb rehabilitation training based on scalp EEG signals and remote guidance.

All participants are enrolled in the test arm; no placebo control or parallel-group design is used, and self-comparison rather than randomization is applied. Blinding of investigators and participants is not feasible.

To minimize or control bias, training will be provided to investigators and participants prior to the formal trial to ensure the entire process follows pre-established procedures and standards, reducing errors caused by operational differences. For data collection and recording, objective indicators will be used to minimize the impact of subjective judgment on results.

This is an exploratory study. Participants will be enrolled sequentially; the next participant will be recruited only after a preliminary safety assessment of intracranial electrode implantation in the previous participant is deemed acceptable.

3.2 Study Flowchart



4. Study Population

4.1 Inclusion Criteria

- 1) Age 18–65 years (no sex restriction).
- 2) Clinically diagnosed motor dysfunction of all four limbs after brainstem or spinal cord injury.
- 3) ≥ 6 months after brainstem or spinal cord injury with clinical stability (spinal shock resolved; no obvious recovery or deterioration of sensory/motor function).
- 4) Manual muscle testing: bilateral upper limbs \leq Grade 2; bilateral lower limbs \leq Grade 3.
- 5) Cognitive function: MMSE ≥ 20 .

4.2 Exclusion Criteria

- 1) Pregnant women.
- 2) Substance abuse or alcoholism.
- 3) Conditions limiting limb movement: fractures (progressive or deformity-inducing), hip dysplasia or other disorders restricting hip movement, diabetic foot, severe osteoporosis, limb joint contractures/deformities, spasticity, hospitalization for autonomic dysreflexia within the past 3 months.
- 4) Neurological diseases/injuries: traumatic brain injury, epilepsy, neurodegenerative disease or neuropathy, severe anxiety/depression, suicidal ideation.
- 5) Surgical contraindications: infectious diseases; unstable angina; severe arrhythmias or other cardiac diseases; immune disorders and major organ disease; coagulopathy/bleeding tendency; ankylosing spondylitis; malignancy; spinal instability; spinal canal stenosis.
- 6) Body mass index (BMI) ≥ 30.0 kg/m².
- 7) Depressive disorder (HAMD > 17).
- 8) Inability to comply with study procedures.

4.3 Criteria for Early Withdrawal

- 1) Participant unwilling or unable to continue.
- 2) Occurrence of an intolerable adverse event or serious adverse event (SAE) that may jeopardize health or safety, where the investigator judges that continued participation poses more risk than benefit.
- 3) Personal request by participant or family; upon investigator's assessment that withdrawal will not adversely affect the participant, the participant may be withdrawn.
- 4) Poor compliance with study procedures.

4.4 Criteria for Removal

- 1) Participant unwilling or unable to continue.
- 2) Discovery after enrollment that the participant does not meet inclusion criteria or meets any exclusion criterion.
- 3) Occurrence of an intolerable adverse event or SAE that may jeopardize health or safety, where the investigator judges that continued participation poses more risk than benefit.
- 4) Personal request by participant or family; upon investigator's assessment that withdrawal will not adversely affect the participant, the participant may be withdrawn.
- 5) Poor compliance with study procedures.

5. Endpoints

5.1 Primary Endpoint

Grasping success rate: proportion of successfully completed pre-specified grasping actions.

- 1) Basic grasp (e.g., grasping a tennis ball, holding a cup): object held stably ≥ 3 seconds without slippage.
- 2) Functional grasp (e.g., grasping and transferring a cup): complete "grasp-subsequent action" without interruption, tipping, or dropping.

5.2 Secondary Endpoint

- 1) Coverage of object types for grasping: range of objects accurately grasped (e.g., cup, mobile phone, paper).
- 2) Accuracy of brain-controlled command recognition: correctness of translating brain signals into grasp commands.
- 3) Grasp latency: time interval from generation of grasp intent in the brain to execution of the action.
- 4) Manual muscle testing.
- 5) Modified Ashworth Scale (MAS) for spasticity.
- 6) 3-meter walking time.
- 7) Motion-capture gait analysis: step width, stride length, step height, cadence, gait speed.
- 8) Plantar pressure values.
- 9) Limb muscle volume.
- 10) Visual Analog Scale (VAS).
- 11) SHIM / SCS-W.
- 12) ICIQ-SF score for urinary retention.
- 13) Bowel function assessment scale.

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- 14) 128-channel electroencephalography (EEG).
 - 15) Electromyography (EMG) and somatosensory evoked potentials (SEP).
 - 16) Functional magnetic resonance imaging (fMRI).

5.3 Safety Endpoints

- 1) Incidence of intracranial infection and hemorrhage.
- 2) Rate of implant rejection reactions.

6. Study Procedures

6.1 Study Steps and Related Assessments

Except for the first participant, all subsequent participants will be enrolled only after preliminary safety and efficacy of upper-limb functional training have been assessed in the preceding participant (Day 14).

6.1.1 Main Study

Screening/Baseline Period:

Participants will undergo one week of scalp EEG-based brain-controlled training. Demographic data, height and weight measurements, medical history, and previous laboratory test results will be collected. After confirming eligibility, participants will sign the informed consent for this study. A comprehensive physical assessment and relevant laboratory and imaging examinations will be completed, particularly of limb motor function (e.g., muscle strength, severity of brainstem or spinal cord injury) and neurological status. Baseline assessments include: manual muscle testing, Modified Ashworth Scale (MAS) for spasticity, 3-meter walking time, motion-capture gait analysis (step width, stride length, step height, cadence, gait speed), plantar pressure values, bilateral lower-limb muscle volume, Visual Analog Scale (VAS), SHIM/SCS–W, International Consultation on Incontinence Questionnaire–Short Form (ICIQ-SF) urinary retention score, bowel function assessment scale, 128-channel electroencephalography (EEG), electromyography (EMG) and somatosensory evoked potentials (SEP), and functional magnetic resonance imaging (fMRI).

Preoperative Preparation Period:

Based on screening test results, a preoperative discussion will be held. Participants will sign surgical informed consent, and the surgical plan and electrode implantation site will be determined.

Intracranial Electrode Surgery Period:

Neurosurgical procedures will be performed under general anesthesia. Electrodes will be implanted according to the preoperative plan. Neural signals will be decoded to control and individualize epidural stimulation parameters. The implanted intracranial electrode (National Medical Device Registration (Magnetic) No. QW2024-4421) is intended to record and monitor deep brain electrical signals in conjunction with an external EEG receiver. Intraoperative impedance testing will verify electrode integrity and connectivity. Neurophysiological monitoring will confirm electrode placement. A head CT will be performed within 2 hours postoperatively to verify electrode position. Within 24 hours postoperatively, electrocardiographic monitoring of vital signs and consciousness will be conducted for safety assessment.

Upper-Limb Functional Training Period:

Starting 24 hours postoperatively, daily electrode impedance testing will be conducted to assess electrode integrity and connectivity. Upper-limb training will be performed using a hand continuous passive motion device controlled by signals from the implanted intracranial electrodes, including attempted movement tasks to build a motor-intent decoding model. Decoded signals will drive the device to perform hand activities. The frequency and duration of each session will be adjusted according to individual participant status. Basic rehabilitation (neuromuscular electrical stimulation, pneumatic therapy, mat-based functional training, sitting-balance training, and other routine rehabilitation measures) will be provided. Throughout the period from intracranial electrode implantation to removal, participants will be closely monitored for complications such as infection, hemorrhage, and electrode migration. Wound dressing will be changed every five days.

6.1.2 Extension Period

Upper-Limb Functional Evaluation Period:

Grasping success rate: proportion of successfully completed specified grasping actions. Coverage of object types for grasping: range of objects (cup, mobile phone, paper, etc.) accurately grasped.

- Accuracy of brain-controlled command recognition: correctness of translating EEG signals into grasp commands.
- Grasp latency: time interval from generation of grasp intent to execution of action.
- Clinical functional evaluation: manual muscle testing, MAS for spasticity, 3-meter walking time test, motion-capture gait data collection, plantar pressure testing, VAS, SHIM/SCS-W, ICIQ-SF urinary retention score, and bowel function assessment scale.
- Auxiliary evaluations: limb muscle MRI, EEG, EMG and SEP, cranial fMRI.

Evaluation schedule:

- Every 3 days: grasping success rate, coverage of object types, accuracy of brain-controlled command recognition, and grasp latency.

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- Monthly: clinical functional evaluation.
 - Every 3 months: auxiliary evaluations.

Spinal Test Stimulator Implantation Period:

After signing surgical informed consent, participants will undergo general anesthesia for implantation of the spinal test stimulator and epidural electrodes according to the preoperative plan. The epidural electrodes (National Medical Device Registration No. 20203120516) and spinal nerve stimulator (National Medical Device Registration No. 20202120489) are approved for adjunctive treatment of refractory pain of the trunk and limbs; this study uses them off-label. Intraoperative impedance testing will verify electrode integrity and connectivity. X-ray monitoring and neurophysiological monitoring will confirm electrode placement. A spinal CT will be performed within 2 hours postoperatively to verify electrode position. Within 24 hours postoperatively, electrocardiographic monitoring of vital signs and consciousness will be conducted for safety assessment. Participants will be closely monitored for complications such as infection, hemorrhage, and electrode migration. Wound dressing will be changed every other day.

Limb Functional Rehabilitation Period:

Starting 24 hours postoperatively, daily electrode impedance testing will be performed. About 21 days of combined upper-limb training (hand continuous passive motion device under implanted EEG control) and lower-limb training under spinal stimulation will be provided, including attempted movement tasks to build a motor-intent decoding model. Decoded signals will drive the device and spinal stimulator for limb activities. Session frequency and duration will be adjusted individually. Basic rehabilitation (neuromuscular electrical stimulation, pneumatic therapy, mat-based functional training, sitting-balance training, and other routine rehabilitation measures) will also be performed. Additionally, based on recovery status, lower-limb rehabilitation will be supported by a weight-reduction gait training platform. After completing this period, the grasping success rate, coverage of object types, accuracy of brain-controlled command recognition, grasp latency, clinical functional evaluation, and auxiliary examinations will be reassessed.

6.1.3 Follow-Up Period

Intracranial Electrode Explantation Period:

At 180 ± 3 days after intracranial electrode implantation, electrodes will be explanted. For participants not receiving long-term spinal stimulators, the spinal test stimulator and epidural electrodes will be removed simultaneously. For participants receiving long-term spinal stimulators, the test stimulator will be replaced with a long-term stimulator (National Medical Device Import Registration No. 20203120514).

Non-Invasive Scalp EEG-Based Brain-Controlled Training:

For participants receiving long-term spinal stimulators, starting 24 hours postoperatively, daily

electrode impedance testing will be performed, followed by approximately 14 days of scalp EEG-based training to control limb movement under spinal stimulation. Attempted movement tasks will be used to build a motor-intent decoding model, and decoded signals will drive the spinal stimulator to activate limb movement. Session frequency and duration will be adjusted individually. Basic rehabilitation (neuromuscular electrical stimulation, pneumatic therapy, mat-based functional training, sitting-balance training, and other routine rehabilitation measures) will also be provided. Additionally, based on recovery status, lower-limb rehabilitation will be supported by a weight-reduction gait training platform. After completing this period, the grasping success rate, coverage of object types, accuracy of brain-controlled command recognition, grasp latency, clinical functional evaluation, and auxiliary examinations will be reassessed.

Remote-Guided Training:

About two weeks after implantation of the long-term spinal stimulator, participants will be discharged and enter a three-month period of remote-guided training. Based on recovery status, lower-limb rehabilitation will be supported by a weight-reduction gait training platform. After completion of remote-guided follow-up, the grasping success rate, coverage of object types, accuracy of brain-controlled command recognition, grasp latency, clinical functional evaluation, and auxiliary examinations will be reassessed.

6.2 Study Completion

For participants not receiving long-term spinal stimulators, removal of the spinal test stimulator and epidural electrodes marks study exit. For participants receiving long-term spinal stimulators, replacement with the long-term stimulator plus completion of 14 days of scalp EEG-controlled lower-limb training marks study exit. After trial completion, participants with long-term spinal stimulators may, according to their condition, enter a three-month remote-guided training period during which investigators will provide remote guidance for weight-supported rehabilitation training.

6.6 Early Termination or Suspension of the Study

Criteria for Suspension of an Individual Participant:

- Occurrence of an adverse event or serious adverse event (SAE) that may jeopardize health and safety, requiring suspension of the participant's clinical study for timely evaluation and intervention.
- Poor compliance or violation of the protocol, lack of cooperation with rehabilitation tasks or data collection; investigators may consider suspending participation until compliance improves.
- Personal request by participant or family; upon investigator's assessment that withdrawal will not adversely affect the participant, the participant may be suspended.

Criteria for Termination of an Individual Participant:

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- Occurrence of an adverse event or SAE which, in the investigator's judgment, poses unacceptable risk if the study continues.
 - Participant requests termination of participation for personal reasons.

Criteria for Suspension of a Portion of the Clinical Study:

- Interim analysis indicating safety concerns or the need to adjust the protocol.
- Discovery of quality problems with trial equipment requiring suspension of that part of the clinical study.
- Suspension required by the Ethics Committee or regulatory authority; investigators and sponsors must comply.

Criteria for Termination of a Portion of the Clinical Study:

- Lack of efficacy: the portion of the study fails to achieve its pre-specified primary endpoint and further research is unlikely to alter the conclusion.
- Serious data quality issues that cannot be remedied by recollection or correction, necessitating termination of that part of the study.

Criteria for Suspension of the Entire Clinical Study:

- Serious safety problems: multiple participant SAEs judged closely related to the study protocol require suspension of the entire study for risk evaluation.
- Policy changes: major changes in national or regional laws/regulations prevent continuation of the clinical study.

Criteria for Termination of the Entire Clinical Study:

- Multiple participant SAEs or deaths judged to pose severe risk if the study continues.
- Ethics Committee or regulatory authority requires termination of the study.
- Other situations where investigators deem continuation inadvisable or impractical.
- Insufficient research funding to continue.
- Violation of ethical principles (e.g., lack of informed consent, withholding critical information) requiring immediate termination.
- Major changes in national or regional laws/regulations preventing continuation.
- Study results showing the treatment to be ineffective or even harmful, requiring termination of the study.

6.4 Clinical Observation, Follow-Up, and Measures to Ensure Participant Compliance

- 1) Comprehensive informed consent: Before enrollment, provide participants with a detailed explanation of the clinical trial's objectives, methods, overall procedures, and potential risks and benefits, and obtain written informed consent. This helps enhance participants' trust and cooperation.
- 2) Establish effective communication channels: Maintain effective communication with participants to ensure that follow-up information is promptly conveyed and participant feedback and opinions are collected.
- 3) Monitor participants' health status: Closely observe participants' health throughout

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- the study, including adverse reactions, and take appropriate measures in a timely manner.
- 4) 4. Provide comprehensive health education: Offer participants thorough health education, including knowledge of the disease, treatment principles, and possible side effects. This improves participants' understanding of the condition and treatment, thereby reducing noncompliance due to misunderstanding or lack of knowledge.
 - 5) 5. Continuous care: Show concern for participants during the study, understand their worries and needs, and promptly provide help and support. This enhances participants' sense of trust and engagement, thereby improving compliance.
 - 6) Simplify trial procedures: Minimize the burden on participants as much as possible.
 - 7) Feedback mechanism: Provide participants with regular updates on trial progress and results to increase their cooperation and sense of participation.

7. Adverse Event Collection and Reporting

Any clinical adverse events and clinically significant abnormal laboratory results occurring during the clinical trial shall be recorded in detail. The relationship to the study intervention shall be evaluated, and the severity of all adverse events shall be determined.

7.1 Definition of Adverse Events

An adverse event (AE) is any symptom, syndrome, new illness, clinically meaningful abnormal laboratory parameter, or worsening of a pre-existing condition that occurs during the period of intervention, observation, or assessment in the clinical trial.

1) Severity of adverse events

Severity is classified as mild, moderate, or severe, as follows:

- Mild: Mild subjective symptoms; tolerable; no impact on activities of daily living; transient; resolves spontaneously while the intervention continues; no treatment required.
- Moderate: More pronounced symptoms; affects activities of daily living; of longer duration; resolves spontaneously or after symptomatic treatment; may interfere with use of the study intervention (e.g., requires reducing intervention time or temporary discontinuation).
- Severe: Functional impairment resulting in loss of normal work or daily living ability; prolonged duration; requires discontinuation of neuromodulation and appropriate management before relief.

2) Serious adverse events

A serious adverse event (SAE) is any untoward medical occurrence at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or constitutes an important medical event or reaction.

Note: In the definition of “serious,” life-threatening refers to events in which the participant was at immediate risk of death at the time of the event/reaction, not hypothetically if the event were to worsen. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or require intervention to prevent one of the outcomes listed above should also be considered serious.

3) Important adverse events

Clinically significant adverse events or obvious laboratory abnormalities other than SAEs that lead to targeted medical measures.

7.2 Recording, Reporting, Prevention, and Management of Adverse Events

Once informed consent is signed, all AEs shall be collected on the case report form (CRF) AE pages. Abnormal laboratory values/results occurring after consent will be regarded as AEs only if they: (i) cause clinical signs or symptoms; (ii) are deemed clinically significant; or (iii) require treatment. Newly occurring or worsening AEs after consent shall be recorded on the CRF AE pages. Pre-existing conditions present at consent shall be recorded on the CRF medical history pages.

When an AE occurs during the trial, the investigator may take necessary measures according to the participant’s condition, such as: no action, temporary suspension of electrical stimulation therapy, discontinuation of the entire trial, or use of concomitant medication. In the event of an SAE, the investigator shall immediately take necessary measures to protect participant safety and report to the Ethics Committee and relevant authorities within 24 hours of SAE occurrence. All AEs (including laboratory abnormalities judged clinically significant by the investigator) shall be documented in detail with management and outcomes until appropriately resolved or

stabilized. Depending on severity, follow-up may be conducted via hospitalization, outpatient visits, home visits, or communications.

For each AE, the following shall be evaluated to the extent possible:

- Severity;
- Duration (start and end dates);
- Relationship to the study device and/or study;
- Whether corrective treatment was administered (concomitant medication/non-pharmacologic therapy);
- Outcome;
- Whether it meets SAE criteria;
- Whether the AE led to withdrawal from the study.

The sponsor shall, upon becoming aware of death or life-threatening study-related SAEs, report within 7 days to the participating clinical trial institutions, Ethics Committees, and principal investigators, and take risk-control measures; for non-fatal/non-life-threatening study-related SAEs and other serious safety risks, report within 15 days. When information arises that may affect participant safety, study conduct, or the Ethics Committee's approval, the sponsor shall promptly organize revisions to the protocol, informed consent form, participant information, and other relevant documents, and submit them for Ethics Committee review.

7.3 Outcomes of Adverse Events

- Recovered: Complete resolution, or return to pre-treatment baseline with/without therapy.
- Improved: Condition is improving and recovery is expected.
- Persistent: The AE results in obvious and permanent disability/incapacity (e.g., blindness, deafness, paralysis). Any AE with sequelae shall be regarded as an SAE.
- Worsened: Increased severity or deterioration of the condition.
- Death: Participant dies as a result of the AE.
- Unknown: Used only for participants lost to follow-up.

7.4 Causality Assessment Between Adverse Events and the Study

Intervention

Based on temporal relationship to use of the study intervention and whether the reaction diminishes, disappears, or reappears after discontinuation/re-challenge, causality is assessed as: definitely related, probably related, possibly related, possibly unrelated, and definitely unrelated. The first three are considered possibly related to the intervention and are evaluated as adverse device reactions (ADR).

- Definitely related: Evidence of use of the study intervention; reasonable temporal relationship; explanation by the intervention is more plausible than other causes; positive dechallenge; positive rechallenge (if feasible).
- Probably related: Evidence of use; reasonable temporal relationship; explanation by the intervention more plausible than other causes; positive dechallenge.
- Possibly related: Evidence of use; reasonable temporal association; may also be explained by other causes; positive dechallenge.
- Possibly unrelated: Evidence of use; event better explained by other causes; negative or indeterminate dechallenge.
- Definitely unrelated: No use of the intervention; or no temporal relationship; or a clear alternative cause.

7.5 Anticipated Major Adverse Events and Measures to Be Taken

Surgery-related:

Infection: Electrode implantation may cause wound infection. Prophylactic antibiotics intraoperatively; standardized postoperative dressing changes and aseptic technique. If infection occurs, promptly manage the wound, administer appropriate antibiotics/anti-inflammatory therapy; in severe cases, remove implanted components, debride, and treat infection. Maintain strict product quality control and sterile surgical procedures to ensure sterility of implants.

Electrical stimulation-related:

Due to parameter computation for epidural stimulation, stimulation field and intensity may vary; displacement or overspreading of stimulation may cause corresponding reactions (e.g.,

paresthesia). These reactions can generally be mitigated or eliminated by adjusting stimulation intensity.

Risk Prevention

- 1) Participant screening and evaluation: Comprehensive assessment before treatment, including medical history, allergies, and contraindications to surgery/electrical stimulation; determine appropriate treatment plan and parameter settings.
- 2) Individualized parameter settings: Adjust stimulation parameters (e.g., intensity, frequency) based on participant condition and therapeutic goals.
- 3) Participant education: Explain procedures, possible sensations, and risks; instruct participants to recognize discomfort or abnormal reactions and report promptly.
- 4) Multidisciplinary team: Include neurology and neurosurgery from Zhongshan Hospital, spine specialists, rehabilitation therapists, and nurses.
- 5) Pre-trial professional preparation: Preclinical research: Refine product design, complete quality testing, animal studies, and risk assessment. Trial documents: Prepare the clinical protocol, informed consent, and other required documents.
- 6) Obtainment of informed consent: Provide detailed informed consent explaining purpose, procedures, risks, and benefits; obtain explicit consent in accordance with laws/regulations and ethical guidelines.
- 7) Device management: Receipt and verification: Device administrator coordinates with logistics; record unboxing and verify conformity. Storage and management: Store by category and requirements; regularly supervise conditions. Use and retrieval: Dispense and recover strictly per medical orders; ensure count reconciliation.
- 8) Strict adherence to the protocol: Compliance: All personnel must operate strictly per protocol; no unauthorized changes. Oversight and quality control: Assign QC personnel to supervise processes and ensure quality. Documentation and reporting: Record all data in detail; report progress and results in a timely manner. Accountability: Investigate and penalize violations that harm participants or compromise data integrity.

Risk Handling

Monitoring and identification of AEs: Closely observe responses during treatment. Upon AE occurrence, immediately suspend the intervention, activate routine emergency plans, organize appropriate personnel for timely and appropriate aid, and record all AEs and management in detail for subsequent review and protocol optimization. Serious events must be reported to regulatory authorities and the Ethics Committee.

During scalp EEG-based attempted-movement training: If fatigue or dizziness occurs, suspend training and allow rest with reassurance; resume after symptoms resolve. If persistent, the clinician will evaluate; if necessary, conduct further examinations and discontinue attempted-movement training.

Intraoperative subdural/epidural hemorrhage during electrode implantation: Immediately stop implantation and notify the surgical team and anesthesiologist. Identify bleeding site/volume; select appropriate hemostatic methods; closely monitor vital signs (blood pressure, heart rate, respiration). Administer hemostatic agents or transfusion as needed. Postoperatively, closely monitor neurological function and vital signs; enhance nursing care to prevent rebleeding and complications.

Postoperative infection/inflammatory reaction at the implant site: Closely observe local signs (erythema, swelling, pain). Initiate anti-infective therapy immediately; select antibiotics/anti-inflammatory agents per culture and susceptibility. Debride the site to remove sources of infection; strengthen nutritional support to improve immunity. If uncontrolled, consider electrode removal.

Falls during rehabilitation: Immediately assess for injury (site and severity); provide first aid (e.g., hemostasis, dressing). If consciousness is impaired or injury is severe, notify a physician immediately. Strengthen safety education for participants and families; adjust the rehabilitation plan to avoid recurrence; consider protective devices (e.g., knee pads).

Emergency Measures

1) Emergency medical response:

Establish detailed emergency plans and procedures, including: immediate cessation of trial

operations upon adverse reactions; prompt first aid and medical support; activation of emergency medical services when necessary to ensure timely treatment.

2) Clear assignment of responsibilities:

Project leader: Overall management, including development and implementation of emergency plans. Multidisciplinary medical team: Neurology, neurosurgery, spine specialists, trained rehabilitation physicians and nurses; implement emergency responses for specific risks (implant-site bleeding, inflammatory reactions, skin erosion, seizures, falls, etc.) per standard plans; provide expert guidance. Coordinating investigators: Assist the project leader in managing trial progress and ensuring timely emergency response.

3) Routine emergency preparedness:

Plan development: Prepare detailed emergency plans in advance, including workflows, role assignments, and reporting processes. Staff training: Provide first-aid training and drills for all trial personnel to ensure familiarity with the plans. Equipment readiness: Ensure necessary emergency equipment and medications are available on site to address potential emergencies.

8. Data Management

To standardize the specific procedures and processes of trial data management and to ensure traceability, readability, timeliness, originality, and accuracy of data, the data management process of this clinical trial is as follows:

1) Assignment of Responsibilities

Clearly define the responsibilities and division of labor among data management team members, including data management, data entry, medical coding, and statistical analysis.

2) Determination of the Data Management System

Use case report forms (CRF) to collect trial data. Establish data security management measures. Before the formal start of the trial, conduct training and testing of relevant personnel to ensure they meet trial requirements.

3) Data Collection and Entry

Use CRFs for data collection to ensure data accuracy and completeness. All observed results and abnormal findings during the clinical trial, as well as all trial conclusions, must be based on data derived from participants' original medical records. Data sources must be consistent with original record forms, laboratory reports, and other source documents. All observations and test results in the study shall be promptly, correctly, normatively, and truthfully entered into forms or databases by the investigator. All personnel participating in this study must thoroughly read and understand the trial protocol and related materials, strictly follow the protocol, and fill in records truthfully. Investigators are responsible for the quality of the entered data, ensuring authenticity and integrity.

4) Data Verification and Modification

Establish a query and resolution mechanism to ensure data accuracy and consistency. The data manager shall regularly perform logical checks of data stored on the server to identify obvious errors or missing data. Any data queries shall be promptly and carefully verified and recorded to ensure reliability. Incorrect data shall be issued as manual queries to investigators. Investigators must respond to each query, ensuring that every query is correctly addressed. Noncompliant data shall be modified or deleted; the system will record all queries and corresponding responses.

5) Data Backup

Store data in a secure and reliable data center to ensure accessibility and security. Regularly back up data to ensure timely recovery in the event of data loss or damage.

The case report form (CRF) shall include at least the following:

- a) Adverse event records.
- b) Medical records of participants' disease progression, nursing records, etc.
- c) Records of participants' routine laboratory tests, including date, time, and content.
- d) Records of participants' daily rehabilitation training content, duration, and status.
- e) Signature of the recorder and date.

9. Statistical Analysis

9.1 Sample Size Estimation

This study is an exploratory pilot trial. The sample size is not derived from a formal calculation; a total of 10 participants will be included.

9.2 Definition and Selection of Analysis Sets

Full Analysis Set (FAS): Based on the intention-to-treat (ITT) principle, obtained after minimal and reasonable exclusion of participants. For missing data on primary efficacy endpoints, the worst-case imputation principle will be applied. Secondary efficacy endpoints will not be imputed.

Per Protocol Set (PPS): The subset of participants with higher protocol adherence, including those with primary endpoint data and excluding those with major protocol deviations.

Safety Set (SS): All participants who undergo electrode implantation and have at least one safety evaluation.

9.3 Statistical Analysis of Study Data

Statistical analyses will be performed using SPSS version 19.0 or higher.

- Descriptive Statistics:

Quantitative variables will be summarized by mean, standard deviation, median, minimum, maximum, lower quartile (Q1), and upper quartile (Q3). Categorical variables will be described by frequency counts and percentages.

- Statistical Inference:

On the basis of descriptive analyses, two-sided tests will be used. A p-value <0.05 will be considered statistically significant. Comparisons of general characteristics will be conducted using appropriate methods according to the type of variable: paired-sample t-tests or linear mixed-effects models for quantitative data (depending on data distribution),

and nonparametric tests for categorical data.

- **Handling of Missing and Abnormal Values:**

The dataset for statistical analysis will consist of clinical data (e.g., EMG, motion-capture data) from all participants who meet inclusion/exclusion criteria and received the study intervention.

- For missing data, regression or other methods will be used to impute values, taking into account the uncertainty of imputation and the relationship between observed complete variables and incomplete variables. Unused data arising from noneligibility or irrelevance to study objectives need not be specially treated. However, unused data due to technical reasons (e.g., data entry errors, equipment failure) should be corrected or recollected where possible and included in the analysis. For illogical data, carefully verify the source and recording process to determine whether the discrepancy is due to data entry error, equipment failure, or human factors. If confirmed, correct it following data recording principles to ensure accuracy. If the specific cause cannot be determined or the corrected data remain illogical, consider excluding it from analysis. When excluding illogical data, ensure the process and rationale are reasonable to avoid misleading results.

- **Efficacy Endpoints:**

Effectiveness: changes from baseline at different postoperative time points for primary and secondary endpoints.

Safety: based on the SS. All AEs during the trial will be recorded in detail; the frequency and incidence will be summarized descriptively by category, with listings attached. In addition, the specific manifestations, severity, and relationship of AEs to rehabilitation treatment will be described in detail.

10. Research-Related Ethics

10.1 Ethics Committee Review

This protocol, the written informed consent form, and all materials directly related to participants must be submitted to the Ethics Committee for review and approved by the

institutional Ethics Committee and the Science and Technology Ethics Review before the study formally begins. Investigators must submit a continuing review report one month before the ethics approval expires to apply for extension of approval.

At study termination and/or completion, the investigator must provide written notification to the Ethics Committee. Investigators must promptly report to the Ethics Committee all changes occurring in the course of the study (e.g., protocol and/or informed consent form amendments) and must not implement such changes without Ethics Committee approval, except when necessary to eliminate an apparent and immediate hazard to participants. In such cases, the Ethics Committee will be notified accordingly.

10.2 Informed Consent

Investigators must provide participants or their legal representatives with an understandable informed consent form approved by the Ethics Committee and allow sufficient time to consider participation. Participants must not be enrolled until signed written informed consent has been obtained from the participant or their legal representative. During participation, all updated versions of the informed consent form and written information will be provided to participants. The informed consent form shall be retained as an essential clinical trial document for future reference.

11. Confidentiality Measures

All participant information must be kept strictly confidential. Personal data relating to participation and activities within the study fall within the scope of confidentiality. Participant information and study data will be identified by a study number rather than by name. Personally identifiable information will not be disclosed to anyone outside the study team without the participant's permission. All study members are required to maintain the confidentiality of participant identities. Participant files will be stored in locked cabinets and will be accessible only to study personnel. To ensure the study is conducted according to regulations, members of government authorities or the Ethics Committee may, when necessary and as stipulated, review

participants' personal records at the study site. When study results are published, no personal data of participants will be disclosed.

Study data are confidential. All study members are required to maintain the confidentiality of study data and shall not disclose study data to individuals outside the project team without the principal investigator's permission, nor transfer study data to external institutions without hospital authorization. Study data involving human genetic resources shall not be transferred to overseas institutions or domestic institutions with foreign investment without prior approval from the National Human Genetic Resources Administration, except for publication of study results in accordance with regulatory requirements.

In addition, results from this project may be published in medical journals. However, we will protect patients' personal information in accordance with laws and regulations; patients' personal information will not be disclosed unless required by applicable law. When necessary, government authorities and the hospital Ethics Committee and its authorized personnel may, as stipulated, review patient records.

12. Expected Timeline and Completion Date of the Study

After approval of the clinical ethics materials, the anticipated schedule from participant enrollment is as follows:

September 2025 – November 2025: Enrollment of the first participant.

November 2025 – May 2027: Completion of enrollment of all participants.

May 2027 – September 2027: Completion of the trial.

13. References

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