Am J Transl Res 2026;18(7):6264-6283
www.ajtr.org /ISSN:1943-8141/AJTR0174153

Review Article

Multimodal brain imaging neurotransmitter marker study of TD: a review of TCM effect mechanisms and precise diagnosis and treatment combining traditional Chinese and western medicine

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Received May 19, 2026; Accepted July 1, 2026; Epub July 15, 2026; Published July 30, 2026

Abstract: Objective: To systematically summarize findings from multimodal brain imaging and neurotransmitter marker studies in Tic disorders (TD), to explore potential neurobiological mechanisms underlying Traditional Chinese Medicine (TCM) interventions, and to propose a precision diagnosis framework integrating TCM and Western medicine. Methods: This is a critical narrative review. A systematic literature search was conducted in PubMed, CNKI, and Wanfang databases up to October 2025 using keywords including "TD", "Tourette syndrome", "multimodal imaging", "neurotransmitter", and "TCM", ensuring comprehensive coverage. However, data synthesis followed a narrative, hypothesis-generating approach rather than a formal systematic review or meta-analysis framework. Results: Structural MRI reveals basal ganglia volume reductions and cortical thickness abnormalities; functional MRI shows disrupted cortico-striato-thalamo-cortical (CSTC) connectivity and compensatory activation; DTI demonstrates white matter microstructural alterations; PET/SPECT identifies dopaminergic hyperactivity and serotonergic dysfunction; MRS indicates GABA-glutamate imbalance. TCM interventions (herbal formulas, acupuncture) modulate these imaging phenotypes with good safety profiles. However, most human imaging evidence for TCM remains correlational and preliminary, with animal models providing mechanistic hypotheses that require cautious translation. Conclusions: Multimodal biomarkers enable objective subtyping and treatment monitoring. Limitations include small sample sizes, cross-sectional designs, comorbidity confounding, and TCM-specific challenges (herbal quality control, blinding difficulties). Future research should prioritize large-scale longitudinal cohorts, standardized TCM randomized controlled trials, and low-cost biomarker translation for primary care implementation.

Keywords: Tic disorders, multimodal brain imaging, neurotransmitter markers, TCM, integrated traditional Chinese and western medicine, precision diagnosis and treatment

Introduction

Tic disorders (TD) is a group of neurological and psychiatric disorders characterized by involuntary [1], rapid, and repetitive muscle tics, including three subtypes: transient tic disorder, chronic tic disorder, and Tourette's syndrome [2-4]. Global epidemiological data shows that approximately 0.15% to 1.1% of school-age children suffer from Tourette's syndrome [5], while the prevalence of transient tic disorder can reach 5% to 20% [6-8]. Although the symptoms of most patients diminish with age, about 30% to 50% of patients still experience significant symptoms in adulthood, which may affect their quality of life [9].

Traditionally, the pathological mechanism of TD has been believed to be related to dysfunction of cortico-striato-thalamo-cortical (CSTC) circuits, with overactivity of the dopamine system being considered one of the core hypotheses [10]. However, a dopamine-centric theory may not fully explain all clinical features of the disease, such as prodromal sensory phenomena, comorbid obsessive-compulsive symptoms, and affective regulation disorders [11]. In recent years, with the development of multimodal

https://doi.org/10.62347/KION8631

neuroimaging technology, researchers have been able to describe the neuropathological features of TD at the structural [12], functional [13], metabolic, and molecular levels [3].

TCM has accumulated some clinical evidence in TD treatment. TCM classifies TD into the categories of liver wind and convulsions, and believes that the pathogenesis is mainly characterized by liver wind internal movement, phlegm fire disturbing the heart, and yin deficiency and yang hyperactivity [14]. Some clinical studies suggest that Chinese herbal compounds such as Tianma Gouteng Decoction, Zhengan Xifeng Decoction and acupuncture and moxibustion therapy have shown certain efficacy and safety in improving the symptoms of TD [15]. However, the targets of TCM treatment are not yet clear, and there is a lack of objective efficacy evaluation standards, which to some extent affects its recognition in the international academic community [16].

In this context, this review attempts to summarize the partial progress of multimodal brain imaging in the study of neurotransmitter markers for Tourette's syndrome, sort out the clinical evidence and brain imaging effect mechanism of TCM treatment for Tourette's syndrome, and explore the integration strategy and development direction of multimodal imaging and neurotransmitter markers under the precision diagnosis and treatment mode of TCM and Western medicine.

Methods

This is a critical narrative review. A systematic literature search was conducted in PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang databases for articles published from database inception to October 2025. Search terms included: ("tic disorder" OR "Tourette") AND ("neuroimaging" OR "MRI" OR "fMRI" OR "DTI" OR "PET" OR "SPECT" OR "MRS" OR "neurotransmitter") AND ("TCM" OR "herbal" OR "acupuncture"). Additional studies were identified through reference lists of retrieved articles. Inclusion criteria: (1) original research or systematic reviews on multimodal neuroimaging in TD, (2) studies on TCM interventions for TD with clinical or imaging outcomes, (3) English or Chinese language. Exclusion criteria: case reports, animal-only studies without human translation potential, and non-peer-reviewed articles. Two authors independently screened titles/abstracts and extracted data; discrepancies were resolved by consensus. The extracted data were then synthesized narratively, with emphasis on critical appraisal of methodological heterogeneity, cross-modal concordance, and the gap between preclinical and clinical evidence, rather than pooled effect estimates.

Progress in multimodal brain imaging research on TD

Structural magnetic resonance imaging study

Structural MRI is a relatively mature modality in the study of TD in brain imaging [17]. Voxel based morphological analysis and surface based morphological analysis have been widely used to evaluate changes in gray matter volume and cortical thickness in patients with TD [18].

In terms of structural abnormalities in the basal ganglia, multiple voxels based morphological analyses have consistently reported a decrease in volume of the caudate nucleus, putamen, and globus pallidus in patients with Tourette's syndrome. A study by Forde et al. [19] published in *Movement Disorders* in 2017 reported that the basal ganglia volume of children with Tourette's syndrome combined with attention deficit hyperactivity disorder was significantly smaller than that of normal controls, and this change was negatively correlated with the severity of tics. However, some studies have reported opposite results, which may be related to sample age, comorbidity status, and drug treatment history [20]. It is worth noting that longitudinal studies suggest that as symptoms improve, the reduction in basal ganglia volume may partially reverse, indicating that structural abnormalities in TD have some plasticity [21].

Controversies in basal ganglia volume findings: sources of heterogeneity: The contradictory results regarding BG volume in TD stem from several potential sources of heterogeneity.

Age and disease duration. Studies in children and adolescents tend to report reduced BG volume, whereas some studies in adults have found normalized or increased volume. This pattern might reflect developmental plasticity,

compensatory hypertrophy, or selection bias (e.g., adults with persistent tics may represent a different subgroup).

Comorbid ADHD and obsessive-compulsive disorder (OCD). Comorbid ADHD is associated with additional GM reductions, particularly in the caudate and putamen. Studies that did not exclude or stratify by comorbidity may have confounded disease-specific effects.

Pharmacological treatment. Antipsychotics, which are commonly used to treat moderate-to-severe tics, can increase BG volume in a dose-dependent manner, possibly via D2 receptor blockade-induced trophic effects. This confounder is particularly relevant in adult studies.

Methodological differences between VBM and SBM. VBM normalizes GM concentration to a template and may be sensitive to registration errors; SBM measures cortical thickness and surface area directly. Discrepancies between studies may partly arise from these technical variations.

Studies on cortical thickness in TD have indicated regional variations in the sensorimotor cortex, prefrontal cortex (PFC), and anterior cingulate cortex (ACC). O'Neill et al. [22] suggested that GM reduction in the ACC may be associated with impaired tic inhibition. In addition, volume changes in the insula and PFC have been reported, regions involved in sensory processing and cognitive control [23].

Graph theory-based analyses of structural covariance networks have suggested that TD patients exhibit altered topological properties, including changes in small-worldness and nodal efficiency. This may imply that TD is not confined to CSTC circuits but rather involves whole-brain network-level alterations [24].

As discussed above, age, comorbidity, medication, and methodological differences contribute to the heterogeneity of basal ganglia volume findings. **Table 2** outlines these potential sources and their proposed mechanisms.

Cross-modal integration: When comparing structural findings with functional alterations (see 2.2), a recurring pattern emerges: regions showing GM reduction (e.g., ACC, sensorimotor cortex) often also exhibit abnormal resting-state connectivity and GABA/glutamate imbalance, suggesting that structural deficits may provide an anatomical substrate for functional and neurochemical disturbances. However, the temporal precedence remains unclear due to cross-sectional designs.

Beyond basal ganglia and cortical thickness changes, emerging evidence suggests that structural alterations in TD may follow a specific spatial gradient, with regions of earlier developmental maturation (e.g., sensorimotor cortices) showing more pronounced abnormalities than later-maturing association cortices. This gradient pattern, if confirmed, could provide clues about the developmental timing of TD pathophysiology. Moreover, the relationship between structural changes and clinical symptoms is not unidirectional: while some studies report correlations between reduced basal ganglia volume and tic severity, others find no such association, suggesting that structural metrics may reflect disease vulnerability or compensatory remodeling rather than current symptom status. This distinction has important implications for interpreting cross-sectional structural findings, as volume reductions could represent either a pathogenic deficit or an adaptive response to chronic tic-related neural activity. Longitudinal studies tracking structural changes alongside symptom fluctuations are critically needed to disentangle these possibilities.

Functional magnetic resonance imaging study

Resting state functional magnetic resonance imaging and task state functional magnetic resonance imaging provide tools for studying the dynamic functional mechanisms of TD [25].

In terms of resting state functional connectivity, Tikoo et al. [26] reported that untreated children with TS exhibited abnormally enhanced functional connectivity between the sensorimotor network and the default mode network (DMN), while connectivity between the PFC and striatal circuit was significantly reduced. This finding suggests a possible deficit in top-down cognitive control and relative overactivity of bottom-up sensorimotor pathways. A systematic review by Ramkiran et al. [27] in 2019 further supports the above findings.

Diversity of task-fMRI paradigms: Task-fMRI studies in TD have employed various paradigms, with partially overlapping but also distinct findings.

Tic suppression paradigm. When patients actively suppress tics, activation levels in the PFC (especially dorsolateral PFC and ACC) are generally lower than in controls, whereas activation of the supplementary motor area (SMA) and putamen is enhanced [28].

Go/No-Go task. This task probes response inhibition. Findings in TD have been inconsistent: some studies reported reduced inferior frontal gyrus activation, while others found normal or increased activation. The heterogeneity may reflect differences in tic severity, comorbidity, or medication status.

Cognitive control tasks (e.g., flanker, Simon tasks). Patients with TD often show hyperactivation of fronto-striatal regions during conflict processing, which may normalize with successful tic suppression or after behavioral therapy. A study published in *Movement Disorders* in 2015 [29] further confirmed the functional deficiencies of the motor regulatory network.

The diversity of task paradigms complicates direct cross-study comparison. For instance, tic suppression tasks tap voluntary inhibition of a prepotent motor act, while Go/No-Go measures reactive inhibition to external cues. The former consistently engages the SMA and putamen, while the latter involves the inferior frontal gyrus more prominently. This distinction suggests that different cognitive components of TD may rely on partially dissociable neural circuits, which should be considered when designing future studies.

Neuroimaging of premonitory urges: Premonitory urges (PUs) is a core sensory phenomenon in TD, often preceding tics and temporarily relieved by tic execution. fMRI studies have consistently implicated the insula and anterior cingulate cortex in the processing of PUs. For example, the insula is thought to integrate interoceptive signals related to urge intensity, while the ACC is involved in the conscious perception of urges and the generation of motor plans to relieve them. Increased insula-ACC connectivity has been reported to correlate with PU severity, suggesting that these regions may serve as potential neuro-markers for sensory aspects of TD.

Dynamic functional connectivity. Time-varying functional connectivity analyses have suggested that the frequency of brain network state transitions is increased in TD [30]. In 2017, Faghihi et al. [31] combined magnetic resonance spectroscopy (MRS) with fMRI and found that lower GABA concentration in the ACC was associated with reduced dynamic stability of functional networks, providing preliminary evidence for an excitation-inhibition imbalance hypothesis.

Overall, functional imaging consistently points to a dual dysfunction: (1) overactive sensorimotor and DMN connectivity, which may drive involuntary tic generation, and (2) underactive prefrontal-striatal top-down control, which fails to suppress these movements. The compensatory hyperactivation seen in some cognitive tasks suggests that patients may recruit additional neural resources to maintain performance, but this compensation appears insufficient for tic suppression. Notably, these functional abnormalities are at least partly correlated with structural and neurochemical measures (see 2.5), supporting a unified model of CSTC circuit dysregulation.

A unifying interpretation of the diverse functional imaging findings in TD is that the disorder may be characterized by a functional imbalance between competing neural systems - specifically, an overactive sensorimotor-DMN network that generates tic urges and actions, and an underactive fronto-striatal control network that fails to adequately inhibit them. This “imbalance model” is supported by the observation that successful tic suppression is associated with increased prefrontal engagement, whereas failed suppression correlates with persistent sensorimotor hyperactivity. However, it remains unclear whether the prefrontal hypoactivation represents a primary deficit or a secondary consequence of chronic tic-related demands on cognitive control resources. Furthermore, the directionality of connectivity changes (i.e., whether enhanced or reduced connectivity is pathogenic) may depend on the specific networks involved and the developmental stage of the patient, highlighting the need for developmental trajectory studies.

Diffusion tensor imaging study

Diffusion tensor imaging is a non-invasive method for evaluating the integrity of white matter microstructure. The diffusion tensor imaging study of patients with Tourette's syndrome mainly focuses on the white matter tracts within CSTC circuits [32].

Multiple meta-analyses have consistently reported a decrease in anisotropy scores and mean diffusivity in areas such as the anterior limb of the internal capsule and the left upper longitudinal bundle in patients with Tourette's syndrome, indicating impaired integrity of white matter microstructure. In a landmark study published in Brain in 2015, Worbe et al. [33] systematically reported the anisotropic changes in the cortical, striatal, pallidal, and thalamic networks of patients with Tourette's syndrome. It is worth noting that there are differences in diffusion tensor imaging patterns between children and adult patients with Tourette's syndrome [34]: children mainly exhibit a decrease in anisotropy score, while adult patients exhibit a complex pattern of increased and decreased anisotropy scores, which may reflect axonal remodeling and myelin repair during development.

In terms of white matter network topology, fiber tracking and network analysis based on diffusion tensor imaging further suggest that the global efficiency of white matter structural networks in patients with Tourette's syndrome is reduced, especially in the sensory motor sub network and striatal and cortical sub networks [35]. The multimodal magnetic resonance imaging study conducted by Liao et al. [36] in 2024 confirmed a certain correlation between structural connectivity abnormalities and functional connectivity changes, providing direct evidence for the coupling imbalance between structure and function.

Advanced diffusion MRI techniques: free-water DTI and NODDI: Conventional DTI metrics (FA, MD) are influenced by both tissue microstructure and extracellular free water. Free-water corrected DTI can separate these components, offering a more specific index of axonal density and myelination. A recent study in TS found that increased free water in the corpus callosum contributed to FA reductions, suggesting that neuroinflammation or edema might play a role. Neurite orientation dispersion and density imaging (NODDI) further disentangles neurite density and orientation dispersion. Preliminary NODDI studies in TD have indicated reduced neurite density in fronto-striatal tracts, supporting the hypothesis of delayed WM maturation. These advanced techniques may help clarify the neurobiological underpinnings of developmental trajectories in TD.

Despite the promise of DTI, conventional FA/MD changes are non-specific; the advent of free-water and NODDI provides a more biologically interpretable picture. Future longitudinal studies should incorporate these advanced metrics to distinguish between true axonal damage, dysmyelination, and neuroinflammation, which may have different therapeutic implications.

Positron emission tomography and single photon emission computed tomography neurotransmitter imaging

Positron emission tomography and single photon emission computed tomography can directly detect the functional status of the neurotransmitter system at the molecular level, and represent a core approach for studying neurotransmitter biomarkers in TD [37].

Dopamine system. This is the most extensively studied neurotransmitter system [38]. [11C] raclopride PET studies have reported controversial findings regarding striatal D2/D3 receptor binding rates in TS, but a relatively consistent observation is increased dopamine release [39]. Wong et al. [40] published a study in Neuropsychopharmacology in 2008, which found that patients with Tourette's syndrome had increased striatal dopamine release and abnormal presynaptic dopamine function.

Serotonin system. Studies investigating dopaminergic and serotonergic neurotransmission have reported reduced serotonin transporter (SERT) binding in the thalamus, striatum, and midbrain, as well as alterations in serotonin 2A receptors. A PET study using the [18F]altanserin radioligand (5-HT2A receptor) found increased receptor binding in the PFC of TS patients [41]. The study of Wong et al. [40] reported complex interactions between the serotonin system and the dopamine system. These findings provide direct evidence for the

involvement of the serotonin system in the pathophysiology of TD.

GABA and glutamate systems. Proton MRS (^{1}H-MRS) studies have indicated that, compared to controls, patients with TS have lower GABA concentration in the ACC and SMA, higher glutamate concentration, and a reduced GABA/glutamate ratio. The studies of Freed et al. [42], Lerner et al. [43], and Puts et al. [44] all reported similar results. The combined study of magnetic resonance spectroscopy and positron emission tomography by Draper et al. [45] further suggests a significant correlation between decreased concentration of gamma aminobutyric acid in the anterior cingulate gyrus and increased dopamine release.

Other neurotransmitter systems. The potential roles of the histamine, acetylcholine, and endogenous opioid systems in TD have been preliminarily explored [46]. Histamine H3 receptor antagonists have shown anti-tic effects in animal models and early-phase clinical trials, indicating that the histamine system may represent a novel therapeutic target [47].

Neurotransmitter system interactions: dopamine, serotonin, and GABA-glutamate crosstalk

Rather than acting in isolation, dopamine, serotonin, GABA, and glutamate systems interact extensively to regulate CSTC circuit function. Converging evidence from PET and MRS studies suggests the following tentative model:

Hyperdopaminergic tone in the striatum may facilitate thalamo-cortical disinhibition, promoting tic generation.

Serotonergic dysfunction, particularly reduced SERT binding, may modulate dopaminergic activity via 5-HT2A receptors on dopamine neurons, potentially exacerbating or mitigating tic severity depending on regional context.

GABAergic deficits in the ACC and SMA may reduce local inhibitory control, while increased glutamatergic drive may further shift the excitation-inhibition balance toward hyperexcitability.

These systems are likely not independent but rather form a complex network of mutual regulation. Future multimodal PET-MRS and PET-fMRI studies are needed to test causal relationships and to identify optimal therapeutic targets.

Taken together, multimodal imaging reveals a consistent picture of CSTC circuit disruption, but the effect sizes are often modest and heavily influenced by confounders (e.g., age, medication, comorbidity). These findings are summarized in **Table 1**. Notably, the association between structural, functional, and neurochemical abnormalities is rarely examined within the same individuals, and most studies are underpowered for subgroup analyses. The field would benefit from large-scale, harmonized, longitudinal cohorts (e.g., ENIGMA) that allow for rigorous control of confounders and examination of developmental trajectories. Furthermore, the causal direction between neurotransmitter imbalances and network dysfunctions remains speculative; interventional designs (e.g., before-after treatment) are needed to establish temporality.

The interaction among dopamine, serotonin, GABA, and glutamate systems in TD can be conceptualized as a push-pull regulatory network rather than a simple linear cascade. Dopaminergic hyperactivity in the striatum may not only facilitates thalamo-cortical disinhibition but also indirectly modulates serotonergic tone through reciprocal projections between the basal ganglia and raphe nuclei. Conversely, serotonergic dysfunction might amplify or dampen dopaminergic signals depending on the specific receptor subtypes and brain regions involved. This complexity explains why pharmacological interventions targeting a single neurotransmitter system often yield partial or variable clinical responses. A particularly intriguing hypothesis is that GABAergic deficits in the ACC and SMA may represent a common final pathway through which diverse upstream abnormalities (dopaminergic, serotonergic, or glutamatergic) converge to produce tic symptoms. If validated, this would suggest that GABAergic modulation could be a particularly promising therapeutic strategy, regardless of the primary etiological factor.

A schematic representation of neurotransmitter interactions within the CSTC circuit, along with potential TCM intervention targets, is provided in **Figure 1**.

Table 1. Summary of key findings from multi-modal neuroimaging studies in TD

Modality	Key Methods	Main Findings	Representative References	Controversies/Limitations
Structural MRI	VBM, SBM	Reduced basal ganglia volume, decreased anterior cingulate cortex thickness, whole-brain network topological abnormalities	Forde [19] 2017, O'Neill [22] 2019	Contradictory BG volume findings (age, medication, comorbidity effects); small samples
Functional MRI	rs-fMRI, task-fMRI	Increased sensorimotor-DMN connectivity, decreased prefrontal-striatal connectivity, compensatory activation	Tikoo [26] 2020, Faghihi [31] 2017	Heterogeneous task paradigms; limited studies on PUs
DTI	FA, MD, tractography	Reduced FA in anterior limb of internal capsule and left superior longitudinal fasciculus, decreased white matter network efficiency	Worbe [33] 2015, Schluter 2022	Conventional DTI lacks specificity; free-water/NODDI studies scarce
PET/SPECT	[^{11}C]raclopride, [^{123}I] β-CIT	Increased striatal dopamine release, elevated DAT density, reduced SERT binding	Wong [40] 2008, Müller-Vahl 2000	Small samples; tracer specificity limitations; few longitudinal studies
MRS	^{1}H-MRS	Decreased GABA and increased glutamate in anterior cingulate cortex, reduced GABA/glutamate ratio	Freed [42] 2016, Puts [44] 2015	Limited spatial resolution; field strength variability; no direct dynamic measurement

Table 2. Potential sources of heterogeneity in contradictory basal ganglia volume findings in TD

Source of Heterogeneity	Typical findings in children/unmedicated patients	Typical findings in adults/medicated patients	Potential mechanism
Age/disease duration	Reduced basal ganglia volume (especially caudate, putamen)	Normal or increased basal ganglia volume	Developmental plasticity, compensatory hypertrophy, selection bias in persistent tic subgroup
Comorbid ADHD	Further volume reduction in caudate and putamen	Limited studies	Additive neurodevelopmental burden, possible shared fronto-striatal circuit abnormalities
Comorbid OCD	Inconsistent findings in putamen volume	Possible globus pallidus enlargement	Involvement of different cortico-striatal subcircuits
Antipsychotic medication	Usually medication-naïve	Dose-dependent increase in basal ganglia volume	Trophic/volume-enlargement effect induced by D2 receptor blockade
Analytical method (VBM vs. SBM)	VBM: reduced GM concentration/volume; SBM: variable cortical thickness changes	Same as left	VBM sensitive to registration errors; SBM directly measures cortical morphology
Sample size/statistical power	Small samples (typically <50) leading to false negatives/positives	Same as left	Low power to detect true effects

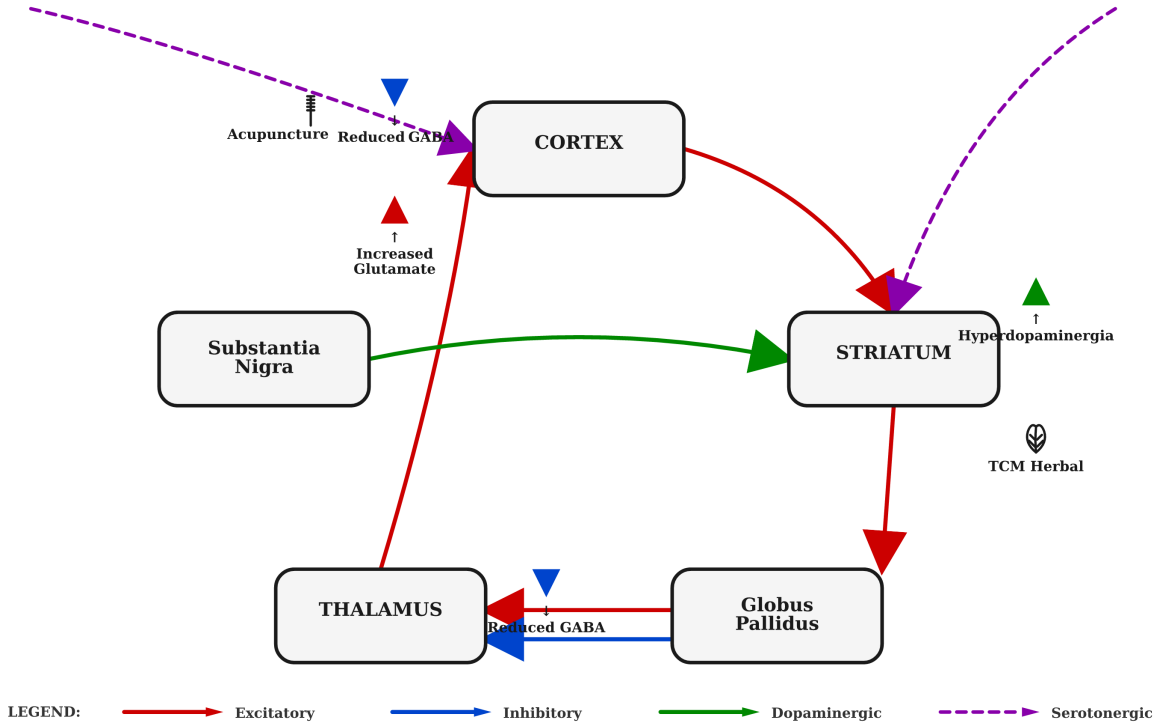

Figure 1. Neurotransmitter interactions in the CSTC circuit and TCM targets in TD. Glutamatergic, GABAergic, dopaminergic, and serotonergic pathways are shown within the CSTC circuit. Hyperdopaminergia, reduced GABA, and increased glutamate characterize TD, with potential TCM targets (herbal and acupuncture) annotated. Abbreviations: CSTC, cortico-striato-thalamo-cortical; GABA, γ-aminobutyric acid; TD, tic disorders; TCM, Traditional Chinese Medicine.

TCM interventions for TD: clinical evidence and neurobiological mechanisms

Overview of TCM syndrome classification

In modern clinical practice of TCM, the core pathogenesis of TD can be summarized as deficiency of the root and excess of the target, namely liver and kidney yin deficiency as the root and liver wind phlegm fire as the target. The common clinical subtypes include liver hyperactivity and wind movement type, phlegm fire internal disturbance type, yin deficiency and wind movement type, and spleen deficiency and liver hyperactivity type [48]. Different syndrome types correspond to different treatment principles and prescription systems. Han Xinmin et al. [49] released a revised version of the TCM diagnosis and treatment plan for children with TD in 2017, providing a more standardized differentiation and treatment guideline for this field. The potential association between these patterns and neuroimaging biomarkers will be further explored below.

The four TCM subtypes described above - liver hyperactivity with wind movement, phlegm-fire internal disturbance, yin deficiency with wind movement, and spleen deficiency with liver hyperactivity - represent a clinically derived taxonomy that may map onto distinct neurobiological substrates. However, this mapping remains largely hypothetical. A major challenge is that TCM pattern diagnosis is inherently subjective and relies heavily on the clinician's experience and training. Even within the same patient, different TCM practitioners may assign different pattern diagnoses, leading to inconsistent treatment strategies. This diagnostic variability constitutes a significant barrier to standardizing TCM treatment protocols and interpreting clinical trial results. The development of quantitative, biomarker-guided pattern differentiation tools - potentially incorporating imaging and neurochemical data - could help address this issue, but such tools are currently in early exploratory stages and require extensive validation.

Clinical efficacy of TCM compound

Growing preclinical evidence suggests that commonly used herbal formulas and their active components may modulate neurotransmitter systems relevant to CSTC circuits. Tianma Gouteng Yin and its modified versions, representative formulas for calming liver wind, have been shown in animal models to reduce striatal dopamine levels and upregulate dopamine D1 receptor expression [50]. Its active components, such as gastrodin and uncarine, may also enhance GABAergic transmission and inhibit glutamate release. However, these findings are derived from rodent models and ex vivo preparations; they provide mechanistic hypotheses but cannot be directly extrapolated to humans without confirmatory in vivo evidence.

Despite these promising preclinical findings, direct human evidence linking herbal components to specific neurotransmitter targets remains limited. A few PET and MRS studies (see Section 3.5) have begun to explore these links, but causality has not been firmly established due to correlational designs and small samples.

Clinical efficacy of herbal formulas

A systematic review of randomized controlled trials (RCTs) has indicated that the total effective rate of Tianma Gouteng Yin in treating TD ranges from 75% to 90%, which is comparable to, or slightly higher than, that of haloperidol or tiapride, with a significantly lower incidence of adverse reactions [51]. HanQi et al. [52] published a meta-analysis in the Asian Journal of Psychiatry including 15 RCTs, confirming the effectiveness and safety advantages of TCM herbal therapy for TS. Jiuwei Xifeng Granules are suitable for patients with yin deficiency and wind type TD, particularly those with vocal tics, irritability, and a red tongue with little coating [53]. A multicenter TCT conducted by Du et al. [54] in 2017, including 144 cases showed that after four weeks of treatment, the reduction in Yale Global Tic Severity Scale (YGTSS) scores was significantly greater than that in the placebo group. Other formulas such as Chuanxiong Chatiao San, Er Chen Tang combined with Wen Dan Tang, and Bu Zhong Yi Qi Tang are used for phlegm-fire and spleen deficiency patterns [55]. The systematic review published by You HZ et al. [56] in 2021 further confirmed the clinical efficacy of TCM in treating Tourette's syndrome.

While the above RCTs suggest efficacy, most have methodological limitations: small sample sizes, lack of adequate blinding (especially for herbal preparations with distinct taste/smell), heterogeneous diagnostic criteria for TCM patterns, and variability in herbal formulations across studies. Moreover, the control interventions often use low-dose conventional drugs or placebos that may not be fully inert. Therefore, the apparent superiority of TCM over Western drugs should be interpreted with caution; the clinically meaningful difference may be smaller than reported.

The clinical efficacy findings for herbal formulas, while encouraging, should be interpreted with several additional caveats. First, the majority of RCTs included in meta-analyses have relatively short follow-up periods (typically 4-12 weeks), leaving the long-term efficacy and safety of TCM herbal therapy largely unknown. Second, the placebo response rate in TD trials is generally high (often exceeding 30%), which may inflate the apparent efficacy of active interventions if blinding is inadequate. Third, the use of YGTSS as the primary outcome measure, while standard, captures only tic severity and does not fully reflect the multidimensional impact of TD on quality of life, emotional well-being, or social functioning - domains that TCM treatments might affect through different mechanisms. Future trials should incorporate patient-reported outcomes and functional impairment measures alongside YGTSS to provide a more comprehensive assessment of treatment effects.

Acupuncture and moxibustion: clinical evidence and mechanisms

Body acupuncture. Commonly used acupoints include Baihui (GV20), Fengchi (GB20), Taichong (Liv3), Hegu (LI4), Zusanli (ST36), and Sanyinjiao (SP6), with the core principle of calming liver wind and regulating the mind [57]. Ma et al. [58] reported that the total effective rate of acupuncture for TD ranged from 85% to 92%, improving both motor and vocal tics, with effects lasting three to six months after treatment cessation.

Based on traditional theory, the combination of Taichong (Liv3, liver channel) and Hegu (LI4, large intestine channel) is known as "opening the four gates" and is believed to regulate qi and blood, calm liver wind, and relieve pain. Existing fMRI studies in TD have reported that needling this pair may simultaneously modulate the prefrontal cognitive control network and the limbic emotional network. For example, Liang et al. [59] found that acupuncture at Taichong induced changes in ACC and insula activity in TS patients. Although direct evidence for the paired effect in TD is still preliminary, studies in other conditions suggest that Liv3-LI4 stimulation can enhance fronto-limbic functional connectivity. Future TD-specific research is warranted.

Scalp acupuncture targets specific cortical zones corresponding to Brodmann areas. The motor zone (anterior to the precentral gyrus) and the "dance tremor control zone" are commonly used for TD. Research suggests that scalp acupuncture may regulate blood oxygen level-dependent (BOLD) signals in the frontal lobe and BG circuits [16]. Dan et al. [60] observed using magnetic resonance spectroscopy in 2023 that after scalp acupuncture treatment, the concentration of gamma aminobutyric acid in the anterior cingulate gyrus of patients with Tourette's syndrome increased while the concentration of glutamate decreased. This provides direct evidence for the regulatory mechanism of gamma aminobutyric acid in acupuncture, though this is a single small-sample (n=30) study without a sham control, so the findings require replication.

Ear acupressure. Commonly used ear points include Shenmen, Heart, Liver, Kidney, and Subcortex. A RCT by Duan et al. [61], including 30 children with TD suggested that ear acupressure combined with TCM was superior to Western medicine alone.

Acupuncture RCTs face unique blinding challenges; most studies are rated as high risk of bias for blinding. Furthermore, the specificity of acupoints is often not validated against sham points, and the physiological mechanisms (e.g., whether effects are mediated via local microcirculation, segmental reflexes, or supraspinal modulation) remain unclear. The MRS study by Dan et al. is promising but needs larger, sham-controlled replication.

While the clinical evidence for acupuncture in TD is reasonably consistent, the underlying mechanisms remain incompletely understood. Several non-exclusive hypotheses have been proposed: (1) acupuncture may modulate the descending pain-inhibitory and motor-control pathways through segmental spinal reflexes; (2) needling at specific points may activate the hypothalamic-pituitary-adrenal axis and influence neuroendocrine regulation; and (3) the somatosensory input from acupuncture may induce plastic changes in sensorimotor cortical maps over repeated sessions. The MRS findings of increased ACC GABA following scalp acupuncture provide preliminary support for the third mechanism, but this study requires replication with larger samples and sham controls. Importantly, the "dose-response" relationship for acupuncture (e.g., frequency, duration, and intensity of stimulation) has not been systematically investigated in TD, representing another critical knowledge gap.

Multimodal imaging evidence for TCM effects

Herbal formulas. A resting-state fMRI study [62] by Jin and Ying et al. in 2024 observed changes in brain functional connectivity in TS patients before and after treatment with modified Tianma Gouteng Yin. They found that after treatment, PFC-striatum functional connectivity was enhanced, and abnormal sensorimotor cortex activity was reduced. This change correlated significantly with YGTSS score improvement. Another DTI study suggested that FA of the ALIC in TS patients showed a trend of recovery after TCM treatment [63].

Acupuncture. In addition to the MRS study mentioned above [60], a task-fMRI study by Liang et al. [59] found that acupuncture at Taichong (Liv3) induced BOLD signal changes in the ACC and insula in TS patients.

Neurotransmitter effects. As noted in 3.2, animal model studies have shown that Tianma Gouteng Yin may reduce striatal dopamine levels and upregulate D1 receptor expression [50]. Uncarine alkaloids may inhibit dopamine release and enhance GABA activity; and acupuncture may modulate D2 receptor density and serotonin content in the BG region [64]. These preclinical observations are broadly consistent with the human imaging changes (e.g., increased GABA by MRS), but the link is correla-

tional, not causal. Direct evidence linking specific TCM interventions to neurotransmitter changes in humans remains limited and largely correlational - for instance, no PET study has yet measured dopamine release before and after TCM treatment in the same patients.

Currently, only a handful of human imaging studies have examined TCM effects in TD, all with small samples (n<50 per arm) and mostly uncontrolled or non-randomized designs. The reported changes in functional connectivity and MRS metabolites are encouraging but should be considered preliminary hypothesis-generating data rather than conclusive evidence of mechanism. Rigorous, large-scale, sham-/placebo-controlled trials with pre-registered imaging endpoints are urgently needed.

Preclinical and human imaging studies have identified several neurotransmitter targets of commonly used herbal formulas. **Table 3** summarizes the main neurochemical targets, available evidence from animal models, and corresponding human imaging findings where available.

Adjunctive TCM non-pharmacological therapies

In addition to acupuncture and herbal medicine, other TCM modalities may provide adjunctive benefits: Tuina (Chinese therapeutic massage). By applying tactile and proprioceptive input, Tuina may modulate sensorimotor integration at the spinal and cortical levels. A few small studies have reported reduced tic frequency after Tuina sessions, but no imaging studies are currently available; Emotion-regulating therapies. Given the frequent comorbidity of TD with anxiety and emotional dysregulation, mind-body interventions (e.g., relaxation training, emotional guidance) may have central effects on limbic circuits; Daoyin (e.g., Baduanjin). This gentle exercise combines movement, breathing, and attention. Preliminary evidence in other neurodevelopmental disorders suggests potential improvements in executive function and emotional regulation, but studies in TD are lacking. These adjunctive approaches highlight the holistic characteristics of TCM and open up future research directions, though current evidence remains preliminary.

Precise diagnosis and treatment strategies combining TCM and western medicine

TCM syndrome differentiation guided by biomarkers

Currently, TCM pattern differentiation for TD relies primarily on the four diagnostic methods (inspection, listening/smelling, inquiry, palpation) and lacks objective standards. The introduction of multimodal brain imaging and neurotransmitter markers offers a possibility for quantitative TCM syndrome diagnosis [65].

Association between functional biomarkers and TCM patterns. Preliminary studies have suggested that patients with liver-hyperactivity wind-type TD may exhibit resting-state functional connectivity characterized by overactivation of sensorimotor networks, while those with yin-deficiency wind-type may show weakened prefrontal executive control network connectivity [66]. These differential brain functional patterns might constitute neuroimaging features of different TCM patterns, but validation in larger samples is needed.

Molecular imaging markers and TCM patterns. Although large-scale studies are lacking, some researchers have hypothesized that liver-yang hyperactivity type may primarily involve hyperactive dopamine system function, whereas yin-deficiency wind type may involve more GABAergic inhibitory deficits. PET, SPECT, and MRS techniques could potentially test these hypotheses and provide objective biochemical evidence for TCM pattern differentiation [67].

These associations are speculative and based on very limited data. Most TCM pattern differentiation in existing studies is performed by different clinicians without standardized operational criteria, and imaging analyses are often post-hoc exploratory. Prospective, hypothesis-driven studies with predefined TCM pattern definitions and imaging protocols are needed before any biomarker can be considered for clinical pattern differentiation.

Efficacy prediction and personalized treatment

Predicting TCM efficacy using imaging biomarkers. One exploratory study suggested that TD patients with lower baseline ACC GABA levels showed better response to TCM treatment,

Table 3. Neurochemical targets of major herbal formula components and corresponding imaging effects

Herbal formula/component	Main neurochemical targets	Preclinical evidence (animal models)	Human imaging evidence	Main imaging modality
Tianma Gouteng Yin	Dopamine (↓), GABA (↑), Glutamate (↓)	Reduces striatal dopamine release, upregulates D1 receptor, enhances GABAergic transmission	↑ PFC-striatum functional connectivity, ↓ sensorimotor cortex hyperactivation	rs-fMRI, DTI
Uncarine (from Uncaria)	Dopamine (↓), GABA (↑)	Inhibits dopamine release, enhances GABA activity	None in humans	-
Gastrodin	GABA (↑), Glutamate (↓)	Upregulates GAD65/67, reduces excitotoxicity	None in humans	-
Zhengan Xifeng Yin	Serotonin (modulation), GABA (↑)	Modulates prefrontal serotonin turnover, normalizes stress-induced GABA changes	None dedicated to TD	-
Jiuwei Xifeng Granules	Dopamine, Serotonin	Improves stereotypic behaviors in TS-like rodent models, modulates dopaminergic and serotonergic systems	No imaging studies (only clinical RCT)	-
Shaomazhijing Granules	Dopamine, GABA	Modulates striatal dopamine and GABA levels	No imaging studies	-
Acupuncture (Taichong, Hegu)	Dopamine D2 receptor density, Serotonin	Modulates D2 receptor density and serotonin content in basal ganglia	BOLD signal changes in ACC and insula	task-fMRI, MRS
Scalp acupuncture (motor area)	GABA (↑), Glutamate (↓)	No direct animal evidence	↑ GABA concentration, ↓ glutamate in ACC (one study)	MRS

Abbreviations: GABA, γ-aminobutyric acid; PFC, prefrontal cortex; ACC, anterior cingulate cortex; BOLD, blood oxygen level-dependent; MRS, magnetic resonance spectroscopy; rs-fMRI, resting-state functional MRI; TD, tic disorders; TS, Tourette syndrome.

Table 4. Summary of existing randomized controlled trials (RCTs) with imaging outcomes for TCM treatment of TD

Author, year	Sample size (TCM/control)	Intervention	Imaging modality	Main imaging finding	Clinical efficacy (YGTSS change)
Jin & Ying, 2024 [62]	42/40	Modified Tianma Gouteng Yin vs. conventional Western medicine	rs-fMRI	↑ PFC-striatum functional connectivity, ↓ sensorimotor cortex hyperactivation	YGTSS ↓ ~45%
Liang et al., 2014 [59]	30/30	Acupuncture at Taichong (Liv3) vs. sham acupuncture	task-fMRI	BOLD signal changes in ACC and insula induced by acupuncture	YGTSS ↓ ~48%
Du et al., 2017 [54]	72/72	Jiuwei Xifeng Granules vs. placebo	None (clinical only)	Not collected	YGTSS ↓ 52% vs. placebo 28%
Hazlett et al., 2012 [63]	14 (non-RCT, pre-post)	Integrative TCM herbal therapy	DTI	Trend of FA recovery in anterior limb of internal capsule	Clinical improvement correlated with FA change
Cheng et al., 2023 [50]	Animal study (rats)	Tianma Gouteng Yin vs. haloperidol	None (behavioral + histology)	Not applicable (non-human)	Behavioral improvement
Liu et al., 2015 [64]	Animal study (PD model)	Tianma Gouteng Yin	None (histology)	Not applicable	Neuroprotective effects

Note: High-quality RCTs of TCM for TD that simultaneously collect imaging data remain few. This table lists published human studies with imaging endpoints (and representative animal studies for reference). YGTSS, Yale Global Tic Severity Scale; ↑, increase/enhancement; ↓, decrease/reduction; FA, fractional anisotropy.

suggesting that MRS might be a candidate biomarker for predicting TCM efficacy [68]. Similarly, baseline resting-state functional connectivity features have been found to predict differential responses to different treatment regimens [69], though these findings await replication.

Monitoring treatment response. Multimodal imaging can be used for longitudinal monitoring of treatment effects. A small-sample prospective study suggested that early changes in resting-state functional connectivity after four weeks of TCM treatment preceded clinical symptom improvement, hinting that functional imaging could serve as an early sensitive indicator of treatment response [70].

These predictive biomarker studies are few, small, and lack independent validation. The reported correlations often do not survive correction for multiple comparisons. It is premature to recommend any imaging biomarker for clinical prediction in TCM practice; current evidence should be viewed as hypothesis-generating.

Several RCTs have incorporated imaging endpoints to assess TCM treatment effects. **Table 4** provides a summary of existing studies, including sample sizes, interventions, imaging modalities, and main findings.

Construction of a three-dimensional biomarker system for imaging, neurotransmitters, and syndrome differentiation

To achieve precision diagnosis and treatment of TD, a multi-level, multimodal biomarker system may be needed. This article tentatively proposes the following framework:

Structural dimension. Structural imaging biomarkers based on VBM and DTI (e.g., BG volume, cortical thickness, WM microstructural integrity) may reflect static anatomical substrates.

Functional dimension. Functional imaging biomarkers based on rs-fMRI and task-fMRI (e.g., functional connectivity, network topology) may reflect dynamic functional states of neural circuits.

Molecular dimension. Neurotransmitter markers based on PET, MRS, and SPECT (e.g., dopamine tone, serotonin function, GABA-glutamate balance) may reflect the biochemical basis of chemical neurotransmission.

Clinical dimension. TCM pattern differentiation via the four examinations provides individualized holistic assessment.

These four dimensions are likely interrelated: structural abnormalities may form the anatomical foundation for functional changes, molecular neurotransmitter imbalances may drive functional circuit dysfunction, and functional changes may eventually manifest in clinical symptoms. Integration of this multidimensional system will require multivariate machine learning and multimodal data fusion.

While the proposed four-dimensional framework offers a comprehensive conceptual model for precision diagnosis, several practical challenges must be addressed for its clinical implementation. First, the cost and accessibility of multimodal imaging (MRI, PET, MRS) currently limit its use to specialized research centers; translating these tools to routine clinical practice will require substantial infrastructure investment and cost reduction. Second, the integration of neuroimaging data with TCM pattern diagnosis requires a common data architecture and standardized data collection protocols across institutions. Third, the development of interpretable machine learning models that can handle high-dimensional, multimodal data while providing clinically actionable outputs remains a significant technical challenge. Fourth, regulatory and ethical considerations, including data privacy, algorithm transparency, and liability for AI-based recommendations, must be addressed before such diagnostic systems can be deployed in clinical settings.

As illustrated in **Figure 2**, the proposed multidimensional biomarker framework integrates structural, functional, molecular, and clinical dimensions.

Translational medicine pathway

A key challenge is how to translate expensive and resource-intensive multimodal biomarkers into affordable, clinically applicable surrogate indicators suitable for primary care settings. Several potential pathways may be considered:

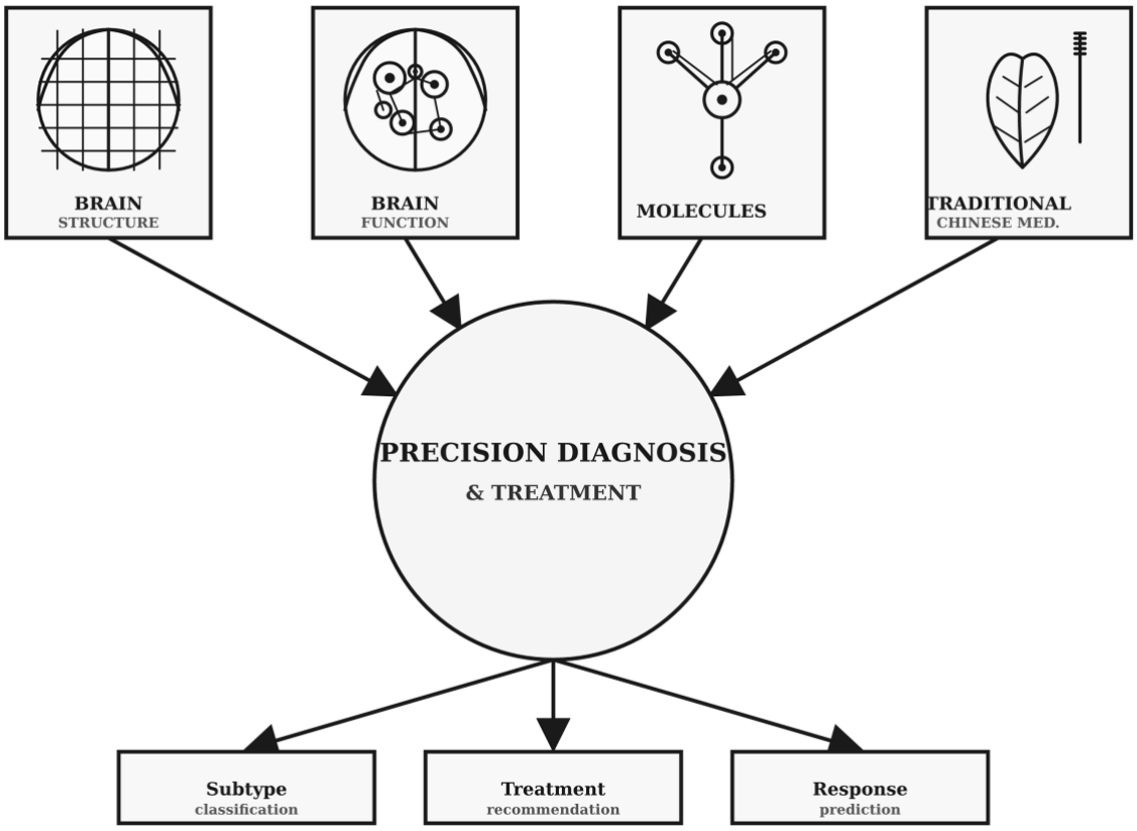

Figure 2. Framework for integrating multimodal biomarkers and TCM syndromes for precision diagnosis of TD. The framework integrates structural (MRI/DTI), functional (fMRI), molecular (PET/SPECT/MRS), and clinical (TCM pattern differentiation) dimensions through multimodal data fusion, converging toward individualized subtyping, treatment recommendation, and response prediction.

Functional near-infrared spectroscopy (fNIRS). fNIRS is a portable, low-cost optical imaging technique that can measure cortical oxygenation changes. Identifying a specific fNIRS activation pattern (e.g., reduced SMA or dorsolateral PFC activation during tic suppression) could serve as a surrogate for task-fMRI findings.

Blood-based biomarkers. A combination of circulating exosomal miRNAs that indirectly reflect GABAergic deficiency (e.g., miRNAs targeting GAD1 or GABRA1 genes) might be developed as a peripheral indicator of central neurotransmitter imbalance.

Electroencephalography (EEG)-derived metrics. Resting-state EEG power ratios or event-related potentials (e.g., error-related negativity) have been associated with tic severity and may be implemented in low-cost mobile devices.

These surrogate indicators would need rigorous validation against gold-standard multimodal imaging before clinical deployment. Nonetheless, they represent a promising direction for scaling up precision medicine to resource-limited settings.

Multimodal data fusion method

Current methods include canonical correlation analysis (CCA) and its extensions, which can identify shared variation patterns across different modalities. Cao et al. [71] used sparse CCA to jointly analyze sMRI and DTI data from TS patients. Multi-kernel learning can integrate different modalities by combining kernel functions; preliminary studies have shown that multi-kernel learning-based classifiers distinguish TS patients from healthy controls with higher accuracy than any single modality [72]. Deep learning methods such as graph convo-

lutional networks and variational autoencoders have shown potential for fusing multimodal brain imaging data. Wen et al. [72] Reported a deep learning framework combining clinical and imaging data for multimodal diagnosis of TS. A noteworthy direction is to incorporate TCM four-examination information into a multimodal deep learning framework to build an intelligent diagnostic model integrating TCM and Western medicine.

Challenges

Limitations of current research

Despite progress, multiple challenges remain.

Small sample sizes and reproducibility. Most imaging studies have small samples, limited statistical power, and heterogeneity across studies, making replication difficult. Greene et al. [73] highlighted the methodological limitations of existing multimodal imaging studies on TD, including small sample sizes and lack of validation cohorts. Establishing multi-center, standardized data collection plans is currently an important task.

Cross-sectional limitations and developmental factors. TD is a developmental disorder, and brain imaging characteristics likely differ among children, adolescents, and adults. Large-sample studies by Greene [74] et al. (2017) revealed the impact of developmental stages on brain structure in TS. The vast majority of cross-sectional studies cannot distinguish disease-related from developmental brain changes, nor separate the effects of medication from the natural history. Longitudinal designs are crucial.

Uncontrolled comorbidity interference. TD often co-occurs with ADHD, OCD, and anxiety disorders, each associated with distinct brain imaging and neurotransmitter changes. For example, ADHD itself involves frontal-striatal circuit dysfunction. Most studies have failed to adequately control for comorbidities, potentially biasing the identification of disease-specific biomarkers. Only a few studies have specifically analyzed subgroups with comorbid ADHD.

Complexity and standardization of TCM herbal formulas. Tianma Gouteng Yin, Zhengan Xifeng Tang, and others are composed of multiple herbs with complex active ingredients. The composition of formulas varies across studies, reducing comparability. Additionally, TCM lacks a gold standard for pattern diagnosis, with diagnostic criteria varying across studies.

Blinding challenges in acupuncture research. It is difficult to set sham or placebo acupuncture controls, and blinding of patients and operators is challenging, introducing high risk of bias. Most RCTs of acupuncture for TD have been rated as having inadequate blinding.

Evidence hierarchy in TCM research. Although some RCTs and systematic reviews exist, high-quality, large-sample, multi-center, rigorously blinded studies remain relatively few, limiting international recognition.

A major gap is the lack of direct, within-subject comparisons between TCM interventions and Western pharmacological treatments using the same imaging protocols. Without such head-to-head trials, it is difficult to determine whether TCM effects are mechanistically distinct or simply reflect nonspecific improvements associated with symptom reduction.

Future research directions

Expanding precision molecular imaging. Development of novel radiotracers, such as PET tracers targeting GABA receptor subtypes, will enhance molecular imaging specificity. Ultra-high field MRS can provide higher-resolution neurochemical profiling.

Establishing longitudinal cohort studies. Large-sample, multi-center longitudinal cohorts for TD (e.g., following the framework of ENIGMA-Tourette syndrome) with periodic synchronous collection of multimodal imaging, neurochemical, TCM pattern, and clinical scale data may enable individual-level biomarker trajectory characterization. A minimum follow-up of three to five years from childhood to adolescence is recommended.

Deep integration of TCM RCTs with imaging. More rigorously designed multicenter RCTs are needed, with synchronous collection of multimodal brain imaging and MRS data before and after TCM treatment, to establish potential causal relationships between imaging changes,

neurotransmitter changes, and clinical efficacy. A short-term goal would be to complete at least one to two RCTs within three to five years with sample sizes of no less than 80 per arm, treatment duration of eight to twelve weeks, including fMRI and MRS, to preliminarily validate efficacy-predictive biomarkers.

AI-driven integrated diagnostic models. With the accumulation of multi-center big data, interpretable AI diagnostic models may become possible. Such models could potentially output TD subtype classification based on multimodal images, recommend optimal treatment strategies (herbal, Western medicine, acupuncture, or combination), predict treatment response and adverse reaction risks, and provide neuroimaging interpretations of TCM patterns.

Low-cost translation and primary care dissemination. Translating brain imaging findings into clinically applicable biomarkers requires cost reduction. fNIRS can measure cortical activation in regions such as SMA and dorsolateral PFC. Low-cost mobile devices such as portable EEG may transfer laboratory findings to community and primary healthcare settings. Feasibility studies of fNIRS in TCM pattern classification and acupuncture efficacy monitoring are suggested.

Perhaps the greatest challenge for the field is bridging the gap between sophisticated research biomarkers and practical clinical tools. The development of low-cost surrogates (e.g., fNIRS, EEG, blood-based markers) is essential, but these surrogates must be validated against gold-standard imaging measures in large, diverse populations before they can be adopted. Additionally, the transferability of findings across different healthcare settings - from tertiary academic centers to community-based primary care - needs to be systematically evaluated. Beyond technological considerations, the clinical adoption of precision medicine for TD will require training clinicians to interpret imaging-derived biomarkers and integrate them with traditional diagnostic approaches. This is particularly relevant for TCM practitioners, who may not be familiar with neuroimaging concepts, and for Western-trained physicians, who may be unfamiliar with TCM pattern differentiation. Interdisciplinary education and collaborative care models will be essential for realizing the full potential of integrated precision medicine.

Conclusion

The combination of multimodal brain imaging technology and neurotransmitter imaging reveals the complex neuropathological basis of TD: abnormal basal ganglia structure, disrupted functional connections in CSTC circuits, overactive dopamine system function, and weakened gamma aminobutyric acid inhibitory function, features of the disease.

TCM acts on this core loop through a multitarget and multi pathway regulatory mechanism, demonstrating certain clinical efficacy and good safety. Classic prescriptions such as Tianma Gouteng Decoction, Zhengan Xifeng Decoction and acupuncture and moxibustion therapy may reverse some brain imaging and neurotransmitter abnormalities while improving the symptoms of TD. However, the current human imaging evidence for TCM is preliminary and correlational; robust causal inferences await large-scale, sham-controlled, longitudinal trials.

The core concept of precision diagnosis and treatment combining traditional Chinese and Western medicine is to establish a multidimensional biomarker system of neuroimaging, neurotransmitters, and TCM syndromes. Through multimodal data fusion and artificial intelligence technology, precise subtyping of TD, personalized treatment strategy selection, and objective evaluation of efficacy can be achieved.

Looking ahead to the future, the comprehensive application of large sample longitudinal queues, high-quality randomized controlled trials of TCM, novel molecular imaging probes, and interpretable artificial intelligence models may promote the transformation of diagnosis and treatment of TD from experience driven to data-driven, from extensive treatment to precise intervention, and provide scientific evidence support for the internationalization and modernization of TCM.

Ultimately, the transition from experience-based to data-driven diagnosis and treatment of TD will be incremental rather than revolutionary. While multimodal imaging and AI hold considerable promise, they are unlikely to replace

clinical judgment in the foreseeable future. Instead, these tools should be viewed as complementary aids that can enhance clinical decision-making by providing objective neurobiological information that is not accessible through clinical examination alone. The success of this integration will depend on continued interdisciplinary collaboration among neurologists, psychiatrists, neuroimagers, TCM practitioners, and data scientists, as well as sustained investment in multi-center, longitudinal research infrastructure.

Acknowledgements

This work was supported by the Heilongjiang Provincial Research Project on TCM (Grant No. ZHY2023-054), Harbin Municipal Science and Technology Program (Grant No. 2023-ZCZJNS063) and the Joint Fund Cultivation Project of Heilongjiang Provincial Natural Science Foundation (Grant No. PL2025H236).

Disclosure of conflict of interest

None.

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