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Reshaping “Cerebellar Inhibition”: Mechanistic Insights and Precision Medicine Perspectives for rTMS in Machado−Joseph Disease*

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Abstract Machado-Joseph disease, or spinocerebellar ataxia type 3 (SCA3), represents the most common autosomal dominant cerebellar ataxia worldwide. Despite its progressive and debilitating nature, disease-modifying therapies remain elusive. Repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising non-invasive intervention; however, its clinical application has been hindered by inconsistent protocols and a lack of mechanistic understanding. A recent landmark study published in *Brain Stimulation* by Chen *et al.* addressed these challenges by combining a high-dose intermittent theta-burst stimulation (iTBS) protocol with concurrent transcranial magnetic stimulation-electroencephalography (TMS-EEG). This commentary provides an in-depth analysis of their findings, highlighting the restoration of cerebello-cortical inhibition (CBI) as a key therapeutic mechanism. Furthermore, we discuss the broader implications of this work, proposing that future translational research should integrate accelerated iTBS (aiTBS) paradigms, cortical response measurements (CRM), and individualized neuro-navigation to establish a new era of precision neuromodulation for ataxia.

Key words Machado-Joseph disease (spinocerebellar ataxia type 3, SCA3), transcranial magnetic stimulation-electroencephalography (TMS-EEG), cerebello-cortical inhibition, neuromodulation, precision medicine

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Machado-Joseph disease (spinocerebellar ataxia type 3, SCA3), caused by abnormal cytosine-adenine-guanine (CAG) repeats expansion in the exon 10 of the *ATXN3* gene[1], is characterized by progressive cerebellar ataxia, ophthalmoplegia, and pyramidal signs, severely compromising patients' quality of life. Currently, management for SCA3 is purely symptomatic, with no approved treatments to halt disease progression. The cerebellum, traditionally viewed as a motor coordinator, is now understood to play a critical role in modulating cortical excitability *via* the cerebello-thalamo-cortical (CTC) pathway[2]. Dysfunction in this circuit is considered a hallmark of SCA3 pathophysiology.

In recent years, non-invasive brain stimulation, particularly repetitive transcranial magnetic stimulation (rTMS), has garnered significant attention as a potential tool to modulate cerebellar excitability. Early studies utilizing low-frequency rTMS or intermittent theta-burst stimulation (iTBS) have reported varying degrees of symptomatic relief[3-5]. However, the field has faced two major hurdles: the optimal dosing parameters (intensity, duration, and pulse number) remain undefined; perhaps more critically, the neural mechanisms driving clinical improvement have remained obscure.

A recent study by Chen *et al.* [6], published in *Brain Stimulation*, represents a pivotal step forward in this field. By conducting a rigorous randomized, double-blind, sham-controlled trial and leveraging

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advanced concurrent TMS-EEG technology, the study not only validated the efficacy of a high-dose iTBS protocol but also visualized the restoration of inhibitory cerebellar output. This commentary dissects the therapeutic and mechanistic breakthroughs of this study and explores future directions for the field.

1 Therapeutic innovation: the cumulative power of high-dose stimulation

One of the most striking features of this study is the robustness of the intervention protocol. While previous trials typically involved 10 to 15 sessions with moderate pulse loads[3-4], Chen *et al.* implemented an intensive regimen consisting of 21 consecutive days of stimulation, delivering a total of 75 600 pulses. This "high-dose" approach is based on the hypothesis that induction of robust, long-term potentiation (LTP)-like plasticity in neurodegenerative circuits requires a high threshold of cumulative stimulation[7].

The clinical outcomes validated this hypothesis. Patients in the active iTBS group demonstrated a statistically significant and clinically meaningful reduction in ataxia severity, as measured by the International Cooperative Ataxia Rating Scale (ICARS). Crucially, unlike many prior studies where benefits waned shortly after treatment cessation, the improvements in this trial were sustained at 3-month follow-up. In contrast, the sham group, which showed a transient placebo response, returned to baseline severity by the follow-up point. This sustained effect suggests that high-dose iTBS does not merely provide a temporary symptomatic mask but may induce structural or functional reorganization that persists over time. This finding sets a new benchmark for dosing in cerebellar ataxia trials.

2 Unveiling the mechanism: restoration of cerebello-cortical inhibition

The true novelty of this study lies in its use of concurrent TMS-EEG to unravel the neurophysiological underpinnings of the treatment. The cerebellum exerts a tonic inhibitory influence on the primary motor cortex (M1), a phenomenon known as cerebello-cortical inhibition (CBI)[8]. Specifically, this circuit is orchestrated by Purkinje cells, which release gamma-aminobutyric acid (GABA) to inhibit the deep cerebellar nuclei (*i.e.*, the dentate nucleus). The dentate nucleus, in turn, sends glutamatergic excitatory projections to the contralateral thalamus, driving the motor cortex[8-9]. In SCA3, the degeneration of Purkinje cells compromises this precise GABAergic regulation, leading to pathological disinhibition and aberrant thalamocortical drive[10]. At the neuronal network level, this loss of cerebellar control may manifest as pathological beta-band synchronization in M1. Such excessive synchronization essentially "locks" the motor cortex into a rigid state, impairing the fluid initiation and execution of movement. By restoring the N45 potential, high-dose iTBS likely re-engages this GABAergic brake, effectively desynchronizing pathological cortical rhythms and refining motor output.

Chen *et al.* utilized TMS-EEG to directly probe this circuitry. At baseline, SCA3 patients exhibited a marked deficit in CBI, reflected by a reduced amplitude of the N45 TMS-evoked potential (TEP). The N45 component is considered a marker of GABAergic inhibition in the cortex[11]. The reduced N45 in patients indicated a failure of the cerebellum to effectively recruit inhibitory interneurons in M1.

Remarkably, the high-dose iTBS treatment reversed this deficit. Post-treatment analysis revealed a significant restoration of the N45 amplitude in the active group, effectively "normalizing" the inhibitory tone. Furthermore, the study identified a remodeling of beta-band oscillations (13−30 Hz) in the motor cortex. As illustrated in Figure 1, cerebellar stimulation does not merely act locally; it remotely modulates the cerebello-thalamo-cortical circuit, restoring the inhibitory "brake" on the motor cortex and refining motor output. By visualizing these changes, the authors provided the first causal evidence that clinical recovery in SCA3 is driven by the repair of specific cerebello-cortical physiological defects.

3 N45: bridging physiology and clinical outcome

A major challenge in neurology is the lack of objective biomarkers to monitor treatment response. Clinical scales such as ICARS or Scale for the Assessment and Rating of Ataxia (SARA) are subject to inter-rater variability and patient fatigue. Chen *et al.* identified a significant positive correlation between the recovery of the N45 amplitude and the

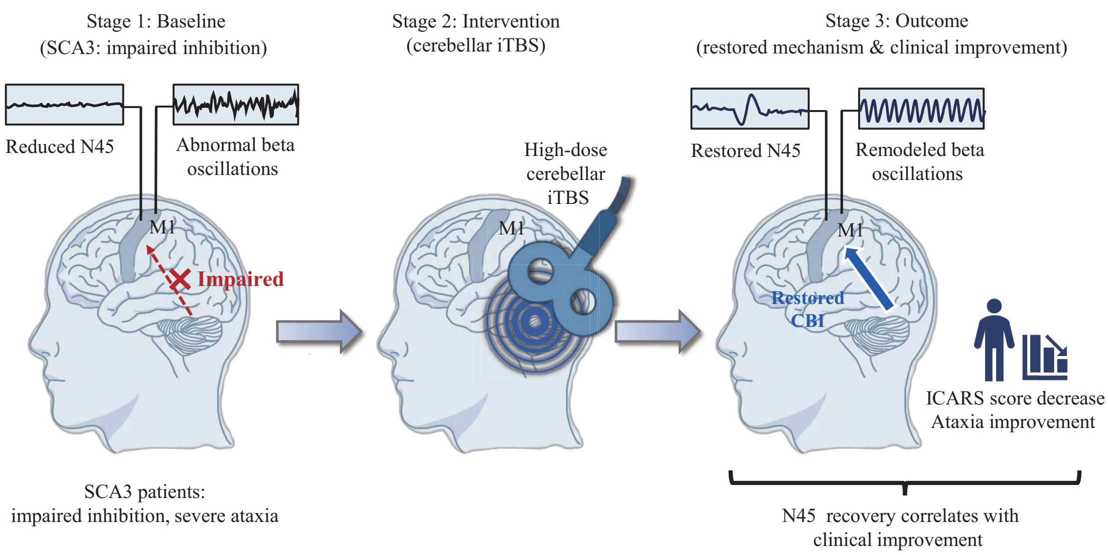

Fig. 1 Neurophysiological mechanisms of cerebellar iTBS

reduction in ICARS scores. Patients who showed the greatest physiological restoration of CBI experienced the most substantial clinical benefit.

This finding positions the N45 potential as a promising candidate biomarker for SCA3. In future clinical practice, N45 could serve multiple roles: as a stratification tool to identify patients with specific circuit defects suitable for rTMS; as a pharmacodynamic marker to determine optimal dosing and as a surrogate endpoint for early-phase clinical trials.

4 Future perspectives: towards accelerated and precision medicine

While the findings of Chen *et al.* are transformative for SCA3, their implications extend significantly to broader neurological conditions characterized by cerebellar dysfunction, such as Parkinson's disease and post-stroke gait impairment. Since the restoration of CBI is a shared therapeutic target across these disorders, the protocols validated here could serve as a blueprint for broader rehabilitation strategies. To fully realize this translational potential, we propose three key directions for future research:

4.1 Accelerated iTBS （aiTBS）

The 3-week daily treatment protocol, while effective, poses a significant logistical burden for patients and caregivers. To address this, future studies should establish efficient aiTBS protocols. Recent groundbreaking work in depression has demonstrated that delivering multiple stimulation sessions per day (10 sessions daily for 5 d) can compress a weeks-long treatment course into a single week[12-13]. This “space-learning” approach has been shown to induce rapid and robust synaptic plasticity. Applying aiTBS to SCA3 could drastically reduce the treatment duration, making it accessible to patients traveling from afar, while potentially achieving even higher cumulative doses and faster symptom relief. However, the translation of aiTBS to SCA3 requires rigorous safety considerations. Unlike the structurally intact brains often seen in depression, SCA3 patients exhibit significant cerebellar atrophy and altered cerebrospinal fluid (CSF) dynamics. The expanded CSF space can shunt current and alter the electric field distribution, potentially creating “hotspots” or modifying seizure thresholds. Therefore, future implementation of aiTBS must prioritize safety by incorporating individualized electric field modeling to optimize dosing and ensuring robust physiological monitoring to mitigate risks associated with the atrophic neuroanatomy.

4.2 TMS−EEG as a cortical response measurement （CRM）

The utility of TMS-EEG has evolved from a basic experimental technique for mapping effective connectivity into a sophisticated clinical tool[14]. Recent work by *Che et al.* [15], published in *Cell Reports Medicine*, has demonstrated the superior sensitivity of TMS-EEG in detecting subtle neuroplastic changes—such as those in prefrontal-limbic circuits—that behavioral assessments often fail to capture. Complementing this network-level perspective, our recent study highlighted the utility of TMS-EEG in indexing long-range connectivity, specifically revealing how stimulation modulates interhemispheric inhibition[16]. This is particularly relevant to the context of cerebellar circuitry, as the cerebellum plays a pivotal role in balancing interhemispheric interactions to coordinate complex motor output. TEPs provide a direct, millisecond-resolution readout of cortical reactivity that is unconfounded by patient motivation or motor execution deficits. The current study by Chen *et al.* [6] completes this translational arc by validating N45 restoration as a predictor of clinical symptomatic relief, mirroring the seminal framework for quantifying cortical responses established by Casali *et al.* [17]. Consequently, TMS-EEG should now be adopted as an effective CRM. In neurodegenerative diseases where behavioral baselines fluctuate, CRM offers a stable, objective metric of brain state to guide future closed-loop precision neuromodulation.

4.3 Individualized precision targeting

A paradigm shift from generalized protocols to individualized precision medicine is imperative. The current study, consistent with conventional methodologies, employed scalp-based landmarks for cerebellar targeting. However, this approach often fails to account for substantial anatomical heterogeneity, resulting in suboptimal target engagement[18]. This limitation is particularly pronounced in SCA3, where heterogeneous cerebellar atrophy alters the depth and orientation of target nuclei[10]. Future therapeutic strategies should necessitate the integration of individualized magnetic resonance imaging (MRI)-based navigation. By mapping patient-specific functional connectivity—specifically, identifying cerebellar voxels exhibiting maximal functional coupling with the primary motor cortex—clinicians can precisely deliver stimulation to the optimal loci, a strategy successfully implemented in other network-based neuromodulation therapies[19-20]. The convergence of structural MRI to correct for atrophy and functional connectivity mapping holds the potential to significantly augment the therapeutic effect size and reproducibility of rTMS interventions.

5 Conclusion

The study by Chen *et al*. represents a pivotal advancement in the therapeutic landscape of SCA3. It provides compelling evidence from a rigorous randomized controlled trial for the efficacy of high-dose cerebellar iTBS and explicitly delineates the underlying circuit mechanism—specifically, the restoration of CBI. By bridging the gap between clinical phenomenology and neurophysiological mechanism, this work establishes a critical framework for next-generation therapeutics. Looking ahead, the integration of accelerated protocols, objective physiological biomarkers and individualized precision targeting holds the potential to elevate rTMS from an investigational adjunct into a precision-medicine-based standard of care for patients with SCA3.

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重塑“小脑抑制”：重复经颅磁刺激治疗马查多-约瑟夫病的机制解析与精准医疗展望*

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摘要 马查多-约瑟夫病（Machado-Joseph disease，又称脊髓小脑共济失调3型，spinocerebellar ataxia type 3，SCA3）是全球最常见的常染色体显性遗传性小脑共济失调类型。SCA3具有进行性致残的特征，目前临床仍缺乏有效的疾病修饰疗法。重复经颅磁刺激（repetitive transcranial magnetic stimulation，rTMS）作为一种极具潜力的非侵入性干预手段备受关注，但其临床应用长期受限于刺激方案不统一及治疗机制不明。近期，Chen等发表在*Brain Stimulation*上的一项里程碑式研究，通过结合高剂量间歇性theta爆发刺激（intermittent theta-burst stimulation，iTBS）与同步经颅磁刺激（transcranial magnetic stimulation，TMS）-脑电图（electroencephalogram，EEG）技术，有效应对了上述挑战。本文对该研究的主要发现进行了深入评述，重点阐述了小脑-皮层抑制（cerebello-cortical inhibition，CBI）功能的恢复是其关键的治疗机制。此外，本文进一步探讨了该研究的广泛意义，提出未来的转化研究应整合加速iTBS（accelerated iTBS，aiTBS）范式、皮层反应测量（cortical response measurements，CRM）及个体化神经导航技术，从而开启共济失调精准神经调控的新纪元。

关键词 马查多-约瑟夫病（脊髓小脑共济失调3型），经颅磁刺激-脑电图，小脑-皮层抑制，神经调控，精准医疗
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