

EXCITATION/INHIBITION IMBALANCE AND NETWORK DYSCONNECTIVITY IN SCHIZOPHRENIA: EVIDENCE FROM TMS-EMG AND RESTING-STATE FMRI

Ph.D. Thesis

Orsolya Lányi

Translational Medicine Program

Mental Health Sciences Division

SEMMELWEIS UNIVERSITY



Supervisor:

Gábor Csukly (M.D., Ph.D.)

Official reviewers:

Bence Lázár (M.D., Ph.D.)

Viktor Gál (M.D., Ph.D.)

Head of the Complex Examination Committee:

Viktor Horváth (M.D., Ph.D.)

Members of the Complex Examination Committee:

Lajos Bogár (M.D., Ph.D.)

Maria Dorobantu (M.D., Ph.D.)

Róbert Sepp (M.D., Ph.D.)

Bence Szabó (Ph.D.)

Budapest

2026

***"The greatest challenge in all of science is to understand how
the mysteries of human nature
— as reflected in our individual experience of the world —
arise from the physical matter of the brain."***

Eric R. Kandel,

The Disordered Mind: What Unusual Brains Tell Us About Ourselves (2018)

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS	6
2. STUDENT PROFILE	8
2.1. Vision and mission statement, specific goals	8
2.2. Scientometrics	8
2.3. Future plans	8
3. SUMMARY OF THE THESIS	9
4. GRAPHICAL ABSTRACT	10
5. INTRODUCTION.....	11
5.1. The clinical and translational challenge of schizophrenia.....	11
5.2. Excitation-inhibition imbalance and dysconnectivity as neurobiological models of schizophrenia.....	13
5.3 Operationalising schizophrenia pathophysiology across local circuit and network levels	15
5.4. Motor cortical inhibition and excitability measured with TMS-EMG	17
5.4.1. Principles of TMS-EMG and motor evoked potentials.....	17
5.4.2. Excitatory and inhibitory TMS-EMG paradigms.....	19
5.4.3. TMS EMG evidence in schizophrenia and rationale for Study I	22
5.5. Cerebello-Thalamo-Cortical circuitry and resting state fMRI dysconnectivity	23
5.5.1. CTC network connectivity as a second biological level of investigation.....	23
5.5.2. Thalamus: anatomy, function and findings in schizophrenia	23
5.5.3. Thalamic findings in schizophrenia	25
5.5.4. Cerebellum and the Cerebello-Thalamo-Cortical circuitry in schizophrenia.....	27
5.5.5. Limitations in the literature and rationale for Study II.....	29
6. OBJECTIVES	31
6.1. Study I. – Excitation-inhibition in schizophrenia, a meta-analysis of TMS-EMG studies	31
6.2. Study II. - Cerebello-Thalamo-Cortical Dysconnectivity in Schizophrenia: A Resting-State fMRI Meta-Analysis	32
7. METHODS	33
7.1. Study I.....	33
7.1.1. Protocol, Eligibility and Search Strategy	33
7.1.2. Study Selection and Data Extraction.....	33
7.1.3. Risk of Bias and Quality of Evidence Assessment	34
7.1.4. Data Synthesis and Analysis	34
7.2. Study II.....	35

7.2.1. Eligibility criteria and search strategy	35
7.2.2. Data synthesis.....	35
7.2.3. Statistical analysis	36
7.2.4. Additional analyses	37
8. RESULTS	38
8.1. Study I.....	38
8.1.1. Search and baseline characteristics	38
8.1.2. Short-Interval Intracortical Inhibition (SICI)	40
8.1.3. Cortical Silent Period (CSP)	42
8.1.4. Intracortical Facilitation (ICF), Long-Interval Intracortical Inhibition (LICI), and Resting Motor Threshold (RMT)	43
8.1.5. Risk of Bias, Publication Bias, and Heterogeneity	43
8.2. Study II.....	45
8.2.1. Search and selection	45
8.2.2. Thalamic hyperconnectivity in SSD.....	46
8.2.3. Thalamic hypoconnectivity in SSD.....	49
8.2.4. Symptom Dimensions, Illness Stage, and Disease Progression	51
8.2.5. Subthalamic results	54
8.2.6. Cerebellar connectivity	55
8.2.7. Sub-cerebellar results	57
8.2.8. Risk of Bias and Heterogeneity.....	57
9. DISCUSSION	58
9.1. Summary of findings: converging evidence for E/I related inhibitory deficit and CTC dysconnectivity in schizophrenia	58
9.1.1. Main findings of Study I and Study II.....	58
9.1.2. E/I imbalance as a mechanistic explanation to integrate biological scales in Schizophrenia.....	60
9.1.3. Predictive processing and sensorimotor pathways as a framework for altered information flow.....	62
9.2. Strengths and Limitations.....	63
10. CONCLUSIONS.....	66
11. IMPLICATIONS FOR PRACTICE.....	67
12. IMPLICATIONS FOR RESEARCH	69
12.1. Methodology and Study Design	69
12.2. New Areas.....	70

13. IMPLICATIONS FOR POLICY MAKERS	72
14. FUTURE PERSPECTIVES	73
15. REFERENCES.....	74
16. BIBLIOGRAPHY	101
16.1. Publications Related to the Thesis.....	101
16.2. Publications not Related to the Thesis	101
17. ACKNOWLEDGEMENTS	103

1. LIST OF ABBREVIATIONS

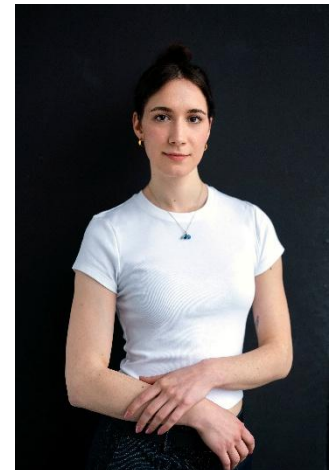
ALE	Activation likelihood estimation
AMT	Active motor threshold
BD	Bipolar disorder
BOLD	Blood oxygen level dependent
CHR	Clinical high risk
CI	Confidence Interval
COBIDAS	Committee on Best Practice in Data Analysis and Sharing
CPZ	Chlorpromazine-equivalent antipsychotic dose
CS	Conditioning Stimulus
CSP	Cortical silent period
CTC	Cerebello-Thalamo-Cortical
DSM	Diagnostic and Statistical Manual of Mental Disorders
E/I	Excitation/inhibition
EEG	Electroencephalography
EMG	Electromyography
FEP	First-Episode Psychosis
fMRI	Functional magnetic resonance imaging
FWE	Family-Wise Error
GABA	Gamma-aminobutyric acid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HC	Healthy control
ICF	Intracortical Facilitation
ISI	Interstimulus Interval
LICI	Long-Interval Intracortical Inhibition
MEP	Motor Evoked Potential
MRI	Magnetic resonance imaging
NMDA	N-methyl-D-aspartate
PANSS	Positive and Negative Syndrome Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RMT	Resting motor threshold
ROI	Region of interest

SAD	Schizoaffective disorder
SDM	Seed-based d Mapping
SICI	Short-Interval Intracortical Inhibition
SIPS	Structured Interview for Psychosis-Risk Syndromes
SSD	Schizophrenia Spectrum Disorder
TFCE	Threshold-free cluster enhancement
TMS	Transcranial Magnetic Stimulation
TS	Test stimulus

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My scientific vision is to advance the understanding of the neurobiology of schizophrenia. My mission is to use neurophysiology, neuroimaging and brain stimulation techniques to identify reproducible circuit-level alterations that may inform future clinical translation.



2.2. Scientometrics

Number of all publications:	6
Cumulative IF:	26
Av IF/publication:	4.96
Ranking (SciMago):	D1: 4, Q1:1
Number of publications related to the subject of the thesis:	2
Cumulative IF:	9
Av IF/publication:	4.5
Ranking (Sci Mago):	D1: 2
Number of citations on Google Scholar:	99
Number of citations on MTMT (independent):	44
H-index:	5

The detailed bibliography of the student can be found on page 101.

2.3. Future plans

Building on my PhD work and the year I spent as a Fulbright visiting researcher at the Yale School of Medicine, my goal is to focus on multimodal clinical neuroscience and biomarker development for schizophrenia. In future work, I aim to extend the results of this thesis and empirically validate whether TMS-EMG and Cerebello-Thalamo-Cortical connectivity can contribute to treatment response prediction and patient stratification.

3. SUMMARY OF THE THESIS

Schizophrenia is a severe and heterogeneous psychiatric disorder associated with substantial clinical, functional, and public health burden. Diagnosis is based on clinical observation without reliable biomarkers, and currently available antipsychotic treatment is limited in its efficacy and cannot adequately address the negative and cognitive symptoms. Schizophrenia remains a major challenge for clinical neuroscience to understand and to establish reliable clinically translatable biological measures to support diagnosis or treatment monitoring.

The aim of this thesis was to evaluate the reliability of two pathophysiological markers of schizophrenia across two complementary biological scales: local cortical physiology and large-scale brain network function. The thesis is built around the excitation-inhibition imbalance hypothesis and the disconnection hypothesis as a guiding theoretical framework.

Study I is a meta-analysis of inhibitory and excitatory transcranial magnetic stimulation paradigms in schizophrenia. The main finding was a robust reduction in Short-Interval Intracortical Inhibition, highlighting impaired motor cortical inhibition in schizophrenia. In contrast, findings for the Cortical Silent Period, Intracortical Facilitation, and Long-Interval Intracortical Inhibition were less consistent and require more cautious interpretation. Study II tested the spatial convergence of published evidence of seed-based resting-state connectivity within the Cerebello-Thalamo-Cortical network using fMRI in Schizophrenia Spectrum Disorders. The strongest evidence supported thalamic dysconnectivity, characterised by reduced connectivity with prefrontal, limbic, thalamic, and cerebellar regions, together with increased connectivity with somatomotor and visual association areas. Cerebellar findings suggested altered connectivity but did not survive multiple comparison correction.

Together, these studies provide converging evidence that schizophrenia is associated with reproducible abnormalities in cortical inhibition, information flow, and large-scale network coordination. Short-Interval Intracortical Inhibition and thalamocortical dysconnectivity, therefore, are promising candidate markers for future multiscale translational research which support the theoretical framework of altered excitability and network communication in schizophrenia.

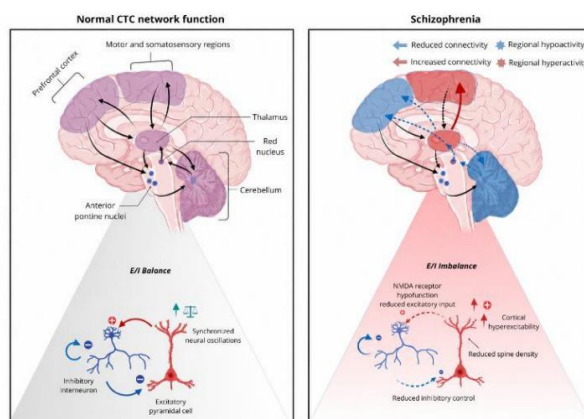
4. GRAPHICAL ABSTRACT

Excitation/Inhibition Imbalance and Network Dysconnectivity in Schizophrenia: Evidence from TMS-EMG and Resting-State fMRI

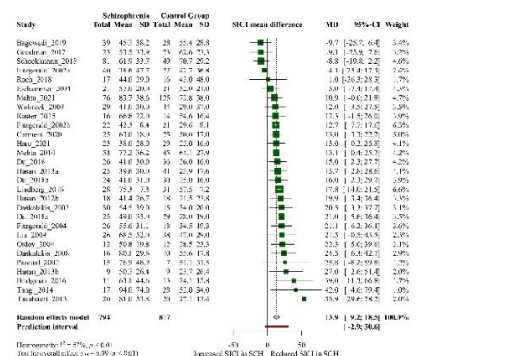
ORSOLYA LÁNYI

PhD Thesis

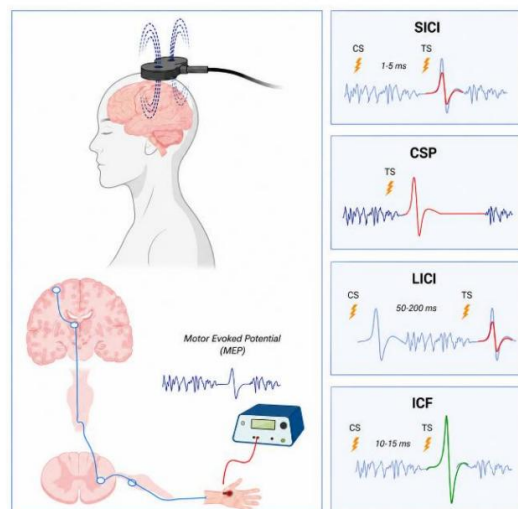
I. BACKGROUND



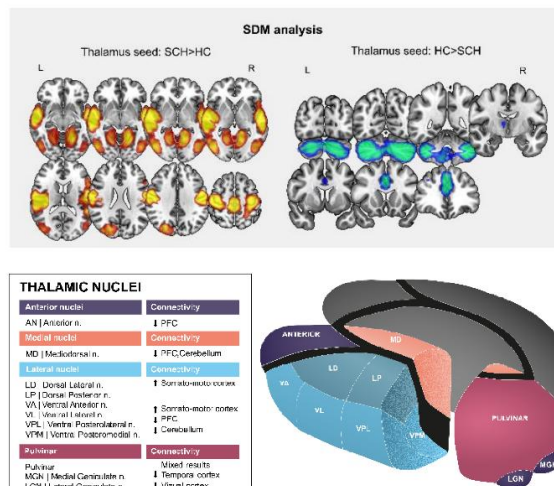
Study I. RESULTS



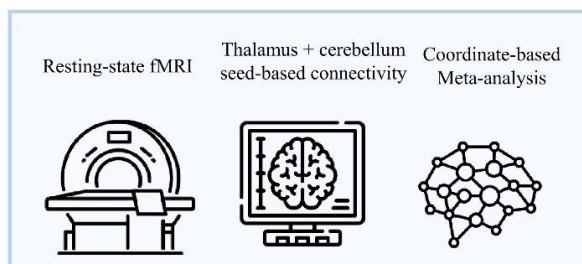
Study I METHODS



Study II RESULTS



Study II METHODS



IV. CONCLUSIONS

Study I: TMS-EMG → motor cortex → ↓ SICI

Study II: rs-fMRI → CTC network → thalamo-prefrontal ↓ / thalamo-sensorimotor ↑

Complementary evidence for multiscale circuit dysfunction in schizophrenia

5. INTRODUCTION

5.1. The clinical and translational challenge of schizophrenia

Schizophrenia is a severe psychiatric condition exerting a disproportionate global health burden affecting an estimated 26.9 million individuals worldwide (1). Despite the relatively low and stable prevalence of approximately 0.3%, schizophrenia accounts for a substantial and increasing proportion of disability associated with mental disorders, including an estimated 17 million disability-adjusted life years globally. Schizophrenia is also associated with 10-15 years shorter life expectancy and 10 times higher risk of suicide than the general population (2). These clinical and public health consequences make schizophrenia one of the most important unresolved conditions in psychiatry and clinical neuroscience.

The clinical presentation of schizophrenia is highly heterogeneous, with the symptoms emerging across neuropsychiatric domains (3). Diagnosis is primarily based on clinical observation, with no available biological markers to support the decision. While positive symptoms such as hallucinations and delusions are often recognised as the most prominent symptom domain, schizophrenia is also characterised by negative symptoms, cognitive deficits, disorganisation of thought and behaviour, and disturbances in sensory and motor functioning (4). This clinical heterogeneity is reflected not only in symptom profile but also in age of disease onset, illness trajectory, functional outcome, treatment response and long-term prognosis (3). Diagnosis remains primarily based on clinical observation, with diagnostic criteria defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) and requiring the presence of symptoms such as delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour, or negative symptoms, together with functional impairment and persistence of disturbance over time (5). Schizophrenia, therefore, is not a uniform diagnostic construct but a heterogeneous syndrome with multiple neurobiological mechanisms contributing to the clinical phenotypes.

Currently available treatment options further illustrate both the progress and the limitations of mechanistic understanding in schizophrenia. Antipsychotic medication was a major breakthrough in psychiatric treatment and strongly informed neurobiological

theories of psychosis, as available antipsychotics primarily act through dopamine D2/D3 receptor blockade (6). However, while these treatments are most effective for positive psychotic symptoms such as hallucinations and delusions, they have limited efficacy for negative symptoms and cognitive dysfunction, which are the main predictors of disability, functional decline and later quality of life (7). In addition, around one-third of the patients show minimal to no response to antipsychotic treatment and meet the criteria for treatment-resistant schizophrenia (8). Treatment resistance is associated with worse prognosis and increased burden on hospitals, as longer duration of untreated psychosis is predictive of more severe symptoms and worse prognosis (9).

Altogether, the clinical burden, the lack of effective treatment options and the lack of disease-specific biomarkers underline the need for a clear understanding of the pathomechanism of schizophrenia. Without that, the ability to predict treatment response, monitor disease progression, stratify patients by pathophysiological mechanisms, or develop targeted interventions for specific biological subtypes is severely limited (10). A clearer understanding of schizophrenia pathophysiology, therefore, requires not only identifying abnormal biological processes, but also determining which human measures can capture these processes reliably and meaningfully in clinical populations (11).

The unifying aim of this thesis is to evaluate whether schizophrenia pathophysiology can be operationalised across complementary biological scales using indirect, yet clinically feasible, human methods. Study I focuses on local cortical circuit excitability using Transcranial Magnetic Stimulation combined with electromyography (TMS-EMG), which provides non-invasive, in vivo insight into cortical excitation-inhibition-related responses. Study II focuses on large-scale network dynamics in the cerebello-thalamo-cortical (CTC) circuit and assesses the reliability of resting-state functional MRI. Together, these two studies test whether TMS-EMG and fMRI provide robust evidence for local circuit and large-scale network abnormalities in schizophrenia, and how these abnormalities can be interpreted within contemporary neurobiological models of the disorder.

5.2. Excitation-inhibition imbalance and dysconnectivity as neurobiological models of schizophrenia

Several theoretical and empirical frameworks have attempted to explain the biology of schizophrenia; however, each of these theoretical accounts faces the challenge of accounting for the heterogeneity of the disorder and integrating evidence from multiple biological levels ranging from genetic and environmental risk factors to synaptic function, neurotransmitter systems, cortical microcircuits, large-scale brain networks, cognition, behaviour, and clinical symptoms (12, 13). Schizophrenia is widely understood as a neurodevelopmental disorder in which genetic and environmental risk factors shape vulnerability to psychosis through effects on synaptic maturation and cortical circuit development (14-23). On the neurochemical level, the most dominant model is the dopamine hypothesis, which suggests that risk factors converge on altered dopamine function, such as striatal hyperdopaminergia and prefrontal hypodopaminergia, which drive the positive symptoms, such as hallucinations and delusions (24). The efficacy of antipsychotic medication, as well as multimodal evidence, supports this hypothesis (4, 25-28); however, the hypothesis does not explain the cognitive and negative symptoms, treatment resistance and the broader heterogeneity of schizophrenia.

Glutamatergic and GABAergic abnormalities provide a more direct framework for altered cortical regulation and may complement downstream dopaminergic dysregulation (29). The glutamatergic hypothesis of schizophrenia emerged largely from pharmacological evidence showing that NMDA receptor antagonists such as ketamine or phencyclidine can induce symptoms resembling the positive, negative and cognitive symptoms of schizophrenia in healthy individuals and is supported by converging postmortem, neuroimaging and preclinical evidence (30-40). One proposed mechanism by which these abnormalities could alter circuit activity across biological scales is excitation/inhibition (E/I) imbalance, one of the core theoretical themes of this thesis.

E/I balance refers to the dynamic relationship between excitatory glutamatergic and inhibitory GABAergic signalling (41). At the synaptic and microcircuit levels, it refers to the relative influence of excitatory and inhibitory inputs on neuronal activity, whereas at the systems level, it refers more broadly to the stability, gain, and coordination of population-level activity. At the cortical circuit level, E/I balance depends primarily on

the dynamic interplay between glutamatergic pyramidal cells and GABAergic inhibitory interneurons. Pyramidal cells provide the main excitatory output of cortical circuits, while inhibitory interneurons such as fast-spiking parvalbumin-positive (PV) interneurons regulate the timing, gain, and synchrony of pyramidal cell firing (42-45).

In schizophrenia, NMDA receptor hypofunction has been proposed to disrupt this balance by impairing excitatory drive onto inhibitory interneurons (46). Reduced interneuron function may weaken inhibitory control over pyramidal cells, leading to disorganised firing, reduced signal-to-noise ratio, altered synchrony, and increased neural noise (47, 48). This mechanism is consistent with pharmacological evidence from NMDA receptor antagonists, which can induce schizophrenia-like symptoms, and with electrophysiological findings suggesting abnormal gamma band activity and impaired neural synchronisation in schizophrenia (49). While the primary pathology underlying E/I imbalance remains debated, the framework provides a useful link between developmental and synaptic vulnerability, cortical circuit dysfunction, and downstream dopaminergic dysregulation (50). In this thesis, E/I imbalance is therefore used as a theoretical framework rather than as a directly measured biological variable. It motivates the investigation of human measures that can indirectly index cortical inhibitory and excitatory physiology.

Although E/I imbalance provides an integrative framework for linking synaptic pathology to altered local circuit-level information processing, cortical computations do not emerge from isolated microcircuit activity alone (41). Perception, cognition, affect, and behaviour depend on the coordinated activity of distributed cortical and subcortical systems, raising the question of how local abnormalities in excitatory and inhibitory regulation may relate to the network dysfunctions consistently implicated in schizophrenia (49). Connectivity and the disconnection hypothesis provide a systems-level framework for this question (51). Connectivity refers to structural or functional coupling among anatomically distant brain regions, whereas dysconnectivity refers to abnormal integration or communication within and between large-scale brain networks (29). From this perspective, the link between molecular or synaptic pathology and clinical symptoms may be partly understood through altered coordination of distributed neural systems.

Importantly, this does not imply that dysconnectivity is equivalent to E/I imbalance. Rather, E/I imbalance, abnormal synaptic gain, altered neural synchrony, and dysconnectivity describe related but non-identical levels of schizophrenia pathophysiology (52). Local E/I-related abnormalities may plausibly influence network organisation through effects on cortical gain, signal-to-noise ratio, oscillatory synchrony and information transfer (53), however this relationship remains indirect and should not be interpreted as evidence for a direct causality. Accordingly, Study I addresses local circuit-level E/I-related physiology by evaluating TMS-EMG measures of motor cortical inhibition and excitability, whereas Study II addresses systems-level dysconnectivity in the cerebello-thalamo-cortical network using resting-state fMRI. The next chapter clarifies how these theoretical constructs can be operationalised in human clinical neuroscience, and what inferences these methods can and cannot support.

5.3 Operationalising schizophrenia pathophysiology across local circuit and network levels

As outlined above, E/I imbalance is a multilevel theoretical construct rather than a single directly measurable biological variable. Due to this complexity, there is no single metric that directly estimates the E/I ratio across the human brain (54). Therefore, for each study and biological scale, it is necessary to define precisely what aspect of E/I-related dysfunction is being operationalised, what the selected metric can capture, and what conclusions it cannot support.

Several human methods provide important but partial approximations of E/I-related pathology, including post-mortem studies, molecular imaging, magnetic resonance spectroscopy, EEG and MEG. These approaches have linked schizophrenia to altered synaptic markers, glutamatergic and GABAergic abnormalities, dopaminergic dysregulation, oscillatory activity, neural gain and signal-to-noise ratio (23, 36, 38, 55-57). These methods are highly informative, but they are not the primary empirical focus of this thesis. Instead, the present work focuses on two complementary levels that map directly onto the thesis publications: one is local cortical inhibition and excitability measured with TMS-EMG, and the second is large-scale connectivity in the cerebello-thalamo-cortical network, measured with resting-state fMRI.

Transcranial magnetic stimulation (TMS), when combined with electromyography (EMG), provides a non-invasive experimental methodology to probe cortical excitability and inhibition in the primary motor cortex (58). Single- and paired-pulse stimulation paradigms, such as Short-Interval Intracortical Inhibition (SICI), Long-Interval Intracortical Inhibition (LICI), Cortical Silent Period (CSP), and Intracortical Facilitation (ICF), are commonly used methods to probe local cortical physiology (59). While extensive pharmacological evidence links these responses to neurotransmitter systems, TMS-EMG remains an indirect but strong estimate of cortical E/I. TMS-EMG is therefore a particularly relevant measure, as it provides an experimental framework for non-invasively modulating local cortical inhibition and excitability. This methodological logic motivates the first study of the thesis, which quantitatively synthesised TMS-EMG evidence in schizophrenia to test whether measures of inhibitory and excitatory motor cortical physiology show reproducible patterns of deficits across studies.

At the macroscopic network level, there are no direct measures of E/I balance available. E/I-related dysfunction can only be inferred indirectly from patterns of coordinated activity across large-scale brain systems. Functional magnetic resonance imaging (fMRI) provides one such approach by estimating functional connectivity, defined as the statistical dependency between activity time series in anatomically separated brain regions at rest or during task performance (60). Resting state functional connectivity indexes the temporal dependency and statistical co-activation of spontaneous low-frequency (0.01-0.1 Hz) fluctuations in the haemodynamic blood oxygen level dependent signal (BOLD) across anatomically separated distant brain regions, and therefore it is several inferential steps away from direct neural function or synaptic excitation-inhibition balance (61). Nevertheless, converging electrophysiological, multimodal imaging, and computational evidence suggest that local neural activity, neurotransmitter systems, feedback inhibition and synaptic gain can influence large-scale functional connectivity patterns, although these associations do not establish a direct mapping between E/I and connectivity (62-64).

Schizophrenia has been associated with profound alterations in intrinsic communication between distant brain regions in various brain networks, depending on illness stage, cognitive state, and measurement modality (65). Among the large-scale networks affected in schizophrenia, the cerebello-thalamo-cortical circuit has emerged as a particularly

relevant system for studying network-level dysconnectivity, as discussed in detail in Chapter 5.5. This motivated Study II, which used coordinate-based meta-analysis to evaluate whether CTC functional dysconnectivity shows reproducible spatial patterns in schizophrenia.

Meta-analysis is necessary in both empirical domains because schizophrenia research is characterised by small samples, clinical heterogeneity, differences in illness stage and medication exposure, and substantial methodological variability (66). In the TMS EMG literature, stimulation parameters, interstimulus intervals, outcome calculations, medication status and diagnostic composition vary across studies (67). In the resting-state fMRI literature, seed definition, preprocessing strategy, statistical thresholding, scanner parameters, and clinical samples differ substantially across reports (68). Individual studies are therefore often insufficient to determine whether a reported abnormality reflects a reproducible pathophysiological feature or a sample-specific or method-specific finding (69). Evidence synthesis allows these literatures to be evaluated cumulatively and helps identify which abnormalities are robust enough to guide future mechanistic and translational research (70).

Together, Study I and Study II address the same broader thesis question at complementary biological levels of local circuit and large-scale network function. The next chapter turns to the first of these operational levels and reviews how TMS EMG can be used to probe motor cortical inhibition and excitability in schizophrenia.

5.4. Motor cortical inhibition and excitability measured with TMS-EMG

5.4.1. Principles of TMS-EMG and motor evoked potentials

Transcranial Magnetic Stimulation (TMS) is a non-invasive neuromodulation technique used to stimulate the human cortex through electromagnetic induction. TMS is widely used as a diagnostic tool to assess the functional integrity and conduction velocity of corticomotor pathways in neurological conditions (71). In cognitive and clinical neuroscience, single- and paired-pulse TMS are used as experimental tools to perturb local cortical pathways and probe cortical excitability (72). Repetitive TMS, on the other

hand, can be used as a therapeutic intervention by inducing long-lasting neuroplastic changes in brain networks via long-term potentiation and long-term depression (73).

TMS operates on the principle of Faraday's law of electromagnetic induction. A high-voltage and high-current discharge is passed through a copper wire coil placed on the scalp and this pulse generates a strong, rapidly changing magnetic field lasting for a short period of time (less than 1 ms), which can pass through the skull to induce an electric field (eddy currents) in the brain (74). Neuronal activation depends on the strength and direction of the induced currents, the anatomy of the cortex, the orientation and position of the coil, and the distance between the coil and the targeted region (75). There are two types of pulse delivery (monophasic and biphasic) and different geometric variations of stimulation coils that produce slightly different physiological effects (75).

When TMS stimulation is applied over the primary motor cortex (M1) at a suprathreshold intensity, the pulse generates descending volleys along the corticospinal tract, which propagate through the peripheral motoneurons and generate muscle activity in the contralateral target muscle, which can be measured with electromyography (EMG) (73). TMS primarily excites pyramidal neurons transsynaptically via lateral interneurons, generating a sequence of longer-latency indirect waves (I-waves) at around 1.5 ms intervals (76).

The coil is usually placed flat over the cortex, at about 45° from the midline and perpendicular to the central sulcus, inducing currents in the M1 in a posterior-to-anterior direction to elicit motor evoked potentials (MEPs). The MEP is quantified by peak-to-peak amplitude and latency and is usually interpreted as an index of net corticospinal excitability (67). Stimulation intensity is defined as the minimum intensity required to elicit a MEP of at least 50 μ V in the relaxed target muscle in approximately 50% of consecutive trials (resting motor threshold, RMT). Active Motor Threshold (AMT) can also be estimated during tonic activation of the target muscle by setting the intensity to elicit MEPs larger than 200 μ V in 5 out of 10 trials (74).

After defining the motor threshold, multiple single- and paired-pulse paradigms can evoke inhibitory or excitatory responses, probing cortical excitability. In this thesis, I focus on three inhibitory paradigms (Short-Interval Intracortical Inhibition, SICI; Long-Interval Intracortical Inhibition, LICI and Cortical Silent Period, CSP) and Intracortical

Facilitation (ICF) as an excitatory paradigm. In the following, I will describe the protocols for these paradigms and explain why they are particularly relevant for studying schizophrenia.

5.4.2. Excitatory and inhibitory TMS-EMG paradigms

Intracortical inhibition can be assessed using paired-pulse paradigms such as SICI and LICI, and a single-pulse paradigm CSP (77). SICI is a paired-pulse paradigm that involves the delivery of a subthreshold conditioning stimulus (CS), typically around 80% of the resting motor threshold, followed by a suprathreshold test stimulus (TS) at 100-120% of the resting motor threshold, with a 1 to 5 ms interstimulus interval (ISI) (76). The subthreshold CS can depolarise local inhibitory interneurons but is not strong enough to activate the corticospinal projections eliciting a MEP. Consequently, if the TS is delivered a few milliseconds later, the resulting MEP amplitude will be suppressed by inhibition (78). The inhibitory response of SICI has been associated with fast-acting GABA-A receptor-mediated inhibition (79). Pharmacological studies have shown that benzodiazepines such as lorazepam, which act as GABA-A agonists, significantly increase SICI (80).

Schizophrenia is widely associated with a reduction in SICI. GABA-A mediated inhibitory deficit as measured by SICI has been reported in clinical high-risk states, first episode psychosis and chronic schizophrenia in medicated and unmedicated populations. While a previous meta-analysis by Radhu and colleagues (59) has shown a significant reduction in SICI in schizophrenia patients, the evidence remained limited in evaluating the robustness of these findings.

Cortical Silent Period (CSP) is a single-pulse inhibitory paradigm elicited by delivering a suprathreshold stimulation while the subject maintains a voluntary tonic muscle contraction. The stimulation evokes a MEP followed by the suppression of voluntary EMG activity for up to 300 milliseconds (81). The magnitude of the inhibitory response is defined as the duration of the suppression. The first 50ms of the CSP is thought to reflect spinal cord refractoriness, while the later parts of the suppression result from cortical inhibition associated with GABA-B receptor-mediated inhibition (82). Pharmacological studies have shown that the administration of GABA-B agonists such as baclofen or tiagabine dose-dependently prolongs the duration of the CSP.

In contrast to SICI, the results regarding CSP in schizophrenia are heterogeneous and seem to be sensitive to the effect of antipsychotic medication. Some studies have shown shortened CSP in unmedicated patient populations or in first episode psychosis (72, 83, 84), whereas other studies, primarily including patients treated with antipsychotic medication, have reported prolonged CSP in the patient population (85, 86). Clozapine directly binds to GABA-B receptors and has been associated with longer CSP; therefore, it might cover illness-related GABA-B deficits (87, 88). The clinical utility of CSP in schizophrenia, therefore, is inconclusive and needs further research to establish.

LICI is a less commonly used inhibitory paired-pulse paradigm, where two suprathreshold stimuli are delivered with a 50-200 ms ISI (89). The first suprathreshold conditioning stimulation activates long-lasting inhibitory networks, which subsequently suppress the MEP amplitude of the second test pulse. Like CSP, LICI is also argued to be associated with GABA-B receptors (90). The exact neural mechanism and the population of interneurons recruited by CSP and LICI, however, might differ (75). The literature on LICI in schizophrenia is less extensive than in SICI or CSP, and the results are quite heterogeneous. Some studies show deficits in schizophrenia, while others found no difference (91). Therefore, further analysis is needed to conclude on the effect of LICI.

Intracortical Facilitation (ICF) is one of the most widely used paradigms to elicit an excitatory response with TMS-EMG. ICF is a paired-pulse paradigm with a similar structure to SICI where a subthreshold conditioning stimulus is followed by a suprathreshold stimulus with a longer, 10-15 ISI (92). Pharmacologically, ICF is recognised to reflect both glutamatergic neurotransmission mediated by NMDA receptors and GABAergic interneuron function (80, 92). NMDA receptor antagonists, such as dextromethorphan or memantine, suppress ICF, and GABAergic agents, such as vigabatrin or baclofen, also modulate ICF (77). The complete mechanism of ICF, however, is not fully understood and appears somewhat nuanced, as ICF was found not to respond to the non-competitive NMDA antagonist ketamine (93).

ICF, therefore, most plausibly is best described as an indirect measure of NMDA receptor function with concurrent GABAergic modulation. However, given the E/I imbalance hypothesis of schizophrenia, the ICF is a great candidate to test NMDA receptor hypofunction-related responses non invasively. ICF findings in schizophrenia, however,

are less consistent than in SICI. Some studies report increased ICF in schizophrenia, while others found no difference (94). Due to the small sample sizes and the heterogeneity of methods and populations, this warrants further investigation.

Beyond the aforementioned TMS-EMG paradigms, several other protocols are used to test cortical excitability and hemispheric connectivity, such as Short-Interval Intracortical Facilitation, I-wave facilitation, short-latency and long-latency afferent inhibition and transcallosal inhibition and facilitation (95). In this thesis, however, I primarily focus on SICI, CSP, LICI, ICF and RMT as these are the most widely reported TMS-EMG paradigms associated with schizophrenia pathology.

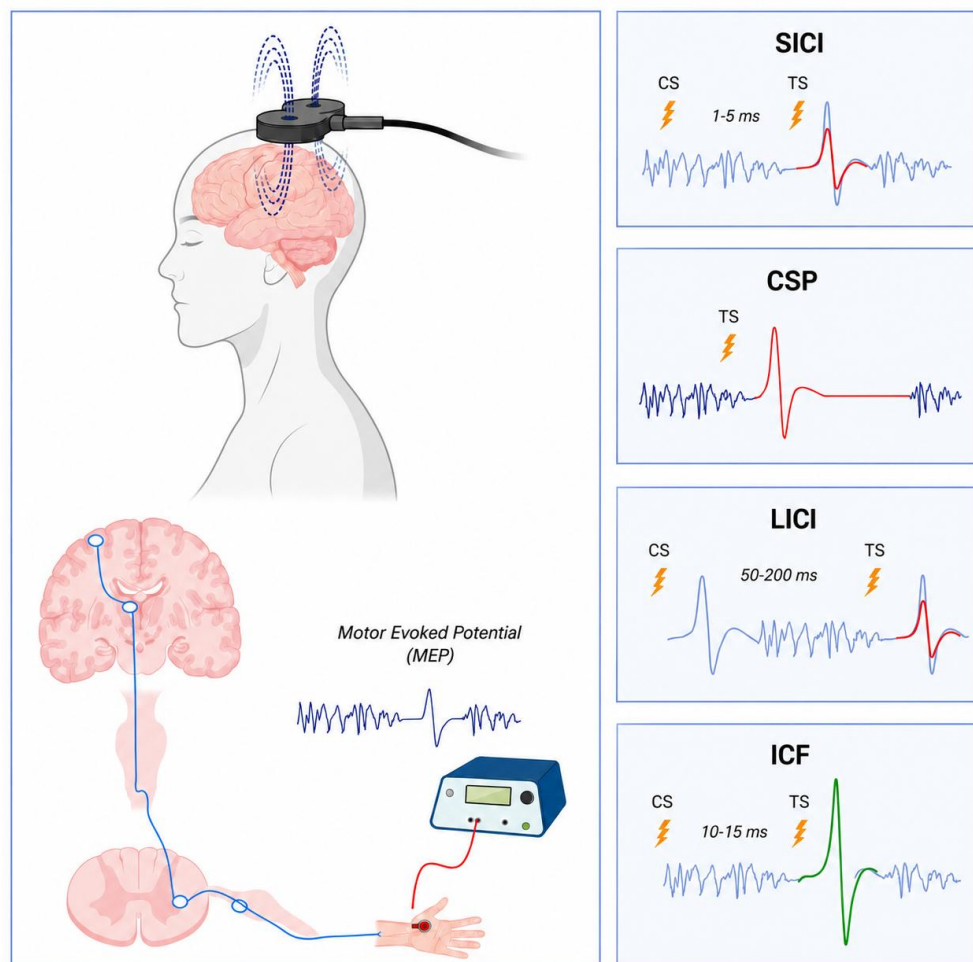


Figure 1.

Schematic outline of the TMS-EMG paradigms.

SICI: Short-Interval Intracortical Inhibition, CSP: Cortical Silent Period, LICI: Long-Interval Intracortical Inhibition, ICF: Intracortical Facilitation, CS: Conditioning Stimulus, TS: Test Stimulus

(Figure created by the author for this thesis using the BioRender software)

5.4.3. TMS EMG evidence in schizophrenia and rationale for Study I

In this chapter, I provided a technical overview of how TMS combined with EMG can be used as an experimental tool to test motor cortical inhibitory and excitatory physiology. While the paradigms listed here have strong pharmacological evidence supporting their association with E/I balance, these measures are not a direct proxy for synaptic E/ ratio and should be treated as a controlled perturbation mechanism of local cortical circuits, including corticospinal output. In this thesis, however, TMS-EMG is used to represent the scale of local circuits at which excitability-related dysfunctions in schizophrenia can be tested.

Schizophrenia has been associated with altered response in multiple TMS-EMG paradigms; the results, however, are inconclusive (96). In addition, TMS-EMG is a useful tool for probing circuit-level E/I dysfunctions in a clinical setting, as it offers a translatable protocol that is easy to set up, quick to measure, and provides a clear physiological marker of cortical function.

In Study I, therefore, I will focus on TMS-EMG paradigms to evaluate the robustness and reliability of SICI, CSP, ICF, LICI, and RMT in probing cortical inhibitory and excitatory responses in schizophrenia.

As described in the earlier chapters, however, local cortical excitability represents only one biological scale at which E/I related dysfunction could manifest in schizophrenia. Local E/I dysfunctions could give rise to network-level alterations in information flow across cortical and subcortical systems, and TMS-EMG cannot be used to probe these systemic changes in brain function. In the next chapter, therefore, I will introduce the topic of Study II, focusing on large-scale functional connectivity in the Cerebello-Thalamo-Cortical network to probe network-level alterations in circuit organisation in schizophrenia.

5.5. Cerebello-Thalamo-Cortical circuitry and resting state fMRI dysconnectivity

5.5.1. CTC network connectivity as a second biological level of investigation

As outlined in the previous chapter, TMS-EMG provides a perturbational experimental approach to assess cortical inhibitory and excitatory physiology. However, local cortical excitability represents only one biological scale at which schizophrenia pathophysiology can be investigated. Schizophrenia also involves distributed network-level abnormalities, including altered neural information flow between cortical and subcortical regions (97). These network-level alterations might be especially relevant for understanding complex cognitive and perceptual symptoms and behavioural characteristics in schizophrenia, which cannot be fully explained by abnormalities within a single local cortical circuit (98).

The present chapter, therefore, turns to the Cerebello-Thalamo-Cortical (CTC) network as a complementary systems-level target of investigation. Resting-state fMRI is well-suited to this question, as it allows the study of large-scale functional connectivity, including interactions between cortical areas and deep subcortical structures (99).

The CTC network is particularly relevant to schizophrenia because the thalamus is increasingly understood as an active regulator of cortical communication, sensory filtering, and cognitive control, while the cerebellum contributes to cortical processing through loops involved in prediction, timing, motor coordination, and higher-order cognition (100, 101). Therefore, CTC connectivity provides a biologically meaningful network-level framework for Study II, which examined whether resting-state fMRI studies show reproducible patterns of CTC dysconnectivity in schizophrenia spectrum disorders.

5.5.2. Thalamus: anatomy, function and findings in schizophrenia

Traditionally, the thalamus has been viewed as a passive relay station that transfers ascending sensory information to higher-order cortical regions. Modern neuroanatomical and neurophysiological evidence, however, has challenged this idea on multiple grounds.

The thalamus is now understood as a heterogeneous set of nuclei with distinct cortical and subcortical connectivity profiles, supporting sensory transmission, cortical communication, attentional control, cognitive flexibility, and state regulation (102). This organization makes the thalamus particularly relevant for schizophrenia, where disturbances in information filtering, cognitive control, and cortical coordination are central features of the disorder (103).

The thalamus is a paired subcortical structure with over 50 distinct nuclei, which can be categorised into anterior, medial, lateral, ventral, midline and posterior regions. However, there are differences in nomenclature between papers, textbooks and labs (101). These nuclei are largely composed of excitatory neurons that form mostly lateral connections. The main inhibitory nucleus is the reticular nucleus, which consists of GABAergic neurons that provide a major source of inhibition to thalamic neurons across all nuclei (104). While the cortex has a vast array of recurrent excitatory loops that define its function, the thalamus is mostly rooted in its long-range connectivity patterns rather than local recurrent circuits.

These long-range projections, formed between the cortex and the thalamic nuclei, primarily support sensory processing (hence the original idea of the thalamus as a relay). Evidence suggests that almost every cortical area receives thalamic input, and for many cortical regions, the thalamus is the only input from subcortical structures (105). Thalamic relay cells receive inhibitory GABAergic input from local interneurons and from the reticular nucleus, which exerts dynamic regulation over the thalamic projections to the cortex (106). The strength of thalamic projections is regulated by inhibitory tone: high inhibitory tone can gate thalamic transmission to the cortex, whereas low inhibitory tone upregulates bottom-up information flow (107). Evidence therefore strongly supports the idea that thalamic gain can influence the effectiveness of signal transmission to cortical regions. Thalamic activity, furthermore, is also shaped by corticothalamic feedback loops and neuromodulation from the brainstem and cerebellum (105). The main extrinsic drive to the thalamus arises from cortical layer 6, providing reciprocal glutamatergic feedback to the bottom-up projecting thalamic relay neurons. Thalamocortical projections, therefore, can be controlled locally and via top-down cortical regulation, suggesting a nuanced and complex computational interplay between the cortex and the thalamus (108).

To better understand thalamic function, it is important to make the distinction between first-order and higher-order thalamic nuclei (109). First-order thalamic nuclei receive input from subcortical sources and the sensory systems and represent the first relay of a sensory information in a specific domain to the cortex. Such examples are the lateral geniculate nucleus for vision, the medial geniculate nucleus for the auditory system and the ventral posterior nucleus for the somatosensory system (110). Higher order nuclei, on the other hand, receive driver input from cortical layer 5 and, as part of the Cortico-Thalamo-Cortical and transthalamic pathways, transfer information from one cortical region to another (111). For example, the latero-posterior carries information from the visual cortex to other cortical regions while the posteromedial nucleus transfers somatosensory information (101). Importantly, higher-order relays also receive reciprocal layer 6 feedback, suggesting that thalamic contributions to cortical processing involve both information transfer and dynamic modulation of that transfer. Emerging evidence suggests that higher-order thalamic nuclei thus play a critical role in communication across cortical hierarchies and support information flow between cortical areas, regulate cortical communication according to behavioural demands, and contribute to predictive or action-related signals that inform higher cortical processing (112).

Within this framework, the thalamus has two major roles. One is to control and gate ascending information coming from the environment, and the second is to fine-tune communication between distant cortical regions and transfer information across domains.

5.5.3. Thalamic findings in schizophrenia

Given its role in regulating cortical communication and its involvement in perception, neural computations and higher-order cognitive processes, the thalamus has become a central structure in network models of schizophrenia, where impairments extend beyond psychosis and include impairments in cognition (102). Structural, postmortem, and molecular studies have reported several thalamic abnormalities, including reduced thalamic grey matter volume (121), neuronal loss (122), and altered neurochemical changes in glutamatergic neurotransmission and receptor expression (37). These studies mainly focused on higher-order thalamic nuclei such as the pulvinar or the mediodorsal nucleus, and although there is evidence of selective involvement, the results stay mixed (113).

Resting-state fMRI has provided a complementary approach to studying thalamic dysfunction at the network level. There is a consistent pattern of reduced connectivity between the thalamus and the prefrontal cortex, together with increased connectivity with the sensorimotor regions, reported across the literature (114). First evidence came from Welsch and colleagues (115) who reported thalamo-prefrontal hypoconnectivity in schizophrenia, establishing the idea that the thalamus plays an important role in schizophrenia pathophysiology. These results were later extended to the prodromal states of clinical high-risk for psychosis, first-episode psychosis (FEP) and were replicated in chronic schizophrenia with a similar pattern of sensorimotor hyperconnectivity among prefrontal hypoconnectivity (110). Thalamic findings have also been associated with deficits in cognitive control, working memory, and attention, which are hallmark impairments of schizophrenia (116).

Pharmacological fMRI studies provide further mechanistic insight to thalamic dysconnectivity in schizophrenia models. Studies have repeatedly shown that ketamine, an NMDA receptor antagonist, alters thalamocortical connectivity in a similar pattern to what is reported in schizophrenia, suggesting that NMDA receptor hypofunction or circuit-level E/I imbalance can disrupt thalamocortical functional connectivity (117). Computational models have also suggested that perturbations in E/I balance can perturb large-scale changes in thalamocortical connectivity, providing a possible bridge between local circuit dysfunction and systems-level connectivity alterations (118, 119). In-vivo evidence from animal optogenetic perturbation models further supports the link between E/I disruptions and thalamocortical dysconnectivity, showing that the mediodorsal nucleus exerts dual control over the prefrontal cortex and increases local functional connectivity while suppressing noise (120).

These findings suggest that thalamocortical connectivity is strongly impaired in schizophrenia and schizophrenia spectrum disorders. However, the thalamus is embedded in a broader circuit of cortico-subcortical loops, including the cerebellum, forming the CTC network. In the next chapter, therefore, I turn to the cerebellum as a second potential hub for network-level schizophrenia pathology.

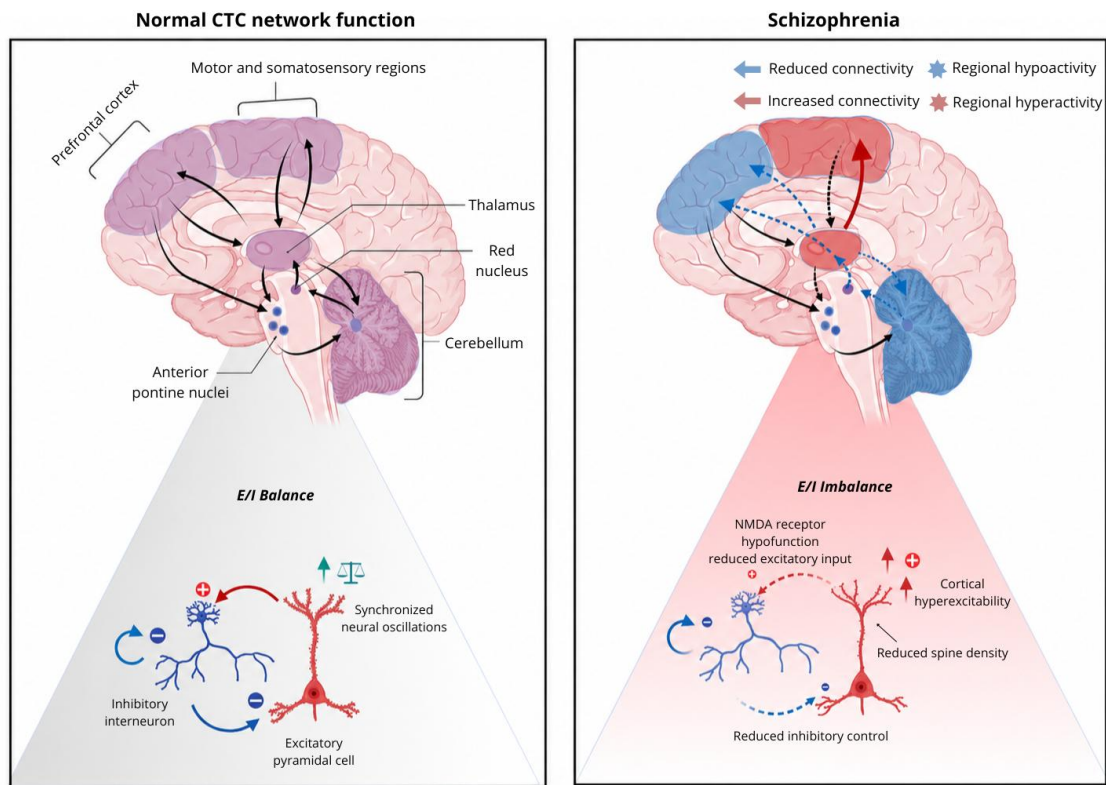


Figure 2.

Schematic visualisation of excitation-inhibition (E/I) homeostasis and Cerebello-Thalamo-Cortical (CTC) network function in healthy and schizophrenia brain.

(Figure was created by the author using the BioRender software and Inkscape software)

5.5.4. Cerebellum and the Cerebello-Thalamo-Cortical circuitry in schizophrenia

Until the past two decades, the cerebellum was understood as a structure primarily responsible for controlling and coordinating motor actions. Clinically, cerebellar lesions result in symptoms such as ataxia, dysmetria, and disturbances of posture and gait, which constitute the cerebellar motor syndrome. The classical view suggested that the role of the cerebellum is purely motor. However, converging anatomical, neuroimaging, and clinical evidence has led to a paradigm shift, underscoring the cerebellum's critical role beyond motor functions in higher-order cognition (121).

The paradigm shift arose from early anatomical and neuroimaging studies demonstrating a cerebellar topography with detailed sensorimotor representations and extensive cerebro-cerebellar connections with prefrontal, posterior parietal, superior temporal, and

parahippocampal association cortices (122). The prefrontal-cerebellar circuits are anatomically distinct from motor-cerebellar circuits and form complex feed-forward and feedback projections often relaying through the thalamus, suggesting an anatomical organisation suited for complex neural computations (123). Clinical studies further strengthened this hypothesis by showing that posterior cerebellar lesions lead to impairments in executive control, working memory and language deficits, which are now understood as the cerebellar cognitive affective syndrome, whereas anterior lobe lesions result in the cerebellar motor syndrome (124, 125). Task-based fMRI studies further demonstrated that sensorimotor functions are localised only at the anterior lobe (lobules I-V) and lobule VIII of the cerebellum, and the majority of the cerebellum (lobules VI, Crus I, Crus II, VIIB and IX) are associated with diverse cognitive functions such as working memory, emotion processing, social cognition, language or mentalizing (126).

These anatomical results and the uniform molecular organisation of the cerebellar cortex have led to the understanding that the cerebellum performs conceptually similar computations across motor and cognitive domains, conceptualised as the universal cerebellar transform (UCT) (127). These computations contribute to the prediction, timing, maintenance and optimisation of cognitive and motor computations. The idea of “dysmetria of thought” emerged early on from this idea of UCT, arguing that just as cerebellar pathology produces dysmetria of movement (ataxia) in the motor regions, disruptions to the cognitive and limbic regions of the cerebellum result in dysmetria of cognition, manifesting in the Cerebellar Cognitive Affective Syndrome (128).

In line with this, in schizophrenia research, an early influential hypothesis extended this model to the “cognitive dysmetria hypothesis” proposing that the cognitive and negative symptoms of schizophrenia, not explained by the dopamine hypothesis, arise from impaired mental coordination due to dysfunction within the Cerebello–Thalamo–Cortical (CTC) circuitry (100). Since the initial cognitive dysmetria hypothesis, a wealth of neurobiological evidence suggests altered CTC network function and cerebellar dysfunctions in schizophrenia (129).

At the cellular level, histological studies in schizophrenia have reported reductions in the size and density of GABAergic Purkinje cells and alterations in glutamatergic granule cell activity in the cerebellum (130). This has been argued to result in a cerebellar E/I

imbalance, affecting cerebellar network function and impairing the cerebellum's ability to integrate information and coordinate cortical signals (122).

Schizophrenia patients also often present with clinical signs of cerebellar involvement, such as neurological soft signs, dyscoordination or procedural learning deficits, which have been associated with reduced cerebellar grey matter volume (131). Functional MRI and PET imaging studies further suggest reduced cerebellar activation at rest and a bidirectional pattern of CTC network dysconnectivity in schizophrenia. Neuroimaging findings suggest a coherent and similar pattern of dysconnectivity with the cerebellum, as we saw in the thalamus. Studies have reported profound hypoconnectivity between the posterior cerebellar lobules related to cognition (Crus I, Crus II) and higher order association cortices (prefrontal and parietal), as well as hyperconnectivity between the anterior, sensorimotor cerebellum and primary somatomotor cortices (132). This pattern of dysconnectivity is in line with the framework of the Universal Cerebellar Transform (128) and the functional organisation of the cerebellum (126). In this view, cerebellar E/I imbalance could contribute to prefrontal-cerebellar hypoconnectivity, driving “cognitive dysmetria” and giving rise to the negative symptoms, thought disorder and impaired social cognition (133), while cerebellar-sensorimotor hyperconnectivity could drive sensory prediction failures and motor abnormalities (132). Consequently, cerebellar pathology in schizophrenia should not be considered as a motor artefact but rather a critical network hub contributing to the systems-level alterations tying together E/I imbalance, thalamocortical dysconnectivity, and an overall CTC circuit dysfunction.

5.5.5. Limitations in the literature and rationale for Study II

In this chapter, I have reviewed evidence suggesting that the thalamus and the cerebellum are central hubs of schizophrenia pathology, forming a functionally and structurally connected network. The evidence is in harmony with the idea of the CTC network showing that both the thalamus and the cerebellum exhibit hypoconnectivity with the prefrontal and other associative cortical regions together with hyperconnectivity with the sensorimotor regions in schizophrenia (134). These results support the notion that circuit-level E/I alterations could lead to network-level dysconnectivity in the CTC loop, and these alterations could manifest in the symptoms of schizophrenia (119). The available evidence however is limited to draw this conclusion. Individual studies considerably vary

in the reported anatomical localization, direction of effect and clinical population. Therefore, although there is emerging evidence supporting the relevance of the CTC network in schizophrenia, it remains necessary to determine the robustness and spatial convergence of these results.

There are several methodological and clinical factors that limit the interpretation of the existing literature. Studies usually include small to modest sample sizes and the patient population often are highly heterogeneous differing in diagnosis, illness stage, illness duration, symptom profile and medication status. These factors however are particularly important in schizophrenia and schizophrenia spectrum disorders where clinical heterogeneity and medication could influence network level measures (135). Methodological considerations further limit the interpretability of existing evidence. Thalamic seed definitions (locations of analysis) vary across studies, where some studies include bilateral whole thalamus and others apply finer resolution looking at connectivity between specific thalamic nuclei and cortical regions (136-138). Preprocessing and data analysis decisions, such as statistical thresholding, could further limit the generalizability of the existing fMRI literature (70).

Coordinate-based meta-analytic methods provide a statistical framework for testing whether reported neuroimaging findings show spatial convergence across individual studies (139). While these methods cannot resolve all sources of clinical and methodological heterogeneity, they can provide strong evidence to test whether the available seed-based resting-state fMRI literature supports a reproducible regional pattern of dysconnectivity beyond single-study effects. These limitations, along with the existing evidence on thalamic and cerebellar connectivity, motivate a quantitative synthesis of findings in schizophrenia. While prior meta-analyses have examined thalamocortical or cerebellocortical connectivity individually (114, 140), none have comprehensively assessed CTC dysconnectivity across the psychosis-spectrum using seed-based resting-state fMRI. Study II, therefore, will focus on statistically synthesising evidence in the CTC network, and the specific objectives and hypotheses are presented in the following chapter.

6. OBJECTIVES

The overall aim of this thesis was to evaluate whether schizophrenia is associated with reproducible abnormalities across two complementary biological levels, local cortical inhibitory and excitatory physiology and large-scale cerebello-thalamo-cortical network organisation. Guided by the excitation/inhibition imbalance and dysconnectivity frameworks, the thesis examined two clinically translatable human neuroscience methods. TMS-EMG was considered as a perturbational measure of motor cortical inhibition and excitability, while resting-state fMRI was considered as a systems-level measure of functional connectivity. The objective of both studies was to quantitatively evaluate the robustness of evidence supporting the reliability and consistency of these measures in schizophrenia using meta-analytic evidence.

6.1. Study I. – Excitation-inhibition in schizophrenia, a meta-analysis of TMS-EMG studies

Study I aimed to evaluate whether TMS-EMG measures of cortical inhibition and facilitation show reproducible abnormalities in schizophrenia. Specifically, the meta-analysis examined inhibitory responses measured by SICI, LICI and CSP, and facilitatory responses measured by ICF, in patients with schizophrenia compared with healthy controls. In light of the E/I imbalance hypothesis, we expected schizophrenia to be associated with impaired cortical inhibitory responses, particularly in inhibitory TMS-EMG paradigms. A secondary objective of Study I was to test whether variability in TMS-EMG findings in the literature could be explained by clinically relevant factors, such as antipsychotic medication, symptom severity, or illness duration. These analyses were used to evaluate whether TMS-EMG paradigms could provide clinically meaningful insight to the heterogeneity in schizophrenia.

A secondary objective was to examine whether variability in TMS-EMG findings could be explained by clinically relevant factors, including antipsychotic medication, symptom severity and illness duration. Resting motor threshold was additionally examined as a baseline measure of corticospinal excitability.

6.2. Study II. - Cerebello-Thalamo-Cortical Dysconnectivity in Schizophrenia: A Resting-State fMRI Meta-Analysis

Study II focused on the systems-level investigation of schizophrenia pathophysiology by evaluating Cerebello-Thalamo-Cortical (CTC) network disconnectivity using seed-based resting-state fMRI. The aim of this meta-analysis was to assess the robustness of CTC network dysconnectivity in schizophrenia and psychosis-spectrum disorders by synthesising existing evidence and to determine whether reported thalamic and cerebellar connectivity alterations exhibit reproducible spatial convergence across independent studies.

Building upon previous literature, we hypothesised that schizophrenia and schizophrenia spectrum disorders (SSDs) would be associated with reduced thalamo-prefrontal and cerebello-prefrontal connectivity, and increased thalamo-sensorimotor connectivity. We also hypothesised that positive symptoms would correlate with thalamic-sensorimotor hyperconnectivity, whereas negative symptoms would be associated with thalamic-prefrontal hypoconnectivity (141, 142).

By applying coordinate-based neuroimaging meta-analytic methods, following the methodological guidelines for neuroimaging meta-analysis (139), and implementing stringent inclusion and exclusion criteria based on the OHBM recommendations (143), Study II aimed to build on and extend prior work with greater methodological rigour and a broader clinical scope.

7. METHODS

7.1. Study I

7.1.1. Protocol, Eligibility and Search Strategy

The study protocol was predefined and registered on PROSPERO (CRD42022373330), and the meta-analysis was conducted following the recommendations of the Cochrane Handbook and reported according to the PRISMA 2020 guidelines. Ethical approval was not required for this meta-analysis, as all data had already been published in peer-reviewed journals. No patients were involved in the design, conduct, or interpretation of our study.

Studies reporting TMS-EMG paradigms (SICI, CSP, ICF, and LICI) in schizophrenia-spectrum populations and healthy control groups were searched for. The systematic search was completed on the 5th of November 2022, using the following search engines: MEDLINE (via PubMed), Embase, and CENTRAL (The Cochrane Central Register of Controlled Trials). The search key is reported in the publication.

After duplicate removal, title and abstract selection, and full-text selection, the process was performed by two independent review authors, and disagreements were resolved by a third author. Studies were included if they met the following eligibility criteria: 1.) single- or paired-pulse TMS paradigms were applied in the primary motor cortex and the response was measured with EMG, 2.) means and standard deviations for SICI, CSP, ICF, or LICI were reported for both patient and control groups, 3.) all patients in the schizophrenia group met the DSM criteria for schizophrenia, schizoaffective disorder or first episode psychosis, and 4.) a detailed methodological description was provided with the calculation of the TMS-EMG outcome measures. Review articles, case reports, conference abstracts, and non-English-language publications were excluded, as were studies measuring TMS excitation with EEG.

7.1.2. Study Selection and Data Extraction

From eligible articles, means and standard deviations were extracted for SICI, CSP, ICF, LICI and RMT, together with group-level demographic, clinical and medication data.

Extracted clinical variables included diagnosis, PANSS scores, medication status, antipsychotic type, CPZ-equivalent dose and illness duration. TMS-EMG methodological variables included interstimulus interval, stimulation intensity, stimulator and coil type, stimulation side, target muscle and EMG electrode type. Where available, data were extracted separately for medicated and unmedicated patient groups. For studies reporting multiple interstimulus intervals, stimulation intensities or medication subgroups, weighted averages were calculated. CSP was extracted in milliseconds. Paired-pulse outcomes were harmonised to a common metric, calculated as conditioned/unconditioned MEP $\times$ 100, where values below 100 indicate inhibition and values above 100 indicate facilitation. Where studies reported outcomes differently, values were transformed to match this calculation. WebPlotDigitizer was used for graphical data extraction when necessary.

7.1.3. Risk of Bias and Quality of Evidence Assessment

Following the recommendations of the previous Cochrane Handbook on case-control studies, the Newcastle-Ottawa Scale (NOS)(144) was used to assess risk of bias. The checklist for TMS studies by Chipchase and colleagues (145) was used to address potential bias in TMS methodology. Studies that scored above 70% on the TMS checklist received an additional point in the NOS. With the additional TMS score in the NOS, the scale ranged from 0-10. Without any guidelines, we used the following cutoffs: 0-4, high risk; 5-7, moderate risk; and 8-10, low risk. Risk of bias assessment was completed independently by two authors (OL and BK).

7.1.4. Data Synthesis and Analysis

Data were analysed in R (version 4.0.3) using RStudio and the meta, metafor, and dmetar packages. A random-effects model was used to estimate the pooled mean difference and its 95% confidence interval. We anticipated variations in the true effect size across studies. To account for sampling error and such variances resulting from differences in experimental conditions, demographics and the heterogeneity of the patient population, we used a random-effects model. Between-study variance of the true effect size was estimated using Tau2 via the restricted maximum likelihood (REML) method. The Hartung-Knapp adjustments were applied to calculate a confidence interval around the

pooled effect size, compensating for small effect sizes reported in the articles. We used the I^2 test to evaluate heterogeneity due to sources other than sampling error. Forest plots were used to visualise mean differences and pooled effect sizes, and funnel plots were used to present publication bias.

To understand potential sources of heterogeneity, we first conducted exploratory analyses to assess the data distribution and evaluate linear relationships among moderator variables, including demographics, disorder characteristics, experimental design, and measurement details. When exploratory analyses revealed tendency-like associations, all moderator variables were added to meta-regressions and subgroup analyses.

7.2. Study II

7.2.1. Eligibility criteria and search strategy

Resting-state fMRI studies employing seed-based connectivity analysis in a case-control design with thalamic or cerebellar seeds were identified. The systematic search was conducted in three databases (MEDLINE via PubMed, Embase, and Scopus) on July 17, 2023 (search key in Supplementary Materials of the published paper).

Following the search, duplicates were identified and removed. After duplicate removal, the abstracts and then the full texts were screened for eligibility by two independent reviewers (OL + DZ). All disagreements were resolved by a third independent author (AS). Included studies are seed-based resting-state fMRI studies using thalamus or cerebellum seeds in schizophrenia-spectrum disorders and clinical-high risk for psychosis.

7.2.2. Data synthesis

Data extraction was performed independently by authors OL and DZ, and author GC resolved disagreements. Data for the thalamus and cerebellum seeds were selected separately. From all eligible articles, peak activation coordinates, contrasts (SSD<HC, HC<SSD), and, if available, t, z, or p values and threshold levels were selected. Talairach coordinates were transformed to MNI space using the GingerALE icbm2tal function.

Effect size and threshold levels were transformed to t values using the SDM web converter (www.sdmproject.com).

Group-level demographic data were also selected for both populations (sample size, age, sex). Diagnosis, PANSS scores, type of antipsychotic medication (atypical/typical or combination), CPZ-equivalent daily medication dose, and illness duration were extracted for the patient group. Coordinates for medicated and unmedicated patients were selected separately, where available. Type of scanner, Tesla, scan time, preprocessing software, atlas, seed definition, significance threshold, and correction method were extracted for the neuroimaging methodology.

7.2.3. Statistical analysis

Two established coordinate-based neuroimaging meta-analysis (CBMA) methods were independently applied to the same dataset to evaluate the spatial convergence of reported regions of brain activity across studies.

First, random-effects Activation Likelihood Estimation (ALE) analysis was conducted using the GingerALE software (PC Version 3.0.2, retrieved from: brainmap.org). ALE is a widely used coordinate-based neuroimaging meta-analysis method to identify spatial convergence of statistically significant effects of brain activity across studies (146). ALE analysis treats reported coordinates as spatial probability distributions centred around the foci. First, for each study, a modelled activation (MA) map is computed to summarise the probability of brain activity at the foci. MA maps are then combined across studies to obtain ALE scores, which are compared to a null distribution to distinguish true convergence from random clustering (147). Statistical significance is reached using permutation testing. Cluster-level family-wise error (FWE) correction ($p < 0.05$) is used for multiple comparison correction (148).

Secondly, Seed-based D Mapping (SDM-PSI Linux version 6.23, available at <http://www.sdmproject.com/>) was used to confirm the ALE findings and account for the variability in effect sizes among the reported studies. SDM incorporates key features from previous meta-analytic methods, such as ALE and Multilevel Kernel Density Analysis (MKDA), while introducing several improvements (149). SDM accounts for both positive and negative activation at the same voxel (e.g., hyperconnectivity and hypoconnectivity)

so that contradictory findings cancel each other; it integrates effect sizes of the peak coordinates into the model, and it considers the irregular local spatial covariance of the different brain tissues. SDM employs Threshold-Free Cluster Enhancement (TFCE) correction to define significant clusters (150). For a more detailed explanation of the methods, we refer the readers to the methodological articles (151-153).

7.2.4. Additional analyses

Subgroup analyses and meta-regressions were conducted using SDM software to evaluate the moderating effects of diagnosis, medication status, seed definition, and age. To assess the association between symptom dimensions and connectivity, as well as the association between hyper- and hypoconnectivity, correlation coefficients for clinical measures were extracted from the included articles and analysed in R (version 4.0.3) in RStudio using the metacor function of the meta-package. Jackknife (leave-one-out) sensitivity analysis was performed on thalamus seed studies in SDM to evaluate the robustness of our results. In addition, funnel plots and Egger's test implemented in the SDM software were used to assess publication bias.

The COBIDAS (Committee on Best Practice in Data Analysis and Sharing) checklist was used to assess the risk of bias (ROB) across the included studies (154).

8. RESULTS

8.1. Study I

8.1.1. Search and baseline characteristics

A total of 1715 case-control articles were identified by our search key and 80 reports were assessed for full-text selection. A final sample of 36 studies met the eligibility criteria and were included in the meta-analysis. See the flowchart of selection in the published paper and baseline characteristics in **Table 1**.

28 studies included SICI with 794 schizophrenia patients and 817 controls (mean age_{SCH} = 32.25, min = 25.30, max = 38.5; mean age_{HC} = 32.25, min = 20.93, max = 40.22). 18 studies reported SICI separately for medicated and unmedicated patients. Schizophrenia patients had a mean illness duration of 6.80 years (min = 0 in FEP, max = 16.40), a mean of 69.71 total PANSS score (min = 50.5, max = 92.4), and medicated patients were treated with a daily mean of 425.54 mg chlorpromazine (CPZ) equivalent antipsychotic dose (min = 283.97, max = 860.8).

CSP was reported in 23 articles (*total N*: HC = 662, SCH = 623), of which 17 reported data from medicated patients and 7 from unmedicated patients. The mean age of schizophrenia patients was 33.35 (min = 25.30, max = 42.60), and 31.81 for the control group (min = 20.93, max = 37.41). The patient population was characterised by an average illness duration of 7.07 years (min = 0 in FEP, max = 18.30), a mean total PANSS score of 71.76 (min = 50.5, max = 101) and a mean CPZ-equivalent medication dose of 425.89mg daily (min = 266.31, max = 860.8). Twenty articles reported on ICF, and only four articles reported on LICI.

Table 1. Basic characteristics of included studies

	Summary
Studies and sample size	36 case-control studies; total patient N = 932; total HC N = 973. Mean sample size per study: patients = 25.9; HC = 27.0.
Age and sex	Weighted mean age: patients = 32.6 years; HC = 32.3 years. Study-level mean age ranged from 25.3–43.7 years in patients and 20.9–42.2 years in HC. Female participants: patients = 322/932, 34.5%; HC = 396/973, 40.7%.
Diagnosis	Schizophrenia-only: 23 studies; schizophrenia + schizoaffective disorder: 6; first-episode psychosis: 6; broader SSD: 1
Medication-status	All patients medicated: 12 studies; medicated and unmedicated data available: 11; all patients unmedicated: 1; mixed or unclear medication status: 12.
Paradigm coverage	SICI was listed in 29 studies, ICF in 20, CSP in 23 and LICI in 4. Analytic sample sizes are reported in the corresponding subsections of the results.
Paradigm combinations	Single-paradigm studies: 11. Most common combination: SICI + ICF + CSP, 12 studies. Other combinations included SICI + ICF, SICI + CSP, SICI + LICI, SICI + LICI + CSP, SICI + ICF + LICI + CSP, CSP only, SICI only and LICI only.
Stimulation parameters	Conditioning stimulus intensity varied across studies and was most often defined as 80% RMT, but also as 80% AMT, 90% AMT, 5% maximum stimulator intensity or 5% below AMT. Test stimulus intensity was defined using 0.5–1 mV MEP, 0.5–1.5 mV MEP, 1 mV MEP, 1.5 mV MEP, 120% RMT, approximately 130% RMT or suprathreshold intensity.
Interstimulus Intervals	SICI was generally assessed at short ISIs, most commonly within 1–4 ms. ICF was assessed at longer ISIs, commonly around 7–30 ms. LICI was assessed at 100 ms in the included LICI studies.
CSP parameters	CSP intensity was variably defined as 120%, 130%, 140% or 150% RMT; 140% AMT; 10–40% above RMT; suprathreshold intensity to elicit 1 mV MEP; or percentage of maximum stimulator intensity.
TMS device and coil	Magstim systems: 24 studies; MagPro systems: 10; Cadwell: 1; device not fully specified: 1. Figure-of-eight coil: 32 studies; round coil: 2; coil type not explicitly stated: 2.
EMG target muscle	FDI: 20 studies; APB: 13; ADM: 3. Bilateral/both-side recordings were used in 8 studies, including both FDI in 7 and both APB in 1.
Main sources of heterogeneity	Diagnostic stage, medication reporting, paradigm selection, CS/TS definition, ISI selection, CSP intensity, TMS device, coil type, target muscle, and unilateral versus bilateral EMG recording varied across studies.

The table summarises study-level clinical and methodological characteristics extracted from the full baseline table, including sample size, age, sex, diagnostic composition, medication status coding, TMS-EMG paradigm coverage, stimulation parameters, TMS device, coil type, and EMG target muscle. Study-level baseline information is reported in the publications.

Abbreviations: CSP: Cortical Silent Period, SICI: Short-Interval Intracortical Inhibition, ICF: Intracortical Facilitation, LICI: Long-Interval Intracortical Inhibition, ISI: Interstimulus Interval, MEP: Motor Evoked Potential, RMT: resting motor threshold, AMT: active motor threshold, CS: conditioning stimulus, TS: test stimulus, ADM: abductor digiti minimi, FDI: first dorsal interosseus, APB: abductor pollicis brevis, SCH: schizophrenia, SAD: schizoaffective disorder, FEP: first episode psychosis, SSD: schizophrenia-spectrum disorder.

Included TMS-EMG studies: (72, 83-88, 94, 155-181)

8.1.2. Short-Interval Intracortical Inhibition (SICI)

Results from the random-effects model revealed a robust (*Cohen's d* = 0.62) reduction in SICI in schizophrenia patients compared to healthy controls (**Figure 3**). The pooled mean difference indicated that the inhibitory response was 13.85% lower in patients with schizophrenia than in healthy controls (95% CI = [9.19; 18.51]). The results remained robust after sensitivity analysis (total mean difference after removing moderate-to-high ROB articles: 13.36%; 95% CI = [7.99; 18.04]). Between-study heterogeneity is moderate ($I^2 = 57\%$, $p < 0.001$), a part of which can be explained by moderate to high ROB (heterogeneity of the sensitivity analysis: $I^2 = 50\%$, $p = 0.01$). In addition to ROB (182), experimental conditions such as the evaluation of task-related SICI (156) and cannabis use (183) could account for cases where SICI was found to be higher in schizophrenia.

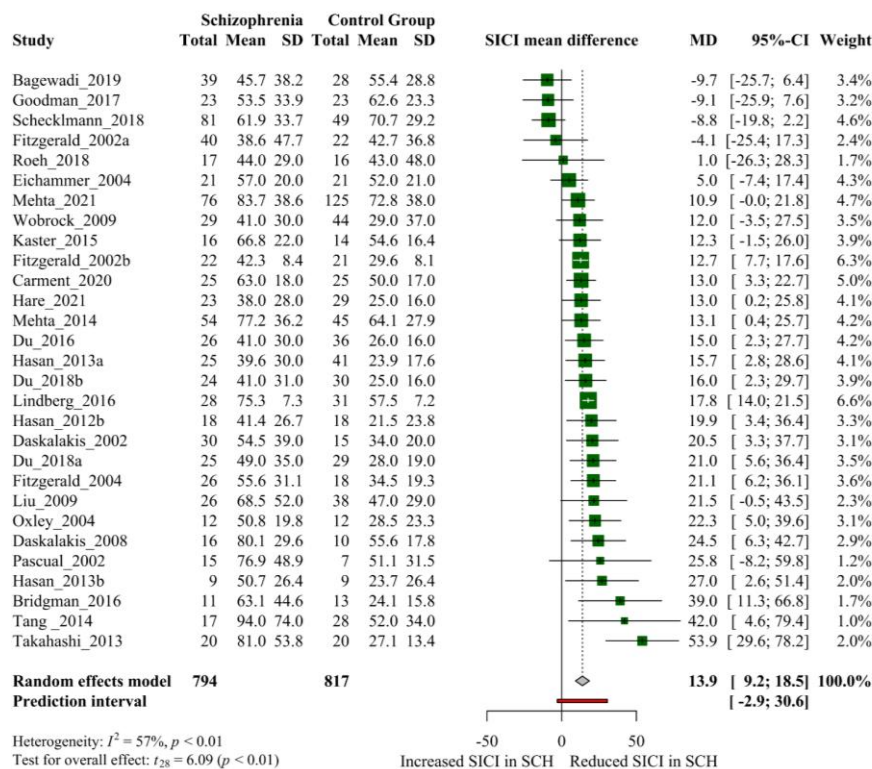


Figure 3.

A forest plot for the random-effects meta-analysis of Short-Interval Intracortical Inhibition (SICI) shows the mean difference in SICI between the schizophrenia (SCH) and healthy control (HC) groups. SICI is expressed as [conditioned/unconditioned MEP $\times$ 100]. Articles from zero to the left show greater inhibition in SCH, whereas articles from 0 to the right show decreased inhibition in SCH.

Subgroup and exploratory analyses revealed a tendency-like association between SICI and medication status as well as SICI and CPZ equivalent antipsychotic dose (**Figure 4D**). Based on exploratory analysis, the effect of medication status appears to be more pronounced than that of medication dose. However, subgroup analysis did not confirm a difference in the extent to which medicated ($n = 375$) and unmedicated ($n = 142$) schizophrenia patients differ from the healthy population (**Figure 4E**). Meta-regressions conducted with covariates such as symptom severity (PANSS scores), illness duration, age and sex did not reveal a significant effect on the pooled effect size. A trend-level association was found between the proportion of females and SICI, suggesting that the inhibitory response was greater in samples with more males than in those with more females. Additionally, subgroup analysis did not show any variation in SICI across different TMS conditions (stimulation side, device, target muscle, interstimulus interval), diagnoses, or publication date.

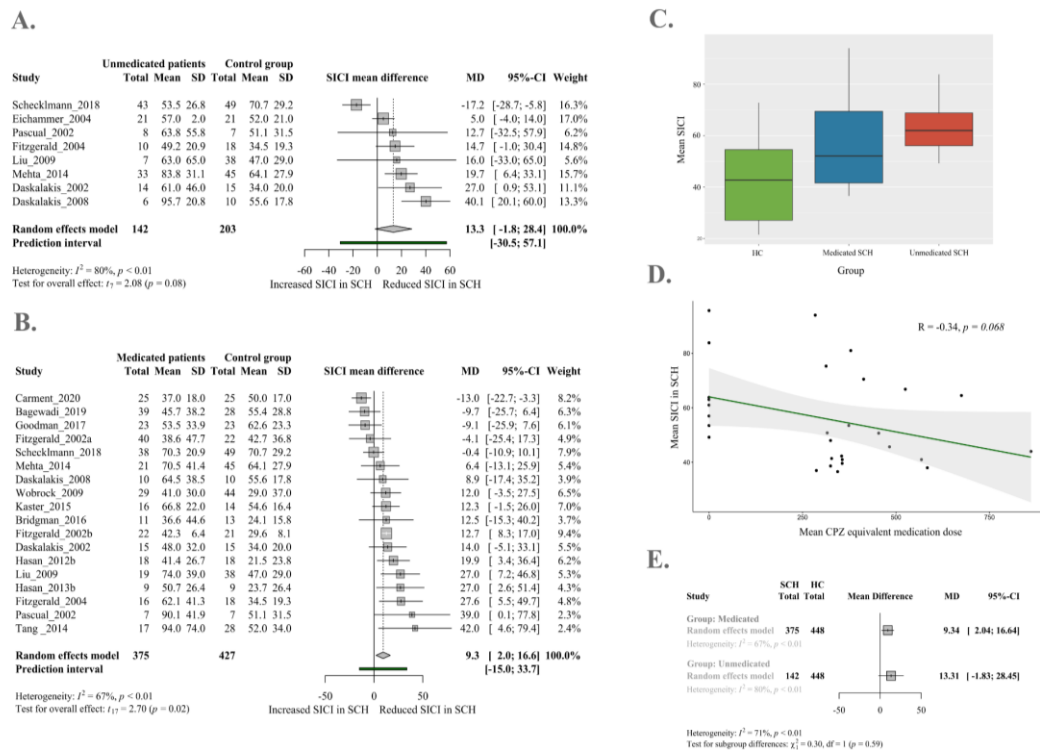


Figure 4.

A: forest plot for Short-Interval Intracortical Inhibition (SICI) between unmedicated schizophrenia patients (SCH) and the healthy control group (HC). B. forest plot for SICI between medicated SCH patients and the HC. C and D: exploratory analysis of medication status and mean CPZ equivalent medication dose of SICI. E: total effect sizes for subgroup analysis of SICI between medicated and unmedicated SCH and HC.

8.1.3. Cortical Silent Period (CSP)

Results for CSP did not show any difference between schizophrenia patients and the control group (**Figure 6**). The pooled effect size showed high heterogeneity between studies ($I^2=89\%$, $p < 0.001$) and a wide confidence interval around the pooled total effect size (mean difference = 6.69, CI = [-6.16;19.54]). Furthermore, the large inconsistency between published results is reflected in the range of CSP within the control group (83.6-195.7 ms), which may be due to biological variability or measurement bias.

Subgroup analyses and meta-regressions of experimental conditions, demographic variables, and medical variables failed to identify a single moderator variable that could account for the variance observed across studies. Nevertheless, a tendency-like association was found between medication status and CSP. Unmedicated patients exhibited a slightly shorter CSP (reduced inhibition), whereas medicated patients showed a slightly longer CSP compared to the control group (**Figure 5**). However, these results are not significant and are highly heterogeneous.

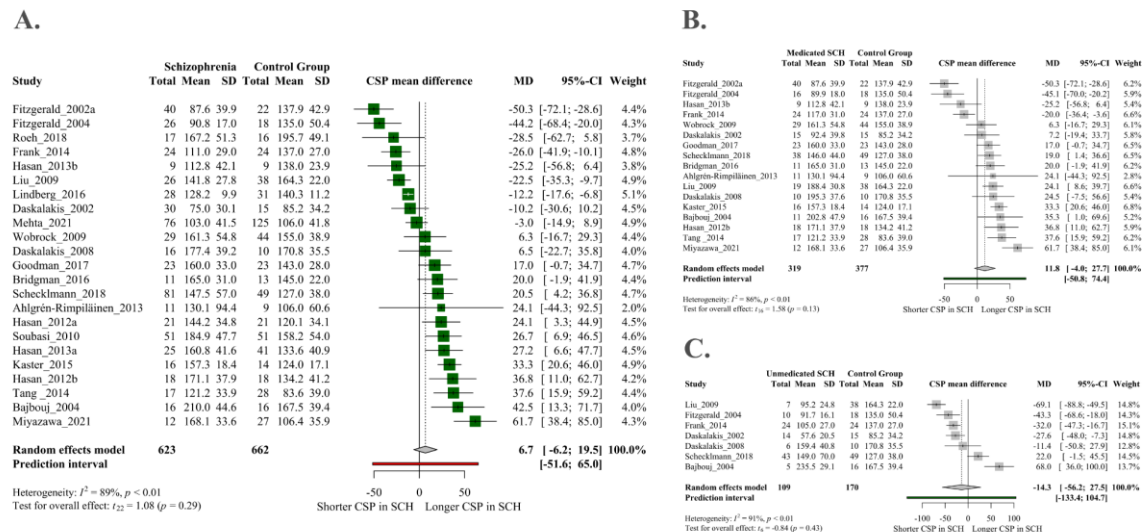


Figure 5.

Forest plots for the random-effect meta-analysis of the Cortical Silent Period (CSP). Panel A. shows the mean difference of CSP between schizophrenia patients (SCH) and healthy control groups (HC). CSP is measured in milliseconds; its length is proportional to the extent of inhibition. Articles from zero to the left show shorter CSP in SCH, whereas articles from 0 to the right show longer CSP in SCH. Panel B. shows the forest plot for CSP between unmedicated SCH patients and HC, whereas Panel C. shows the forest plot for CSP between medicated SCH patients and HC.

8.1.4. Intracortical Facilitation (ICF), Long-Interval Intracortical Inhibition (LICI), and Resting Motor Threshold (RMT)

We found no clear difference between schizophrenia patients and control groups in terms of excitatory response ICF or the inhibitory response LICI (**Figure 6**). Results of the ICF are reliable, and the relatively large sample size (SCH = 532, HC = 498) and the low between-study heterogeneity ($I^2=37\%$, $p = 0.005$) confirm that there is no clear difference between the two groups. Sensitivity analysis (excluding moderate to high ROB articles) did not improve or change the overall results of ICF (total mean difference = 0.45, 95% CI= [-12.66; 13.56]). Subgroup analyses and meta-regressions (depending on the variable type) did not account for heterogeneity in experimental conditions, medical conditions, demographic variables, or publication year.

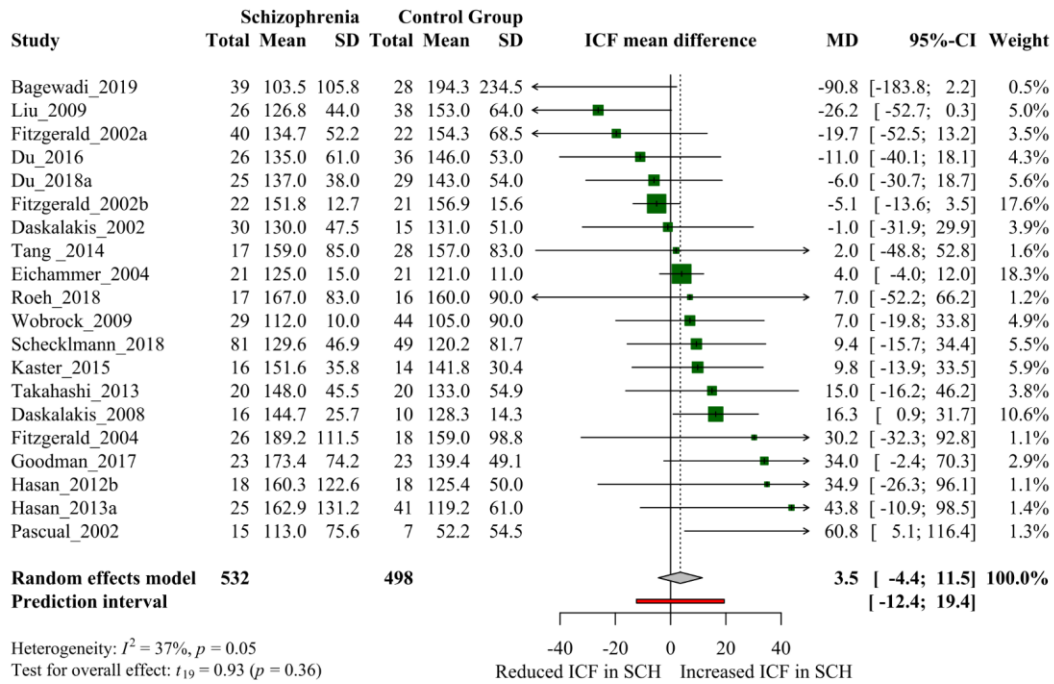
Due to the small number of articles included ($n = 4$) and the relatively small pooled sample size (SCH = 170, HC = 201), the results of LICI are not sufficient to draw conclusions from.

A powerful analysis of RMT, including 33 studies and an impressive sample size (SCH=902, HC=932), did not reveal any group differences in baseline excitability. A sensitivity analysis based on ROB did not change the overall effect (total mean difference = 1.69, 95% CI = [-0.37; 3.75]).

8.1.5. Risk of Bias, Publication Bias, and Heterogeneity

Of the 36 articles included, 2 had a combined high risk of bias on the NOS and TMS checklists, 13 had moderate risk, and 21 had a low risk of bias (results available online at <https://osf.io/8cef3/>). Funnel plots and Egger's test were used to assess publication bias across the included studies. The funnel plots showed relative symmetry across all TMS-EMG paradigms except CSP, raising concerns about potential publication bias. No significant publication bias was detected with the Egger's test.

A.



B.

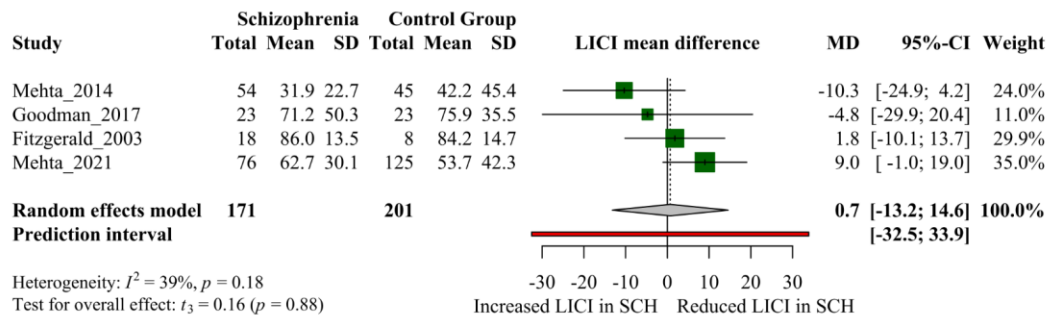


Figure 6.

Panel A: Forest plot for Intracortical Facilitation (ICF). Articles from zero to the left show decreased ICF in schizophrenia (SCH), whereas articles from zero to the right show increased ICF in SCH. There is no significant difference between the two groups. Panel B: Forest plot for Long-Interval Intracortical Inhibition (LICI). Articles from zero to the left show increased inhibition in schizophrenia (SCH), whereas articles from zero to the right show decreased inhibition in SCH. There is no significant difference between the two groups, and a conclusion cannot be drawn from these results due to the small number of included articles.

8.2. Study II

8.2.1. Search and selection

6,540 studies were identified through the search process (PRISMA flowchart is reported in the publication). 4,509 articles were screened by title and abstract, and 348 articles were subjected to full-text selection. Studies with thalamic or cerebellar seeds were evaluated separately. 29 studies were included using thalamic seeds, reporting data from 2768 patients and 2826 controls (115, 116, 136, 138, 142, 184-208). Additionally, 19 studies with cerebellar seeds were selected, totalling 1159 patients and 1222 controls (132, 194, 203, 209-224). Baseline characteristics are reported in Table 2.

Table 2. Baseline characteristics of the included articles using thalamus and cerebellum seeds.

Domain	Thalamic-seed studies	Cerebellar-seed studies
Included studies	N = 29	N = 19
Sample size	N patient/at-risk = 2,768; N HC = 2,826	N patient/at-risk = 1,159; N HC = 1,222
Age	Mean age: patient/at-risk = 31.6; HC = 30.6 years. Age range: patient/at-risk = 16.1–43.0; HC = 14.8–39.9	Mean age: patient/at-risk = 26.5; HC = 26.5 years. Age range: patient/at-risk = 18.5–42.0; HC = 17.8–39.5
Diagnosis	SCH = 25; SAD and/or mixed psychosis = 5; FEP = 2; CHR = 3; ROC = 1; early-onset psychosis = 1; broad psychosis = 1	SCH = 8; FEP = 7; CHR = 5; non-clinical psychosis = 1
Illness duration	Reported in 19 studies; range = 0.36–20.2 years	Reported in 10 study/subgroup entries; range = 14.6 months / <1 year to 20.3 years
Medication status	Reported in 18 studies; medicated range = 19–100%; antipsychotic-naïve sample = 1 study	Reported in 10 studies; medicated range = 19–100%; antipsychotic-naïve samples = 2 studies
CPZ dose	Available in 17 studies; range = 33.64–915.33 mg/day	Available in 6 studies; range = 139.8–428.1 mg/day
PANSS / symptom scale	PANSS total = 18 studies; range = 39.84–88.1	PANSS total in 9 studies; range = 60.4–91.42; SIPS = 2 studies; BPRS = 1 study
Seed definition	Bilateral whole thalamus = 16; segmented = 12; left thalamus = 2	Dentate nucleus = 3; lobule-specific seeds = 3; multiple cerebellar ROI/cluster seeds = 11; bilateral/left-right cerebellum = 2
Scanner manufacturer	Siemens = 14; GE = 9; Philips = 4; multiple scanners = 3	Siemens = 13; GE = 4; Philips = 1; scanner not reported = 1
Scanner field strength	3T = 25; 7T = 1; mixed 3T/1.5T = 1; multiple/unspecified scanners = 3	3T = 18; not reported = 1
Risk of bias	Low = 25; moderate = 5; high = 0	Low = 16; moderate = 3; high = 0

The study-level data is reported in the publication. SCH = schizophrenia, SAD: schizoaffective disorder, CHR = Clinical High-Risk for Psychosis, FEP = First Episode Psychosis

8.2.2. Thalamic hyperconnectivity in SSD

ALE analysis with the SSD>HC contrast included 24 studies and 435 foci. Significant convergence was observed across 6 clusters, with 13 significant peaks (**Figure 7A, Table 3**). Thalamic hyperconnectivity was found in the left visual association cortex, bilateral somatosensory and motor areas, and sections of the cerebellar culmen.

SDM analysis yielded two significant clusters, each with bilateral primary motor cortical peaks. The left (Hedges g : 0.15) and right (Hedges g : 0.17) clusters spread through the parietal and temporal lobes, including 3019 and 7133 voxels, respectively (**Figure 8A, Table 4**). The two clusters show compelling overlap with areas within the visual and somatosensory association areas, as revealed by the ALE analysis.

Between-study heterogeneity was low for both significant peaks (Left M1: $I^2 = 13.63\%$, $\text{Tau}^2 = 0.004$, Right M1: $I^2 = 3.74\%$, $\text{Tau}^2 = 0.001$), and the clusters were unaffected by the sensitivity analysis (excluding moderate risk articles).

Table 3. Significant regions of Activation Likelihood Estimation showing regions of thalamic hyperconnectivity (contrast: SSD>HC).

Cluster	Region	x	y	z	ALE	Z
1	Left Inferior Temporal Gyrus	-48	-74	4	0.0367	5.92
1	Left Middle Temporal Gyrus (Brodmann area 37)	-54	-64	2	0.0245	4.45
2	Left Precentral Gyrus (Brodmann area 4)	-56	-10	36	0.0272	4.81
2	Left Precentral Gyrus (Brodmann area 6)	-50	-10	26	0.0252	4.54
3	Left Inferior Parietal Lobule (Brodmann area 40)	-36	-34	62	0.0234	4.31
3	Left Postcentral Gyrus (Brodmann area 3)	-36	-20	50	0.0209	3.99
3	Left Inferior Parietal Lobule (Brodmann area 40)	-38	-30	50	0.0188	3.70
4	Right Postcentral Gyrus (Brodmann area 2)	48	-20	50	0.0346	5.67
4	Right Precentral Gyrus (Brodmann area 4)	54	-12	42	0.0198	3.85
5	Right Paracentral Lobule (Brodmann area 5)	4	-30	64	0.0379	6.05
6	Right Cerebellar Culmen	16	-54	-2	0.0291	5.03

Clusters are FWE-corrected at $p < 0.05$. Number of foci = 435, Number of experiments = 24, Total number of subjects = 1888; Threshold Method: Cluster-level Inference (Thresholding Value = 0.01), N permutations = 1000, Cluster-Forming Method: uncorrected p -value of 0.001, Volume > Threshold = 9264 mm³, minimum cluster size = 968 mm³

Table 4. Regions of thalamic hyperconnectivity (contrast SSD>HC) in schizophrenia-spectrum disorders based on the SDM analysis.

Voxels	Region	x	y	z	Hedges g	SDM- Z	P
Cluster I.							
7133	Peak: Right precentral gyrus, BA 4	36	-24	50	0.17	4.863	0.001
Cluster breakdown							
698	Corpus callosum	10	-28	66		4.635	0.001
521	Right precentral gyrus, BA 6	36	-16	58		3.804	0.001
495	Right middle temporal gyrus, BA 21	60	-10	- 16		4.388	0.001
483	Right postcentral gyrus, BA4	56	-10	40		3.776	0.001
483	Right precentral gyrus, BA 4	36	-24	50		4.863	0.001
416	Right rolandic operculum, BA 48	52	-16	14		4.141	0.001
318	Right superior temporal gyrus, BA 48	50	-28	8		3.696	0.001
253	Right paracentral lobule, BA 4	6	-24	62		4.582	0.001
Cluster II.							
3019	Peak: Left precentral gyrus, BA 4	-40	-18	52	0.15	4.632	0.001
Cluster breakdown							
379	Left postcentral gyrus, BA 4	-52	-8	36		4.225	0.001
266	Left postcentral gyrus, BA 3	-54	-12	38		4.336	0.001
264	Left superior temporal gyrus, BA 4	-54	-14	10		3.961	0.004
250	Left middle temporal gyrus, BA 22	-60	-20	-6		4.147	0.003

Peak and contributing regions are larger than 200 voxels and are TFCE corrected. Blobs are of ≥ 3019 voxels with all voxels $SDM-Z \geq 2.383$ and all peaks $SDM-Z \geq 4.632$.

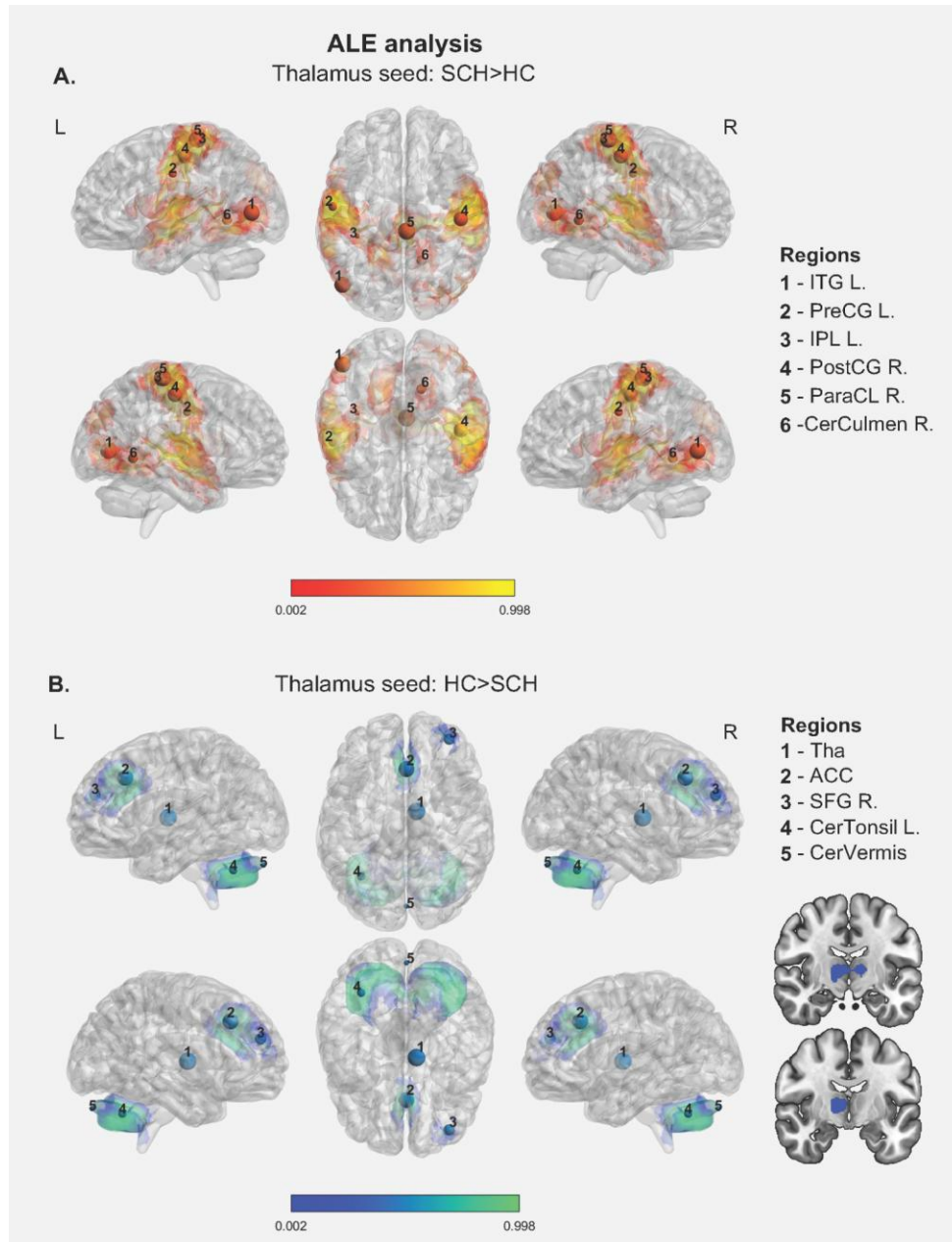


Figure 7.

Results of the ALE analysis. Significant clusters of the Activation Likelihood Estimation (ALE) (cluster-level FWE corrected $p < 0.05$). Panel A shows regions of thalamic hyperconnectivity in schizophrenia spectrum disorders with SSD>HC contrast (summarised in Table 3), Panel B shows regions of thalamic hypoconnectivity with HC>SSD contrast (summarised in Table 4). Abbreviations: ALE: Activation Likelihood Estimation, SSD: schizophrenia spectrum disorders, HC: healthy control group.

Regions: ITG: Inferior Temporal Gyrus, PreCG: Precentral Gyrus, IPL: Inferior Parietal Lobule, PostCG, Postcentral Gyrus, ParaCL: Paracentral Lobule, CerCulmen: Cerebellar Culmen, Tha: Thalamus (bilateral), ACC: Anterior Cingulate Gyrus, SFG: Superior Frontal Gyrus, CerTonsil: Cerebellar Tonsil, CerVermis: Cerebellar Vermis. L: left, R: right.

8.2.3. Thalamic hypoconnectivity in SSD

ALE analysis with the SSD<HC contrast was performed on 361 peak activation coordinates from 28 studies. Significant convergence of the reported locations of thalamus hypoconnectivity was found in 5 clusters and 12 peaks (**Figure 7B, Table 5**). Hypoconnectivity in SCH was observed in the bilateral thalamus, the right prefrontal regions, the left limbic lobe, and the cerebellum. Reduced thalamo-thalamic connectivity had the highest load, with 19 foci contributing to the first cluster. SDM analysis confirmed that SSD individuals exhibit reduced thalamocerebellar and frontothalamic connectivity compared to the healthy control group, with small effect sizes (*Hedges g* = 0.21 and 0.18, respectively; **Figure 8B, Table 6**). Intrathalamic hypoconnectivity detected by the ALE analysis did not survive TFCE correction in the SDM analysis. Positive and negative findings in the same region cancel each other out in the SDM analysis, which could potentially explain this difference between the two statistical methods. Between-study heterogeneity was low for both significant peaks (Left cerebellum: $I^2 = 32.57\%$, $Tau^2 = 0.01$, Superior Frontal Gyrus: $I^2 = 26.63\%$, $Tau^2 = 0.009$), and the significant clusters were unaffected by sensitivity analysis (excluding articles with moderate risk of bias).

Table 5. Significant regions of Activation Likelihood Estimation (ALE) analysis showing regions of thalamic hypoconnectivity (contrast: HC>SSD) in schizophrenia spectrum disorders.

Cluster	Region	x	y	z	ALE	Z
1	Right Thalamus	10	-8	6	0.0370	6.17
1	Left Thalamus	-12	-14	8	0.0251	4.74
1	Left Thalamus, Medial Dorsal Nucleus	2	-14	6	0.0211	4.22
2	Left Cingulate Gyrus (Brodmann area 32)	2	26	38	0.0349	5.93
2	Left Cingulate Gyrus (Brodmann area 32)	2	26	32	0.0247	4.68
3	Right Superior Frontal Gyrus (Brodmann area 9)	36	50	24	0.0285	5.17
3	Right Superior Frontal Gyrus (Brodmann area 10)	36	56	16	0.0207	4.16
4	Left Cerebellar Tonsil	-46	-62	-36	0.0248	4.69
4	Left Cerebellar Tonsil	-34	-60	-36	0.0248	4.69
5	Left Cerebellar Vermis	2	-84	-32	0.0207	4.16
5	Right Cerebellum, Vermis	8	-80	-28	0.0195	3.99
5	Left Cerebellum, Vermis	0	-74	-22	0.0181	3.78

Clusters are FWE-corrected at $p < 0.05$. Number of foci = 361, Number of experiments = 28, Total number of subjects = 2544; Threshold Method: Cluster-level Inference (Thresholding Value = 0.01), N permutations = 1000, Cluster-Forming Method: uncorrected p-value of 0.001, Volume > Threshold = 9112 mm³, minimum cluster size = 840 mm³

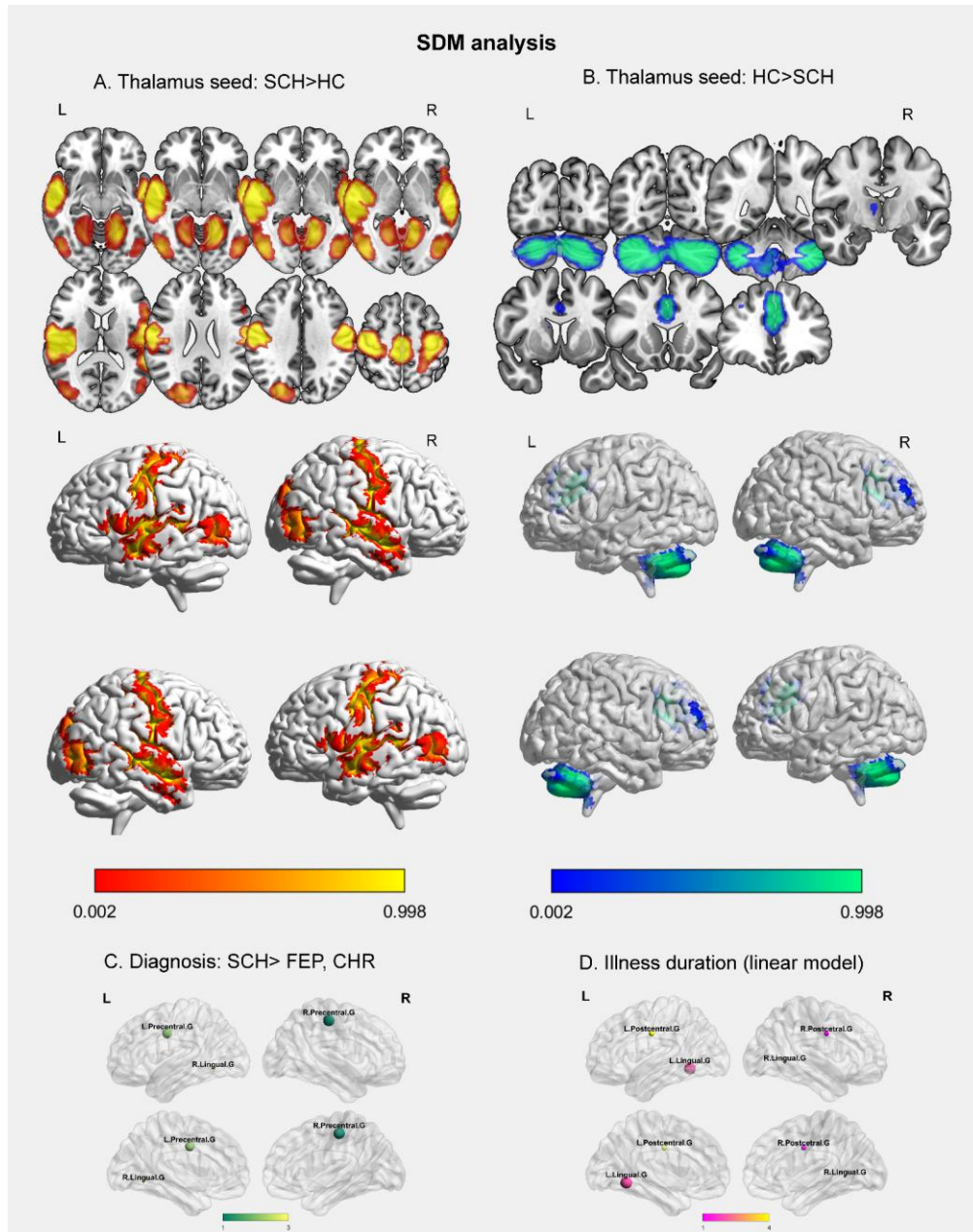


Figure 8.

Results of the SDM analysis. A. Significant threshold-free cluster enhancement (TFCE) corrected clusters from the Seed-based d Mapping (SDM) meta-analysis showing increased connectivity in schizophrenia-spectrum disorders (Table 4). B. Significant clusters of the SDM meta-analysis showing decreased connectivity in schizophrenia-spectrum disorders (TFCE corrected) (Table 6). (C) Results of the subgroup analysis based on diagnosis. A binary contrast (SCH vs. FEP or CHR) revealed significant clusters reflecting regions where hyperconnectivity is more pronounced in schizophrenia. D. Results of the linear SDM model based on illness duration. Significant TFCE-corrected clusters indicate regions where hyperconnectivity is more pronounced across the moderator variables. Abbreviations: SSD: schizophrenia spectrum disorders, HC: healthy control group, SCH: schizophrenia, FEP: First episode psychosis, CHR: Clinical High-Risk for Psychosis

Table 6. SDM analysis. TFCE corrected cluster peaks and the contributing main regions of thalamic hypoconnectivity (contrast HC>SSD) in schizophrenia spectrum disorders.

Voxels	Region	x	y	z	Hedges g	SDM-Z	P
Cluster I.							
7133	Peak: Left cerebellum, crus II	-40	-62	-40	0.21	-5.157	<0.001
Cluster breakdown							
862	Left cerebellum, crus II	-36	-64	-42		-5.151	0.009
700	Left cerebellum, crus I	-36	-36	-36		-4.258	0.001
676	Right cerebellum, crus I	16	-78	-28		-2.885	0.028
386	Right cerebellum, crus II	16	-78	-28		-2.885	0.289
335	Right cerebellum, hemispheric lobule VIII	8	-60	-40		-3.131	0.018
Cluster II.							
813	Peak: Right superior frontal gyrus, medial, BA 8	4	30	42	0.18	-4.587 (Hedges g = 0.18)	0.007
Cluster breakdown							
128	Left superior frontal gyrus, medial, BA 32	-6	32	34		-4.075	0.009
88	Left anterior cingulate gyrus, BA 24	-4	30	30		-4.192	0.008

Blobs are of ≥ 3019 voxels with all voxels $SDM-Z \geq 2.383$ and all peaks $SDM-Z \geq 4.632$

8.2.4. Symptom Dimensions, Illness Stage, and Disease Progression

The correlation meta-analysis of clinical scores indicate that hyperconnectivity between the thalamus and sensorimotor ($r = 0.20$, 95% CI = [0.05; 0.33]; $r = 0.19$, CI = [0.04; 0.33]), and the temporal auditory areas ($r = 0.18$, 95% CI: 0.09-0.27; $r = 0.18$, CI = [0.06; 0.34]) is slightly more pronounced with greater positive and negative symptom severity respectively (**Figure 11**). In contrast, hypoconnectivity between the thalamus and the prefrontal cortex appears unrelated to symptom severity. Regions exhibiting hypoconnectivity with the thalamus show a tendency toward a negative correlation with symptom severity, whereas regions with hyperconnectivity show a positive correlation at the trend level.

All reported correlation values, both significant and non-significant, were included in the analysis. It is important to note that the majority of these correlations were weak and non-significant, resulting in overall weak effects. Fifteen of the included studies did not find any significant correlation with symptoms and connectivity and did not report the correlation coefficients (116, 137, 185, 188, 190, 194, 196, 201, 206, 207, 225-227).

Additionally, three studies did not conduct any correlation analyses (115, 204, 205). Missing data likely contributes to the limitations of the meta-analysis, as unpublished or unreported results may introduce bias and reduce its reliability.

Correlational meta-analysis investigating the association between hyper- and hypoconnectivity revealed moderate negative correlation in SSD individuals (N studies = 5, N SCH = 661, $r = -0.63$, 95% CI = [-0.86; -0.19]) and HC and SSD participants combined (N studies = 6, N = 1100, $r = -0.68$, 95% CI = [-0.85; -0.37]).

Linear models in SDM were employed to assess the moderating effects of illness duration and diagnostic group. A binary contrast was applied to compare chronic schizophrenia cohorts to early-stage groups (FEP, early-onset psychosis, recent-onset psychosis, and CHR; mean illness duration < 2 years; $n = 8$ studies). Combining diagnostic groups provided a sufficient sample size to examine illness-stage effects. Results revealed that hyperconnectivity in the visual association areas and the motor cortex is more pronounced in schizophrenia compared to early psychosis and clinical high-risk (**Figure 10C**). Meta-regression looking at the effect of illness duration revealed hyperconnectivity in the visual association areas and the somatosensory cortex is similarly more pronounced with disease progression (**Figure 10D**).

No association was found between hypoconnectivity and diagnosis or illness duration.

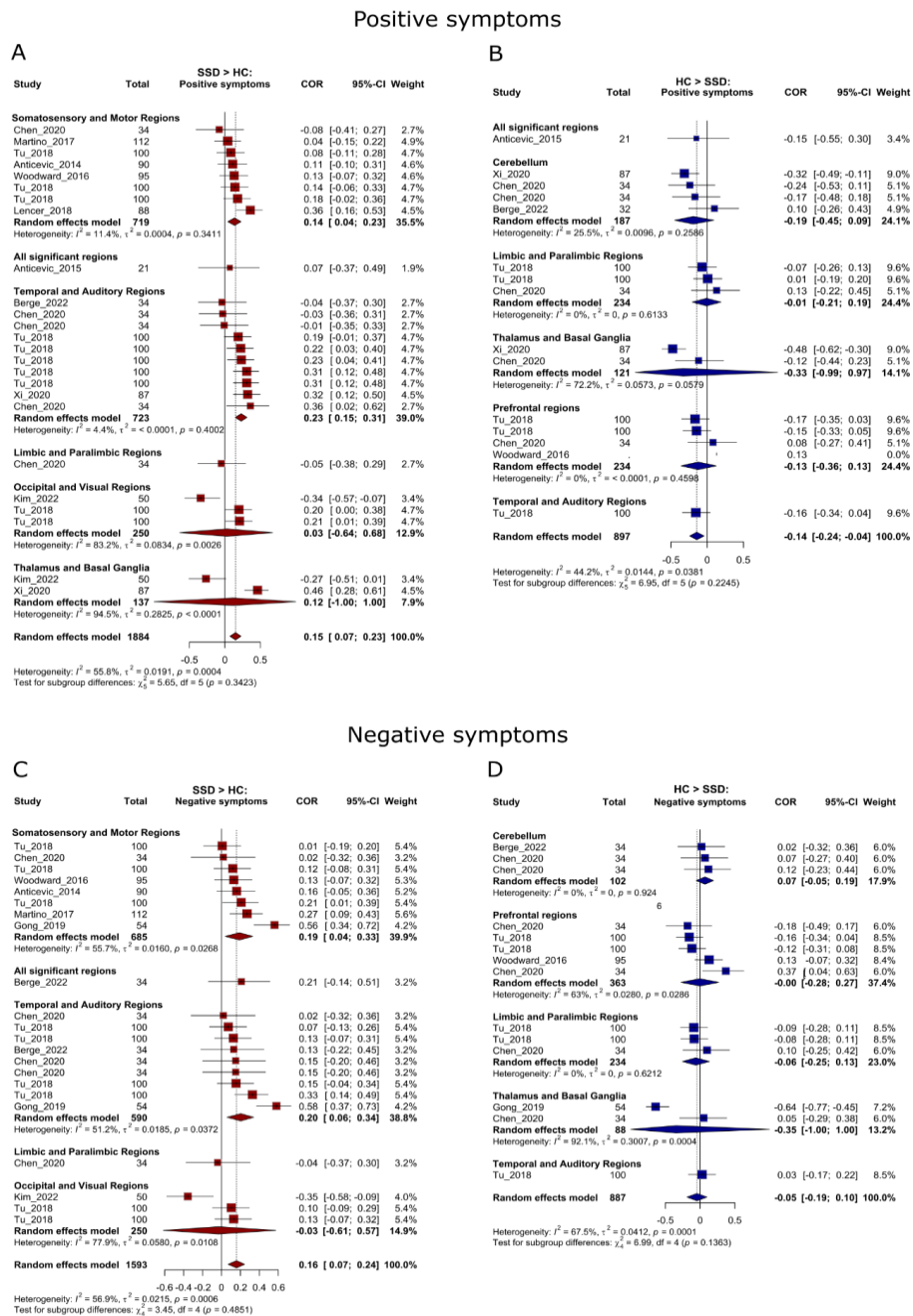


Figure 9.

Results of the Correlation Meta-Analysis of Symptom Dimensions.

(A, B) Regions of hyperconnectivity between the thalamus and cortical areas associated with positive symptom severity (PANSS positive subscale and SAPS scores).

(C, D) Regions of hyperconnectivity and hypoconnectivity associated with negative symptom severity (PANSS negative subscale and SANS scores).

Abbreviations: SSD: schizophrenia spectrum disorders, HC: healthy control group, PANSS: Positive and Negative Syndrome Scale, SAPS: Scales for the Assessment of Positive Symptoms, SANS: Scales for the Assessment of Negative Symptoms

8.2.5. Subthalamic results

11 included articles segmented the thalamus into subregions for seed-based analysis. Since the definition of seed ROI varied across studies, and available data was not sufficient for subthalamic meta-analysis for each thalamic nucleus, subthalamic results are reviewed qualitatively and are summarised in **Figure 10**. To evaluate the impact of seed definition, a sensitivity analysis was conducted in SDM, excluding studies that used segmented thalamic seeds ($n = 12$). The results of unilateral and bilateral thalamic seeds showed patterns of hyperconnectivity similar to those of the full analysis, and smaller clusters of hypoconnectivity were observed only in the cerebellum.

A systematic qualitative review of subthalamic regions revealed that articles differed in the number of subregions into which the thalamus was segmented, the atlas used for segmentation, and whether a histologic or functional approach was employed.

Sensorimotor hyperconnectivity was frequently reported, particularly involving the ventral anterior nucleus (VA), ventral posteromedial nucleus (VPM), and laterodorsal nucleus (LD)(137, 206, 228). Reduced connectivity between the mediodorsal nucleus (MD) and the prefrontal cortex (PFC) was observed, reflecting disruptions in cognitive control networks. Results on the pulvinar did not reveal a consistent pattern(136, 137, 196, 227).The pulvinar was found to have increased connectivity to visual and sensory regions and reduced connectivity with prefrontal and higher-order cognitive areas (137, 218, 228, 229). Reduced connectivity was reported between the lateral geniculate nucleus (LGN) and visual processing areas, as well as between the medial geniculate nucleus (MGN) and auditory regions (218) (**Figure 10**).

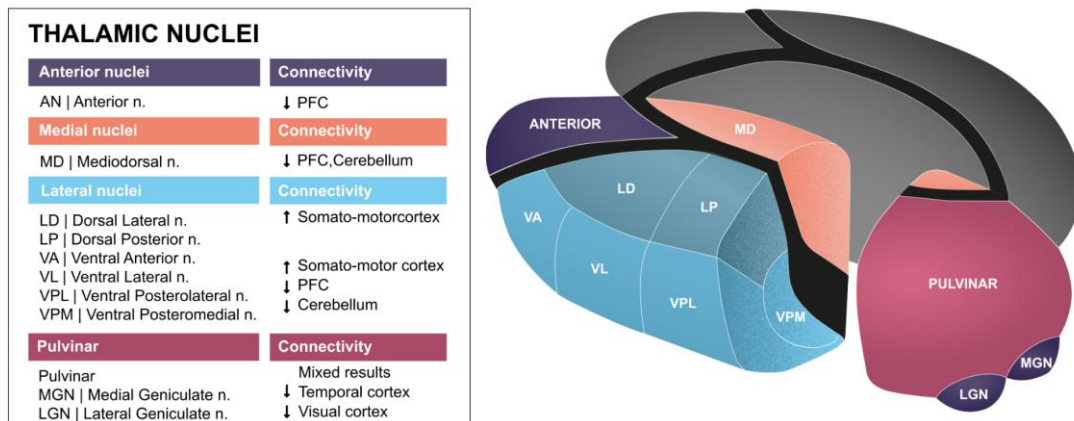


Figure 10.

Results of the Correlation Meta-Analysis of Symptom Dimensions.

(A, B) Regions of hyperconnectivity between the thalamus and cortical areas associated with positive symptom severity (PANSS positive subscale and SAPS scores).

(C, D) Regions of hyperconnectivity and hypoconnectivity associated with negative symptom severity (PANSS negative subscale and SANS scores).

Abbreviations: SSD: schizophrenia spectrum disorders, HC: healthy control group, PANSS: Positive and Negative Syndrome Scale, SAPS: Scales for the Assessment of Positive Symptoms, SANS: Scales for the Assessment of Negative Symptoms

8.2.6. Cerebellar connectivity

ALE and SDM analyses were conducted separately for the studies with cerebellum seed, and 19 articles and 247 foci were included in both analyses. 148 foci indicated cerebellar hypoconnectivity in SSD, and 99 foci indicated cerebellar hyperconnectivity in the patient population.

Neither ALE nor the SDM analysis revealed significant convergence of the foci. Uncorrected significant blobs of more than 15 voxels with peaks of an SDM-Z value greater than 1.99 or smaller than -1.99 were identified with the SDM analysis; however, the results did not survive TFCE correction. Uncorrected results of the SDM analysis revealed cerebellar hypoconnectivity in SSD within the cerebellum, Left Middle Temporal Gyrus, and the left Superior Frontal Gyrus (largest cluster size: 599 voxels, **Table 7**). Uncorrected clusters (all clusters are smaller than 100 voxels) of hyperconnectivity centred around the left postcentral gyrus and medial frontal gyrus (**Figure 11**).

Table 7. Centre of mass regions extracted for cerebellar SDM analysis.

Cluster	Cluster size	Region (Centre of mass)	x	y	z	Peak SDM-Z
Hyperconnectivity						
1	54	~ Medial Frontal Gyrus	2	51	-14	2.3495
2	94	Left Postcentral Gyrus	-52	-18	44	4.123
Hypoconnectivity						
1	599	Left cerebellum, posterior lobe	-37	-63	-38	2.7923
2	569	Right cerebellum, posterior lobe	36	-72	-36	2.6936
3	145	Left Middle Temporal Gyrus	-60	-23	-4	1.9162
4	207	Left Superior Frontal Gyrus	-2	29	49	2.1218

Clusters of hyperconnectivity of **uncorrected** blobs are smaller than 100 voxels. Regions of hypoconnectivity include **uncorrected** blobs of > 200 voxels. All studies using cerebellum seeds were included in the analysis (N=19 articles, total 247 foci).

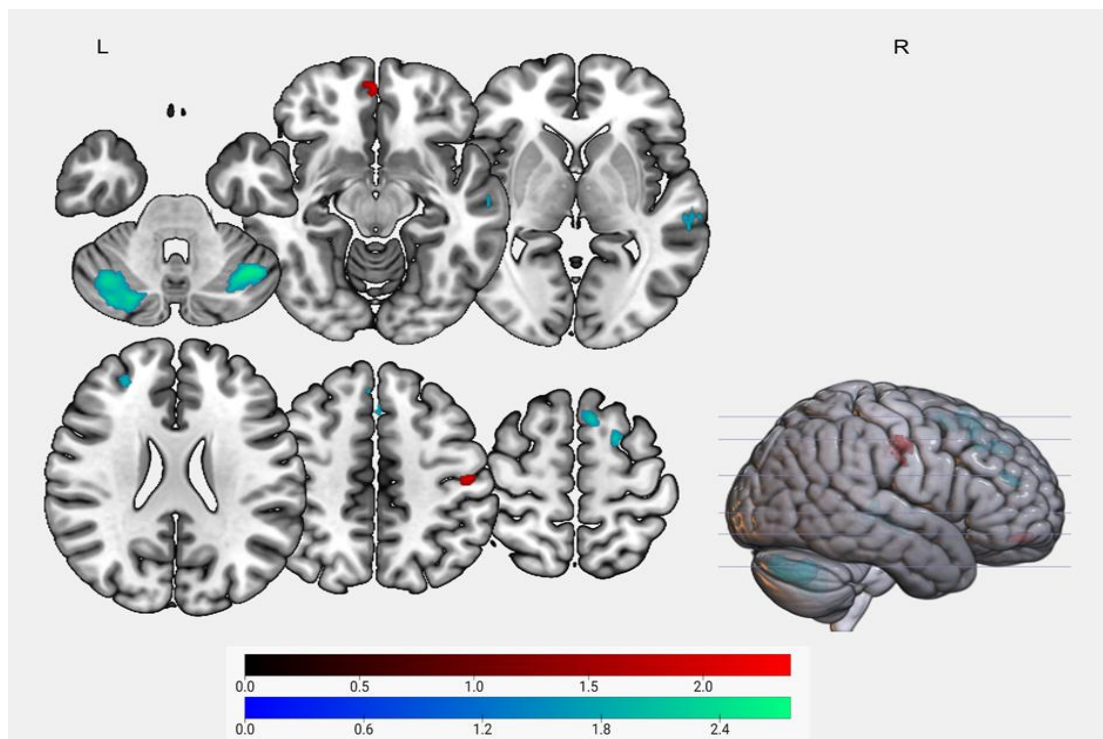


Figure 11.

Cerebellar results. Uncorrected significant clusters of cerebellar hypoconnectivity (blue) and hyperconnectivity (red) in schizophrenia spectrum disorders (SPD). Clusters did not survive TFCE (threshold-free cluster enhancement) correction. Cluster information is reported in Table S7.

8.2.7. Sub-cerebellar results

16 of the included studies used sub-cerebellar seeds. All included articles showed considerable variation in seed definitions and cerebellar segmentation approaches, preventing direct comparisons of findings. A qualitative review of the sub-cerebellar results is summarised in the Supplementary Results S14 of the publication.

Studies showed high heterogeneity in methods used for parcellation. Multiple studies targeted similar regions (such as Crus I, Crus II, or Lobule IX), but the underlying definitions of these regions are inconsistent.

Despite segmentation variability, some consistent connectivity patterns were identified across studies. Crus I showed a recurring pattern of reduced connectivity to frontal cortical regions and the DMN in SSD (214, 215, 222, 224). This disruption of fronto-cerebellar connectivity was observed in SSD and in CHR. Similarly, Lobule IX exhibited reduced connectivity to frontal regions and the DMN (214, 221, 222). In contrast, studies of the dentate nucleus found consistent patterns of increased connectivity with parietal regions and decreased connectivity with the PFC (203, 209).

8.2.8. Risk of Bias and Heterogeneity

Jackknife sensitivity analysis confirmed that significant clusters remained consistent across 95%, 90% and 80% of the iterations.

Results of the ROB assessment and funnel plots for the thalamic results are provided in the Supplementary Materials of the published paper. Overall, ROB was low across studies due to strict eligibility criteria, with three cerebellar and five thalamic studies scoring moderate risk. Excluding these studies did not alter the overall effect. Funnel plots and Egger's test showed no significant publication bias for thalamic peaks. Cerebellar results that did not survive multiple-comparison correction were not assessed for bias.

9. DISCUSSION

9.1. Summary of findings: converging evidence for E/I related inhibitory deficit and CTC dysconnectivity in schizophrenia

The central aim of this thesis was to evaluate whether schizophrenia shows reproducible neurobiological alterations across complementary levels of circuit function. Building on the E/I imbalance hypothesis and dysconnectivity frameworks outlined in the Introduction, the thesis focused on two theoretically motivated domains of analysis. Study I evaluated local cortical excitability using TMS-EMG paradigms, while Study II evaluated large-scale CTC network function using resting-state fMRI.

Both studies used meta-analytic methods to test the reliability and robustness of these measures in the literature. This is a critical step in determining the clinical potential and validity of empirical evidence (66). The scientific contribution of this thesis, therefore, is to identify which findings are reproducible and robust enough in schizophrenia to support further mechanistic and translational work.

9.1.1. Main findings of Study I and Study II

Study I pooled data from 36 articles investigating single- and paired-pulse TMS-EMG paradigms in schizophrenia. To our knowledge, it was the first meta-analysis to confirm reduced SICI across medicated and unmedicated samples while also systematically evaluating CSP, ICF, LICI, and RMT using a TMS-specific risk-of-bias assessment.

Our results confirmed the hypothesised inhibitory deficit in schizophrenia, as measured by SICI, using a relatively large pooled sample (SCH=794, HC=817) and a moderate-to-large effect size (Cohen's $d = 0.62$). The pooled mean difference indicates that schizophrenia patients show a 13.85% (95% CI=9.19-18.51) reduction in their TMS-evoked inhibitory response linked to GABAergic receptor function (**Figure 1**). The stability and robustness of this effect across methodological heterogeneity and sensitivity analyses support reduced SICI as one of the most reproducible TMS-EMG abnormalities in schizophrenia.

This finding supports impaired motor cortical inhibitory regulation as a robust neurophysiological abnormality in schizophrenia. Importantly, the evidence did not indicate a generalised abnormality across all motor cortical excitability paradigms, as CSP, ICF, and LICI showed no clear group differences. The strongest TMS-EMG evidence, therefore, concerns SICI, a paradigm pharmacologically linked to GABA-A-mediated inhibitory responses (79).

At the same time, interpreting SICI requires caution. Although previous research suggested that SICI could be influenced by antipsychotic medication and symptom severity, our study was underpowered to confirm these results with subgroup analysis or meta-regression. Exploratory analyses indicated trend-level associations between SICI, medication status, and medication dose, suggesting that medication exposure may influence the magnitude of the SICI deficit. However, these analyses were underpowered and should be interpreted cautiously.

Study II extended the thesis to the network level by synthesising seed-based resting-state fMRI studies of CTC connectivity in schizophrenia spectrum disorders. The strongest evidence emerged for thalamic dysconnectivity. Across ALE and SDM methods, thalamic seeds showed hypoconnectivity with prefrontal, anterior cingulate, cerebellar, and association regions, alongside hyperconnectivity with somatosensory and motor cortical regions. This pattern indicates regionally specific cortical-subcortical dysconnectivity rather than a simple global increase or decrease in thalamocortical connectivity. These results support thalamic dysconnectivity as one of the more robust large-scale network findings in schizophrenia spectrum disorders (99).

Cerebellar findings were conceptually relevant to the CTC framework but less robust. Cerebellar connectivity alterations did not survive multiple-comparison correction, likely reflecting smaller samples, heterogeneous seed definitions, and the anatomical and functional complexity of the cerebellum. Illness-stage, symptom-correlation, and subregional analyses were also informative but preliminary.

Together, Studies I and II identify two biologically distinct but complementary abnormalities of impaired local cortical inhibitory physiology and altered large-scale thalamocortical network organisation. Both findings concern systems that regulate the flow, gain, and precision of neural information, which are particularly relevant to the

mechanistic interpretation of these results. Building on this, in the following sections, I will interpret these findings in relation to E/I imbalance and predictive processing while considering their translational relevance and methodological limitations.

9.1.2. E/I imbalance as a mechanistic explanation to integrate biological scales in Schizophrenia

A central interpretive question for this thesis is how a local inhibitory deficit could be relevant to large-scale network dysconnectivity. As outlined in the Introduction, excitation/inhibition (E/I) imbalance provides one of the central neurobiological frameworks for interpreting schizophrenia pathophysiology and the results of this thesis (41). The E/I framework provides a mechanistic framework for linking impaired inhibitory regulation to altered neural gain control, signal-to-noise ratio, neural synchrony and network communication (41).

Functionally, E/I balance is not only a homeostatic mechanism preventing pathological runaway excitation or network quiescence. It also shapes how neural circuits represent, amplify, filter, synchronise, and propagate information (49). Impaired inhibitory regulation may therefore reduce signal-to-noise ratio, degrade the precision of neural representations, and destabilise communication within and between networks (47). Computational and neuroimaging models further suggest that local E/I parameters influence the stability and information capacity of large-scale resting-state networks (230). This provides a biologically plausible route through which local inhibitory dysfunction could contribute to broader disturbances in network organisation.

Study I provides circuit-level evidence for this interpretation. Reduced SICI indicates impaired inhibitory control over motor cortical output, and while SICI is not a direct molecular measure of synaptic E/I balance, it is one of the most established *in vivo* perturbational probes of intracortical inhibitory physiology linked to GABA-A receptor function (78, 95, 231).

The next question is how such local inhibitory regulation could scale to network dysconnectivity (62). While the thesis did not directly test this, the E/I framework provides a plausible conceptual link between the two levels of analysis (232). One plausible explanation is through degraded signal fidelity. If local circuits generate noisier,

less temporally precise or less well-regulated output, communication between distributed regions may become less stable and efficiently coordinated (120). From this perspective, impaired inhibition could affect not only local cortical excitability but also the quality and timing of neural information flow between cortical and subcortical regions (29).

Study II provides the network-level anchor for this interpretation. The thalamic dysconnectivity identified in Study II can be interpreted as a systems-level alteration compatible with E/I-related models of abnormal information flow (184). The thalamus is involved in gating, filtering, amplifying, and coordinating sensory, motor, associative, and prefrontal information (29, 120, 233, 234). Within the broader CTC circuit, the cerebellum contributes to timing, prediction, and error-based coordination, thereby supporting the alignment of ascending sensorimotor signals with cortical contextual control (235). Although thalamic connectivity is not equivalent to local inhibition, both processes contribute to the regulation of information flow, where inhibition shapes local gain and signal fidelity, whereas thalamic and cerebellar circuits coordinate the routing, timing, and integration of information across distributed networks.

The pattern observed in Study II is therefore theoretically meaningful and could suggest disrupted alignment between higher-order cortical modulation and ascending sensorimotor communication (184). Thalamic hypoconnectivity with prefrontal and association regions may reflect impaired integration with higher-order cortical systems involved in cognitive control, contextual regulation, and top-down modulation (141, 193). In contrast, thalamic hyperconnectivity with somatosensory and motor cortices may reflect altered coupling with ascending sensory and motor systems (236). This pattern is in line with models proposing that schizophrenia involves both impaired top-down regulation and abnormal bottom-up sensory signalling (237).

The combined strength of the two thesis findings lies in their complementary positions within this multilevel framework. Reduced SICI identifies impaired local inhibitory control, which may compromise the signal-to-noise ratio and cortical output. Thalamic dysconnectivity indicates altered network coordination within circuits responsible for integrating sensory, motor, cerebellar, and prefrontal information (238). These two findings are biologically distinct, and the thesis does not demonstrate that reduced SICI causes thalamic dysconnectivity. However, these findings are in line with the E/I

hypothesis, in which schizophrenia involves disrupted regulation of neural information across local and distributed circuit levels (41). This framework suggests that local inhibitory dysfunction and large-scale dysconnectivity may represent interacting levels of the same broader pathophysiological architecture rather than isolated deficits (239).

9.1.3. Predictive processing and sensorimotor pathways as a framework for altered information flow

A computational framework that may further clarify the relationship between the circuit and network-level findings of this thesis is the Bayesian brain hypothesis (237). In this framework, perception is an active inferential process in which incoming sensory evidence is continuously compared with internal models of the world. Higher-order cortical systems are thought to generate top-down predictions, whereas lower levels of the cortical and subcortical hierarchy transmit sensory evidence and prediction errors when incoming signals diverge from expectations (240). Predictive coding is a useful concept as it provides a computational language for linking altered cortical inhibition, thalamocortical dysconnectivity, and abnormal sensorimotor information flow in schizophrenia.

Predictive coding accounts of psychosis propose that hallucinations and delusions may arise from altered weighting of prior expectations and sensory evidence (241). Neurobiologically, these computational alterations have been linked to mechanisms highly relevant to this thesis, including E/I imbalance, NMDA receptor hypofunction, altered cortical gain, and thalamocortical dysconnectivity (242). In this context, reduced SICI may reflect impaired intracortical inhibition, which could contribute to altered cortical gain control. In parallel, thalamo-sensorimotor hyperconnectivity may reflect abnormal coupling within sensorimotor thalamocortical circuits, while thalamo-prefrontal hypoconnectivity may reflect reduced integration with higher-order cortical systems involved in contextual regulation and top-down control (141, 233, 243). While these interpretations are theoretically plausible, the present meta-analyses did not directly test prediction errors, prior weighting, sensory precision, or computational model parameters.

The sensorimotor system is a particularly relevant convergence point for the two levels of evidence discussed in this thesis. First, the sensorimotor system aligns with the computational framework outlined above, as perceptual processing is the core computational mechanism described by the Bayesian brain hypothesis. Furthermore, schizophrenia is increasingly understood to involve basic sensory, perceptual, and motor abnormalities in addition to positive, negative, and cognitive symptoms (244-247). Historically, motor and sensorimotor abnormalities were often treated as secondary medication-induced extrapyramidal side effects. Contemporary evidence, however, increasingly supports the view that they are part of the schizophrenia phenotype itself and are associated with functional disability, social impairment, and disease progression (248, 249). This is particularly relevant to the present thesis as both reduced motor cortical inhibition and thalamo-sensorimotor hyperconnectivity highlight altered regulation of sensorimotor information flow.

Together, these findings may be interpreted computationally as disturbances in the regulation of sensory precision, prediction-error signalling, and sensorimotor information flow (242). However, this model should be treated as a theoretical interpretation rather than a direct conclusion of the thesis. Future studies could test this interpretation more directly by combining TMS-EMG with resting-state or task-based fMRI and computational modelling in the same individuals. Such multimodal designs could determine whether impaired intracortical inhibition and thalamocortical dysconnectivity predict individual differences in sensory precision, prediction-error signalling, prior weighting, sensorimotor abnormalities, and symptom expression. In this way, predictive processing and sensorimotor pathways help situate reduced SICI and CTC dysconnectivity within a broader, testable framework of altered information regulation across biological scales (250).

9.2. Strengths and Limitations

This thesis statistically synthesised two heterogeneous bodies of human clinical neuroscience evidence addressing complementary levels of schizophrenia pathophysiology. By integrating two lines of TMS-EMG and fMRI literature quantitatively, the thesis aimed to distinguish findings that are reproducible across studies from those that remain uncertain due to limited statistical power, methodological

variability or clinical heterogeneity. This distinction is central to the interpretation of the thesis, as schizophrenia research is characterised by substantial variability in methods, samples, illness stages, medication status, and theoretical frameworks. The value of the present synthesis, therefore, lies not only in summarising available evidence but in clarifying which local circuit and network-level abnormalities provide the most reliable measures for future mechanistic and translational research.

The main strength of Study I was the rigorous evaluation of inhibitory and excitatory TMS-EMG paradigms in schizophrenia using meta-analytic methods and a TMS-specific risk-of-bias assessment. Reduced SICI emerged as the most consistent finding, supporting impaired short-interval intracortical inhibition as the most reproducible TMS-EMG abnormality identified in the literature. In contrast, conclusions regarding other paradigms were more limited: the LICI analysis included only four studies, while CSP and ICF showed substantial or clinically unexplained heterogeneity. These findings indicate that the TMS-EMG evidence is strongest for SICI, whereas LICI, ICF, and CSP remain constrained by small study numbers, protocol variability, biological heterogeneity, and limited power for moderator analyses.

A related limitation concerns the clinical interpretation of reduced SICI. Previous research suggested that SICI may be associated with antipsychotic medication and symptom severity (251), but Study I was underpowered to confirm these associations using subgroup analysis or meta-regression. Exploratory analyses suggested trend-level associations between SICI, medication status, and medication dose, but these findings remain difficult to interpret because of the small number of unmedicated samples, heterogeneous definitions of medication status, inconsistent reporting of benzodiazepine use, and variation in antipsychotic receptor-binding profiles. These limitations indicate that although reduced SICI is a robust group-level finding, the effects of medication status, antipsychotic class, benzodiazepine use, symptom severity, and clinical specificity remain unresolved.

The main strength of Study II was the use of two spatial statistical methods to synthesise seed-based fMRI results. Across both methods, thalamic dysconnectivity emerged as the most robust CTC finding in schizophrenia spectrum disorders, with hypoconnectivity between the thalamus and prefrontal or association regions and hyperconnectivity

between the thalamus and sensorimotor cortical regions. This patterned alteration suggests regionally specific thalamocortical dysconnectivity rather than a simple global increase or decrease in CTC connectivity.

At the same time, several limitations constrain the anatomical and clinical interpretation of these findings. Study II was underpowered to run separate meta-analytic models for different thalamic and cerebellar seeds. Therefore, thalamic and cerebellar regions with distinct hierarchical and functional roles had to be pooled, reducing anatomical specificity and potentially masking nuclei-specific differences in their effects. Subthalamic and subcerebellar results were reviewed qualitatively. The study also could not directly compare chronic schizophrenia, schizoaffective disorder, first-episode psychosis, and clinical high-risk populations. In addition, despite strict eligibility criteria, the included studies varied in seed placement, atlas selection, scanning protocols, preprocessing methods, and clinical reporting. These issues were particularly relevant for the cerebellar analyses, which were based on fewer studies and smaller samples and did not survive multiple-comparison correction. Study II therefore provides stronger evidence for thalamic than for cerebellar dysconnectivity, while conclusions regarding specific subregions, illness-stage differences, and cerebellar contributions remain preliminary.

Altogether, the interpretation of the thesis has important inferential limitations. Although SICI is highly relevant to the E/I framework, it is not a direct measure of the synaptic excitation-inhibition ratio. Similarly, resting-state fMRI connectivity does not directly measure excitation, inhibition, or causal information flow between regions. The two meta-analyses also synthesised separate literatures, meaning that the thesis does not provide within-subject evidence that reduced SICI and thalamic dysconnectivity co-occur, covary, or reflect a shared mechanism. In addition, the thesis did not directly test predictive processing parameters such as sensory precision, prediction error signalling, or prior weighting. Therefore, the strongest conclusions of the thesis concern reproducible group-level abnormalities and their theoretical integration across local circuit and network levels. Conclusions regarding causality, biomarker validity, disease specificity and sensitivity, functional relevance, and clinical applicability remain limited and require direct, multimodal, and longitudinal validation, as well as computational modelling.

10. CONCLUSIONS

This thesis examined how schizophrenia pathophysiology can be operationalised across circuit and large-scale network levels using TMS-EMG and fMRI. The two included meta-analyses provide converging evidence that schizophrenia is associated with reproducible abnormalities in both motor cortical excitability and Cerebello-Thalamo-Cortical network organisation.

Study I demonstrated a significant reduction of SICI in schizophrenia, supporting altered motor cortical inhibitory physiology as one of the most robust findings in the TMS-EMG literature. Given the pharmacological relevance of SICI to GABA-A receptor function, this finding supports that E/I imbalance could be at the core of schizophrenia pathophysiology and can be captured at the cortical circuit level (56, 79). Study II, on the other hand, provided meta-analytic evidence for altered CTC connectivity in schizophrenia spectrum disorders, with the strongest evidence emerging for thalamocortical dysconnectivity. The results suggest a pattern of thalamo-sensorimotor hyperconnectivity and thalamo-prefrontal hypoconnectivity, supporting the relevance of large-scale cortical-subcortical network dysfunction in schizophrenia. While cerebellar findings were less robust, they are theoretically meaningful and warrant further research.

Together, the findings of this thesis support a multilevel interpretation of schizophrenia pathophysiology in which local inhibitory dysfunction and large-scale thalamocortical dysconnectivity represent complementary levels of altered brain function (4). Within the theoretical framework outlined in the Discussion, both outcome measures can be interpreted within the E/I framework and reflect altered circuit and network-level neural information flow (252). In addition, the overlap between motor cortical inhibitory findings and thalamo-sensorimotor connectivity alterations suggests that sensorimotor systems may represent one relevant point of convergence between local physiology and network dysfunction (253, 254).

The main contribution of this thesis is to identify reduced SICI and thalamocortical dysconnectivity as two reproducible group-level abnormalities that can serve as empirical anchors for future mechanistic, multimodal, and translational research in schizophrenia.

11. IMPLICATIONS FOR PRACTICE

The findings of this thesis do not support immediate diagnostic implementation or direct clinical use of either TMS-EMG or resting-state fMRI in schizophrenia. However, with thorough future clinical testing, SICI, a measure of motor cortical inhibitory physiology, and resting-state fMRI reflecting cerebellar, thalamic, and cortical function may eventually contribute to mechanistically informed clinical phenotyping, treatment monitoring, or target engagement.

The robustness of reduced SICI reported in this thesis, with an effect size of Cohen's $d = 0.62$ and a 13.85% reduction of inhibitory response in schizophrenia, justifies further clinical validation of this paradigm. However, its clinical value will depend on whether future studies confirm its diagnostic specificity and its ability to predict illness course, treatment response, functional outcome, or symptom progression in schizophrenia (255). Given its future validation, SICI may have the potential to serve as a measure of pharmacological treatment response or to indicate disease status (87, 256).

Resting-state fMRI measures of CTC connectivity, on the other hand, provide a complementary network-level perspective. The findings of Study II, particularly the robustness of thalamo-sensorimotor hyperconnectivity and thalamo-prefrontal hypoconnectivity, suggest that thalamocortical connectivity may have future clinical value for illness-stage characterisation, patient stratification, risk prediction, and treatment-outcome research (141, 142, 184, 257). Nevertheless, resting-state fMRI remains far from routine clinical use in schizophrenia. Its clinical applicability is limited by methodological variability, scanner and preprocessing effects, medication exposure, illness heterogeneity, and the lack of validated individual-level thresholds (68).

The potential clinical value of CTC connectivity may also depend on whether distinct dysconnectivity profiles map onto clinical heterogeneity. Because the thalamus and cerebellum are topographically organised, specific functional dysconnections could plausibly relate to different symptom dimensions, cognitive profiles, or treatment trajectories (102, 258). For example, thalamic and cerebellar abnormalities involving the sensory and motor cortices have been linked to positive symptoms in some studies, whereas altered connectivity between higher-order thalamic, cerebellar, and prefrontal regions has been associated with negative symptoms or cognitive control deficits (133,

259). In Study II, meta-analytic evidence suggested stronger associations between hyperconnectivity and symptom severity across domains, whereas hypoconnectivity was not clearly associated with symptom severity. If, therefore, future research confirms a reliable association between dysconnectivity and symptoms, it could be useful to identify common neurobiological subgroups within the heterogeneity of schizophrenia.

The CTC network may also serve as a target for therapeutic interventions, such as repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), or Transcranial Ultrasound Stimulation (TUS) (260). The cerebellum is an accessible node of the CTC circuit and has been investigated as a potential stimulation target in schizophrenia, while thalamic circuits are theoretically relevant because of their role in sensory gating, cortical communication, and signal-to-noise regulation (234). Results of clinical trials testing cerebellar stimulation have shown improvement in negative and cognitive symptoms, supporting the cerebellum as a promising therapeutic target (261-263).

The highest clinical value of the measures examined in this thesis is likely to emerge from their combination rather than from either modality alone. A multimodal approach could use TMS-EMG to quantify cortical inhibitory state, resting-state fMRI to characterise CTC connectivity profiles, sensorimotor or perceptual tasks to capture behavioural expression, and computational modelling to estimate latent parameters such as sensory precision, prediction-error signalling, and prior weighting (264, 265). Such designs could test whether patients with marked SICI reduction and pronounced thalamo-sensorimotor dysconnectivity form clinically meaningful subgroups or show differential response to pharmacological, cerebellar, motor cortical, or network-guided interventions (266). In addition to response prediction, SICI may be further investigated as a measure of individual brain state to support the timing of state-dependent or closed-loop brain stimulation (267, 268).

Taken together, reduced SICI and thalamocortical dysconnectivity are promising candidate translational markers, and future studies are required to test their reliability, specificity and sensitivity.

12. IMPLICATIONS FOR RESEARCH

12.1. Methodology and Study Design

As discussed in the previous chapter, both SICI and CTC connectivity may have future translational relevance as candidate measures for mechanistic stratification, treatment monitoring, or target engagement in schizophrenia spectrum disorders. However, before these measures can be evaluated for clinical utility, future research must establish their reliability, specificity, and predictive validity at the individual patient level. And for that, future studies need to address some of the methodological limitations that affect the results of our analysis and move beyond case-control designs to test longitudinal effects.

A first methodological implication concerns the standardisation of TMS-EMG protocols and reporting. Study I showed that reduced SICI was robust across a methodologically heterogeneous literature, however CSP, ICF, and LICI were quite sensitive to heterogeneity. TMS-EMG measures have been shown to vary with methodological factors such as stimulation intensity, interstimulus interval, pulse waveform, coil orientation, motor threshold determination, EMG monitoring, number of trials, and the calculation of conditioned and unconditioned MEP amplitudes (71). Future studies should therefore use standardised reporting checklists, such as those recommended by Chipchase and colleagues (145). In addition, we believe that it is also important to clearly define whether SICI or LICI refers to the magnitude of inhibition or to the conditioned/unconditioned MEP ratio. This is essential for improving comparability across studies and preventing misinterpretation of paired-pulse measures.

A second methodological priority is the systematic assessment of medication and clinical characteristics. Future research should therefore distinguish antipsychotic-naïve, currently unmedicated, and medicated patients, and should report antipsychotic class, dose, treatment duration, treatment resistance, clozapine exposure, and concomitant benzodiazepine use. Longitudinal within-subject studies before and after antipsychotic initiation, medication switch, clozapine initiation, or neuromodulatory intervention would be especially valuable because they could distinguish trait-like inhibitory abnormalities from treatment-sensitive physiological changes (84, 85).

Resting-state fMRI studies of thalamic and cerebellar connectivity require further anatomical and methodological specificity. Study II found robust thalamic dysconnectivity, the interpretation of cerebellar findings was more limited, potentially since available studies varied in seed definition, atlas choice, and anatomical specificity. Future research should therefore segment thalamic seeds to nuclei and distinguish between cognitive and motor cerebellar regions (110, 124, 136). Furthermore, transparency in preprocessing pipelines, consistent atlas choice and segmentation protocols will further improve the replicability and translatability of future research (269, 270).

Longitudinal study designs will be essential for determining the biological and clinical utility of SICI and CTC connectivity. Cross-sectional studies cannot determine whether reduced SICI or thalamic dysconnectivity should be interpreted as trait markers, state markers, markers of illness progression, or treatment-sensitive markers. Future studies should therefore examine these measures across risk, early illness, chronic illness, and treatment-resistant stages, ideally distinguishing clinical high-risk converters from non-converters and following patients before and after treatment initiation (186).

Altogether, the next central step for future research could be to measure local cortical inhibitory physiology and CTC connectivity within the same individuals. Such studies could determine whether reduced SICI is associated with thalamo-sensorimotor hyperconnectivity, thalamo-prefrontal hypoconnectivity, cerebellar connectivity alterations, sensorimotor behaviour, cognitive performance, or clinical outcome. This would clarify whether combined neurophysiological and connectivity profiles explain clinically meaningful heterogeneity in schizophrenia.

12.2. New Areas

Building on the theoretical frameworks discussed in this thesis, future empirical work should empirically test the hypothesised mechanistic link between microcircuit E/I imbalance, macroscopic CTC dysconnectivity and altered perceptual inference. In the discussion, reduced SICI and altered CTC connectivity were interpreted within a multilevel framework in which local inhibitory dysfunction may interact with large-scale abnormalities in thalamocortical information flow. However, this thesis did not directly

test whether reduced SICI and thalamic dysconnectivity are related within individuals. Future multimodal studies combining TMS-EMG and fMRI should therefore test whether more pronounced thalamo-sensorimotor hyperconnectivity directly correlates with larger SICI deficits. Such designs would move the field from theoretical integration toward direct testing of the proposed multilevel model.

A second direction is to test the computational interpretation proposed in the Discussion. Future studies could combine psychophysics, computational modelling, TMS-EMG, EEG/MEG, and functional neuroimaging to examine whether local inhibitory abnormalities and thalamocortical dysconnectivity are associated with measurable parameters such as sensory precision, prediction-error sensitivity, prior weighting, internal sensory noise, or signal-to-noise ratio (242, 271). This would extend predictive-processing accounts of psychosis by testing whether altered perceptual inference is linked to specific neurophysiological and network-level abnormalities in the same individuals. Preliminary steps toward testing this hypothesis were undertaken during the third year of my PhD research at Yale University, where I investigated how altered perceptual processing relates to computational estimations of sensory noise and E/I imbalance using EEG and psychophysics. As these data are still under analysis and are not included in the present thesis, they should be viewed as future directions.

A third related direction is to further investigate the sensorimotor system as a network in which these multilevel hypotheses can be tested (248). The results of both studies included in this thesis highlight the relevance of reduced inhibition in the sensorimotor network and thalamo-sensorimotor hyperconnectivity. Future research should therefore test whether TMS-EMG measures reflect local motor cortical E/I-related dysfunction or index a broader shift in cortical inhibitory deficit (272). This could be tested by combining paired-pulse TMS-EMG with TMS-EEG, resting-state fMRI, and behavioural measures of sensorimotor function (273). Such studies could clarify if sensorimotor circuits represent a clinically and experimentally relevant system of altered inhibitory physiology and functional impairment in schizophrenia (274).

13. IMPLICATIONS FOR POLICY MAKERS

Schizophrenia places a major epidemiological, clinical, and economic burden on patients, families, and health-care systems, highlighting the need for more effective approaches to early identification, treatment stratification, and therapeutic innovation (275). However, this thesis also demonstrates why translating neurobiological research into clinical practice remains difficult (11). Although this thesis provides meta-analytic evidence for robust reduced motor cortical inhibition and large-scale thalamocortical dysconnectivity in schizophrenia spectrum disorders, these findings do not provide sufficient evidence for immediate diagnostic implementation, clinical risk prediction, or treatment monitoring (276, 277). One potential direction for policymakers would be, therefore, to support standardised, longitudinal, and multimodal clinical neuroscience research(278) .

A key implication for policy makers and funding bodies is the need to encourage open science and standardisation protocols for clinical neuroscience research, including fMRI and TMS-EMG measures (69, 143). As discussed previously, the clinical translation largely depends on methodological harmonisation across studies and on resolving heterogeneity and statistically underpowered study designs (66). Therefore, investment in prioritising standardised protocols and reporting and large-scale multi-centre collaborations could further advance the field.

In addition, the clinical translatability of findings like the TMS-EMG paradigms or connectivity needs future research, including longitudinal cohorts across clinical high-risk, first-episode, chronic, and treatment-resistant stages; studies that combine neurophysiology, neuroimaging, cognition, symptoms, functioning, and treatment response; and trials that use mechanistic measures as target-engagement markers for pharmacological or neuromodulatory interventions. The main policy implication of this thesis is therefore to support future validation studies of potential biomarkers of schizophrenia.

14. FUTURE PERSPECTIVES

A central challenge in understanding schizophrenia pathophysiology is that the clinical heterogeneity of the disorder reflects disturbances across multiple biological scales, while no single biomarker or theoretical framework has provided a complete account of it (3, 4). The findings of this thesis contribute to a multilevel perspective by identifying two reproducible abnormalities in the literature: reduced cortical inhibition, measured with SICI, and altered Cerebello-Thalamo-Cortical connectivity, with the strongest network-level evidence emerging for thalamocortical dysconnectivity. As discussed in the preceding chapters, the value of these findings lies in providing robust empirical anchors for future research on how local inhibitory physiology and large-scale network organisation may jointly contribute to schizophrenia pathophysiology, grounded in the E/I imbalance hypothesis (252).

A central future direction is therefore to move from separate biological markers toward integrated, within-subject models (266). Future studies will need to test how E/I-imbalance, thalamocortical dysconnectivity, electrophysiological activity, computational parameters, and clinical outcomes are related within individuals (279). Such work would help determine whether SICI and CTC connectivity reflect distinct manifestations of a shared pathophysiology or mark distinct patient subgroups. Instead of a single biomarker of schizophrenia, a more plausible approach is to develop validated multilevel profiles that combine multimodal neuroscience markers with computational modelling, clinical symptoms, and cognitive performance. In this framework, measures such as SICI and CTC connectivity could be components of a broader mechanistic profile (278).

This thesis also defines the direction of my own future work. The ongoing EEG and psychophysics studies initiated during my Fulbright research period at the Powers Laboratory (Yale University) extend the same overarching question of how altered sensory processing, sensory noise, and E/I-related physiology may contribute to psychosis-relevant perceptual inference. These data are not part of the present thesis; however, they continue the research theme discussed here.

The future challenge is not simply to identify more abnormalities, but to determine how reproducible biological markers can be combined at the patient level to better understand clinical heterogeneity and support treatment development.

15. REFERENCES

1. GBD 2023 Mental Disorder Collaborators. Updated trends in the global prevalence and burden of mental disorders, 1990-2023: a systematic analysis for the Global Burden of Disease Study 2023. *Lancet*. 2026;407(10543):2040–64.
2. Hjorthoj C, Sturup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *Lancet Psychiatry*. 2017;4(4):295–301.
3. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia—An Overview. *JAMA Psychiatry*. 2020;77(2):201–10.
4. Howes OD, Bukala BR, Beck K. Schizophrenia: from neurochemistry to circuits, symptoms and treatments. *Nat Rev Neurol*. 2024;20(1):22–35.
5. Association AP. Diagnostic and statistical manual of mental disorders (5th ed., text rev.)2022.
6. Kaar SJ, Natesan S, McCutcheon R, Howes OD. Antipsychotics: Mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology. *Neuropharmacology*. 2020;172:107704.
7. Correll CU, Schooler NR. Negative Symptoms in Schizophrenia: A Review and Clinical Guide for Recognition, Assessment, and Treatment. *Neuropsychiatr Dis Treat*. 2020;16:519–34.
8. Mouchlianitis E, McCutcheon R, Howes OD. Brain-imaging studies of treatment-resistant schizophrenia: a systematic review. *Lancet Psychiatry*. 2016;3(5):451–63.
9. Howes OD, Whitehurst T, Shatalina E, Townsend L, Onwordi EC, Mak TLA, et al. The clinical significance of duration of untreated psychosis: an umbrella review and random-effects meta-analysis. *World Psychiatry*. 2021;20(1):75–95.
10. Fernandes BS, Williams LM, Steiner J, Leboyer M, Carvalho AF, Berk M. The new field of 'precision psychiatry'. *BMC Med*. 2017;15(1):80.
11. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Mol Psychiatry*. 2012;17(12):1174–9.
12. Lisman JE, Coyle JT, Green RW, Javitt DC, Benes FM, Heckers S, et al. Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends Neurosci*. 2008;31(5):234–42.

13. Stephan KE, Baldeweg T, Friston KJ. Synaptic plasticity and dysconnection in schizophrenia. *Biol Psychiatry*. 2006;59(10):929–39.
14. Murray RM, Bhavsar V, Tripoli G, Howes O. 30 Years on: How the Neurodevelopmental Hypothesis of Schizophrenia Morphed Into the Developmental Risk Factor Model of Psychosis. *Schizophr Bull*. 2017;43(6):1190–6.
15. Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rossler A, Schultze-Lutter F, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry*. 2013;70(1):107–20.
16. Pinto JG, Jones DG, Murphy KM. Comparing development of synaptic proteins in rat visual, somatosensory, and frontal cortex. *Front Neural Circuits*. 2013;7:97.
17. Petanjek Z, Judas M, Simic G, Rasin MR, Uylings HB, Rakic P & Kostovic, I. Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *PNAS*. 2011;108(32):13281–6.
18. Radua J, Ramella-Cravaro V, Ioannidis JPA, Reichenberg A, Phiphopthatsanee N, Amir T, et al. What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry*. 2018;17(1):49–66.
19. Howes OD, McCutcheon R, Owen MJ, Murray RM. The Role of Genes, Stress, and Dopamine in the Development of Schizophrenia. *Biol Psychiatry*. 2017;81(1):9–20.
20. Ripke S, Neale BM, Corvin A, Walters JTR, Farh K-H, Holmans PA, et al. Biological Insights From 108 Schizophrenia-Associated Genetic Loci. *Nature*. 2014;511(7510):421–7.
21. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, et al. Schizophrenia risk from complex variation of complement component 4. *Nature*. 2016;530(7589):177–83.
22. Sellgren CM, Gracias J, Watmuff B, Biag JD, Thanos JM, Whittredge PB, et al. Increased synapse elimination by microglia in schizophrenia patient-derived models of synaptic pruning. *Nat Neurosci*. 2019;22(3):374–85.
23. Osimo EF, Beck K, Reis Marques T, Howes OD. Synaptic loss in schizophrenia: a meta-analysis and systematic review of synaptic protein and mRNA measures. *Mol Psychiatry*. 2019;24(4):549–61.
24. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III--the final common pathway. *Schizophr Bull*. 2009;35(3):549–62.

25. Seeman P, Lee T. Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. *Sci*. 1975;188(4194):1217–9.
26. Davis KL, Kahn RS, Ko G, Davidson M. Dopamine in schizophrenia: a review and reconceptualization. *Am J Psychiatry*. 1991;148(11):1474–86.
27. Grace AA. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. *Nat Rev Neurosci*. 2016;17(8):524–32.
28. McCutcheon RA, Krystal JH, Howes OD. Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. *World Psychiatry*. 2020;19(1):15–33.
29. Stephan KE, Friston KJ, Frith CD. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. *Schizophr Bull*. 2009;35(3):509–27.
30. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger, GR., Bowers, MB, Jr, & Charney, DS. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry*. 1994;51(3):199–214.
31. Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry*. 1991;148(10):1301–8.
32. Stone J, Kotoula V, Dietrich C, De Simoni S, Krystal JH, Mehta MA. Perceptual distortions and delusional thinking following ketamine administration are related to increased pharmacological MRI signal changes in the parietal lobe. *Journal of Psychopharmacology*. 2015;29(9):1025–8.
33. Moghaddam B, Javitt D. From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. *Neuropsychopharmacology*. 2012;37(1):4–15.
34. Beck K, Hindley G, Borgan F, Ginestet C, McCutcheon R, Brugger S, et al. Association of Ketamine With Psychiatric Symptoms and Implications for Its Therapeutic Use and for Understanding Schizophrenia: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2020;3(5):e204693.
35. Catts VS, Lai YL, Weickert CS, Weickert TW, Catts SV. A quantitative review of the postmortem evidence for decreased cortical N-methyl-D-aspartate receptor expression levels in schizophrenia: How can we link molecular abnormalities to mismatch negativity deficits? *Biol Psychol*. 2016;116:57–67.

36. Merritt K, Egerton A, Kempton MJ, Taylor MJ, McGuire PK. Nature of Glutamate Alterations in Schizophrenia: A Meta-analysis of Proton Magnetic Resonance Spectroscopy Studies. *JAMA Psychiatry*. 2016;73(7):665–74.
37. Nakahara T, Tsugawa S, Noda Y, Ueno F, Honda S, Kinjo M, et al. Glutamatergic and GABAergic metabolite levels in schizophrenia-spectrum disorders: a meta-analysis of (1)H-magnetic resonance spectroscopy studies. *Mol Psychiatry*. 2022;27(1):744–57.
38. Onwordi EC, Halff EF, Whitehurst T, Mansur A, Cotel MC, Wells L, et al. Synaptic density marker SV2A is reduced in schizophrenia patients and unaffected by antipsychotics in rats. *Nat Commun*. 2020;11(1):246.
39. Radhakrishnan R, Skosnik PD, Ranganathan M, Naganawa M, Toyonaga T, Finnema S, et al. In vivo evidence of lower synaptic vesicle density in schizophrenia. *Mol Psychiatry*. 2021;26(12):7690–8.
40. Kruse AO, Bustillo JR. Glutamatergic dysfunction in Schizophrenia. *Transl Psychiatry*. 2022;12(1):500.
41. Sohal VS, Rubenstein JLR. Excitation-inhibition balance as a framework for investigating mechanisms in neuropsychiatric disorders. *Molecular Psychiatry*. 2019;24:1248–57.
42. Tremblay R, Lee S, Rudy B. GABAergic Interneurons in the Neocortex: From Cellular Properties to Circuits. *Neuron*. 2016;91(2):260–92.
43. Rubin R, Abbott LF, Sompolinsky H. Balanced excitation and inhibition are required for high-capacity, noise-robust neuronal selectivity. *Proc Natl Acad Sci U S A*. 2017;114(44):E9366–E75.
44. Turrigiano G. Too many cooks? Intrinsic and synaptic homeostatic mechanisms in cortical circuit refinement. *Annu Rev Neurosci*. 2011;34:89–103.
45. Dehghani N, Peyrache A, Telenczuk B, Le Van Quyen M, Halgren E, Cash SS, et al. Dynamic Balance of Excitation and Inhibition in Human and Monkey Neocortex. *Sci Rep*. 2016;6:23176.
46. Chung DW, Fish KN, Lewis DA. Pathological Basis for Deficient Excitatory Drive to Cortical Parvalbumin Interneurons in Schizophrenia. *Am J Psychiatry*. 2016;173(11):1131–9.
47. Krystal JH, Anticevic A, Yang GJ, Dragoi G, Driesen NR, Wang XJ, et al. Impaired Tuning of Neural Ensembles and the Pathophysiology of Schizophrenia: A

Translational and Computational Neuroscience Perspective. *Biol Psychiatry*. 2017;81(10):874–85.

48. Sohal VS, Zhang F, Yizhar O, Deisseroth K. Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature*. 2009;459(7247):698–702.

49. Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nature Reviews Neuroscience*. 2010;11(2):100–13.

50. Howes OD, Shatalina E. Integrating the Neurodevelopmental and Dopamine Hypotheses of Schizophrenia and the Role of Cortical Excitation-Inhibition Balance. *Biol Psychiatry*. 2022;92(6):501–13.

51. Friston KJ. The disconnection hypothesis. *Schizophr Res*. 1998;30(2):115–25.

52. Friston K, Brown HR, Siemerikus J, Stephan KE. The dysconnection hypothesis (2016). *Schizophrenia Research*. 2016;176(2-3):83–94.

53. Uhlhaas PJ. Dysconnectivity, large-scale networks and neuronal dynamics in schizophrenia. *Curr Opin Neurobiol*. 2013;23(2):283–90.

54. Tao HW, Li Y-t, Zhang LI. Formation of excitation-inhibition balance: inhibition listens and changes its tune. *Trends in Neurosciences*. 2014;37(10):528–30.

55. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Archives of General Psychiatry*. 2000;57(1):65–73.

56. Jardri R, Hugdahl K, Hughes M, Brunelin J, Waters F, Alderson-Day B, et al. Are Hallucinations Due to an Imbalance Between Excitatory and Inhibitory Influences on the Brain? *Schizophrenia Bulletin*. 2016;42(5):1124–34.

57. Gao R, Peterson EJ, Voytek B. Inferring synaptic excitation/inhibition balance from field potentials. *NeuroImage*. 2017;158:70–8.

58. Reis J, Swayne OB, Vandermeeren Y, Camus M, Dimyan MA, Harris-Love M, et al. Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. *J Physiol*. 2008;586(2):325–51.

59. Radhu N, de Jesus DR, Ravindran LN, Zanjani A, Fitzgerald PB, Daskalakis ZJ. A meta-analysis of cortical inhibition and excitability using transcranial magnetic stimulation in psychiatric disorders. *Clin Neurophysiol*. 2013;124(7):1309–20.

60. van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur Neuropsychopharmacol*. 2010;20(8):519–34.

61. Lu H, Jaime S, Yang Y. Origins of the Resting-State Functional MRI Signal: Potential Limitations of the "Neurocentric" Model. *Front Neurosci.* 2019;13:1136.
62. Stagg CJ, Bachtiar V, Amadi U, Gudberg CA, Ilie AS, Sampaio-Baptista C, et al. Local GABA concentration is related to network-level resting functional connectivity. *eLife.* 2014;3:e01465.
63. Chen X, Fan X, Hu Y, Zuo C, Whitfield-Gabrieli S, Holt D, et al. Regional GABA Concentrations Modulate Inter-network Resting-state Functional Connectivity. *Cereb Cortex.* 2019;29(4):1607–18.
64. Rajkumar R, Regio Brambilla C, Veselinovic T, Bierbrier J, Wyss C, Ramkiran S, et al. Excitatory-inhibitory balance within EEG microstates and resting-state fMRI networks: assessed via simultaneous trimodal PET-MR-EEG imaging. *Transl Psychiatry.* 2021;11(1):60.
65. Pettersson-Yeo W, Allen P, Benetti S, McGuire P, Mechelli A. Dysconnectivity in schizophrenia: where are we now? *Neurosci Biobehav Rev.* 2011;35(5):1110–24.
66. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci.* 2013;14(5):365–76.
67. Bunse T, Wobrock T, Strube W, Padberg F, Palm U, Falkai P, et al. Motor cortical excitability assessed by transcranial magnetic stimulation in psychiatric disorders: a systematic review. *Brain stimulation.* 2014;7(2):158–69.
68. Cole D, Smith S, Beckmann C. Advances and pitfalls in the analysis and interpretation of resting-state FMRI data. *Front Syst Neurosci.* 2010;4.
69. Poldrack RA, Baker CI, Durnez J, Gorgolewsky KJ, Matthews PM, Munafo MR, et al. Scanning the horizon: towards transparent and reproducible neuroimaging research - PubMed. *Nature Reviews Neuroscience.* 2017;18(2):115–26.
70. Wager TD, Lindquist M, Kaplan L. Meta-analysis of functional neuroimaging data: current and future directions. *Soc Cogn Affect Neurosci.* 2007;2(2):150–8.
71. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol.* 2015;126(6):1071–107.

72. Daskalakis ZJ, Christensen BK, Chen R, Fitzgerald PB, Zipursky RB, Kapur S. Evidence for impaired cortical inhibition in schizophrenia using transcranial magnetic stimulation. *Archives of general psychiatry*. 2002;59(4):347–54.
73. Klonjaj W, Katz R, Lackmy-Vallée A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Annals of Physical and Rehabilitation Medicine*. 2015;58(4):208–13.
74. Groppa S, Oliviero A, Eisen A, Quartarone A, Cohen LG, Mall V, et al. A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. *Clin Neurophysiol*. 2012;123(5):858–82.
75. Hallett M. Transcranial magnetic stimulation: a primer. *Neuron*. 2007;55(2):187–99.
76. Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, et al. Magnetic transcranial stimulation at intensities below active motor threshold activates intracortical inhibitory circuits. *Exp Brain Res*. 1998;119(2):265–8.
77. McClintock SM, Freitas C, Oberman L, Lisanby SH, Pascual-Leone A. Transcranial magnetic stimulation: a neuroscientific probe of cortical function in schizophrenia. *Biological Psychiatry*. 2011;70(1):19–27.
78. Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, et al. Corticocortical inhibition in human motor cortex. *J Physiol*. 1993;471:501–19.
79. Ziemann U. Pharmacology of TMS measures. In: Wassermann EM, Peterchev AV, Ziemann U, Lisanby SH, Siebner HR, Walsh V, editors. *The Oxford Handbook of Transcranial Stimulation*. 2. ed: Oxford University Press; 2021.
80. Ziemann U, Lönnecker S, Steinhoff BJ, Paulus W. Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. *Annals of Neurology*. 1996;40(3):367–78.
81. Fuhr P, Agostino R, Hallett M. Spinal motor neuron excitability during the silent period after cortical stimulation. *Electroencephalography and Clinical Neurophysiology*. 1991;81(4):257–62.
82. Chen R, Lozano AM, Ashby P. Mechanism of the silent period following transcranial magnetic stimulation. Evidence from epidural recordings. *Exp Brain Res*. 1999;128(4):539–42.

83. Eichhammer P, Wiegand R, Kharraz A, Langguth B, Binder H, Hajak G. Cortical excitability in neuroleptic-naïve first-episode schizophrenic patients. *Schizophrenia Research*. 2004;67(2-3):253–9.
84. Liu S-K, Fitzgerald PB, Daigle M, Chen R, Daskalakis ZJ. The relationship between cortical inhibition, antipsychotic treatment, and the symptoms of schizophrenia. *Biological Psychiatry*. 2009;65(6):503–9.
85. Frank E, Landgrebe M, Poepl TB, Schecklmann M, Kreuzer PM, Prasser J, et al. Antipsychotic treatment with quetiapine increases the cortical silent period. *Schizophrenia Research*. 2014;156(1):128–32.
86. Miyazawa A, Kanahara N, Nakata Y, Kodama S, Kimura H, Kimura A, et al. Clozapine Prolongs Cortical Silent Period in Patients with Treatment-Resistant Schizophrenia. *Psychopharmacol Bull*. 2021;51(2):20–30.
87. Daskalakis ZJ, Christensen BK, Fitzgerald PB, Moller B, Fountain SI, Chen R. Increased cortical inhibition in persons with schizophrenia treated with clozapine. *J Psychopharmacol*. 2008;22(2):203–9.
88. Kaster TS, de Jesus D, Radhu N, Farzan F, Blumberger DM, Rajji TK, Fitzgerald PB, Daskalakis ZJ. Clozapine potentiation of GABA mediated cortical inhibition in treatment resistant schizophrenia. *Schizophrenia Research*. 2015;165(2-3):157–62.
89. Valls-Solé J, Pascual-Leone A, Wassermann EM, Hallett M. Human motor evoked responses to paired transcranial magnetic stimuli. *Electroencephalography and Clinical Neurophysiology*. 1992;85(6):355–64.
90. McDonnell MN, Orekhov Y, Ziemann U. The role of GABA(B) receptors in intracortical inhibition in the human motor cortex. *Exp Brain Res*. 2006;173(1):86–93.
91. Fitzgerald PB, Brown TL, Marston NAU, Oxley TJ, De Castella A, Daskalakis ZJ, Kulkarni, J. A transcranial magnetic stimulation study of abnormal cortical inhibition in schizophrenia. *Psychiatry Research*. 2003;118(3):197–207.
92. Ziemann U, Chen R, Cohen LG, Hallett M. Dextromethorphan decreases the excitability of the human motor cortex. *Neurology*. 1998;51(5):1320–4.
93. Di Lazzaro V, Pilato F, Oliviero A, Dileone M, Saturno E, Mazzone P, Insola A, Profice P, Ranieri F, Capone F, Tonali PA, Rothwell JC. Origin of facilitation of motor-evoked potentials after paired magnetic stimulation: direct recording of epidural activity in conscious humans. *Journal of Neurophysiology*. 2006;96(4):1765–71.

94. Pascual-Leone A, Manocha DS, Birnbaum R, Goff DC. Motor cortical excitability in schizophrenia. *Biological Psychiatry*. 2002;52(1):24–31.
95. Rogasch NC, Daskalakis ZJ, Fitzgerald PB. Cortical Inhibition, Excitation, and Connectivity in Schizophrenia: A Review of Insights From Transcranial Magnetic Stimulation. *Schizophrenia Bulletin*. 2014;40(3):685–96.
96. Mehta UM, Thanki MV, Padmanabhan J, Pascual-Leone A, Keshavan MS. Motor cortical plasticity in schizophrenia: A meta-analysis of Transcranial Magnetic Stimulation - Electromyography studies. *Schizophrenia Research*. 2019;207:37–47.
97. Ji JL, Diehl C, Schleifer C, Yang G, Creatura G, Repovs G, Murray J, Winkler A, Anticevic A. Schizophrenia exhibits BI-directional brain-wide alterations in cortico-striato-cerebellar circuits. *Biological Psychiatry*. 2017;81(10):S388–S9.
98. Fornito A, Zalesky A, Pantelis C, Bullmore ET. Schizophrenia, neuroimaging and connectomics. *NeuroImage*. 2012;62(4):2296–314.
99. Woodward ND, Karbasforoushan H, Heckers S. Thalamocortical dysconnectivity in schizophrenia. *The American journal of psychiatry*. 2012;169(10):1092–9.
100. Andreasen NC, Paradiso S, O'Leary DS. 'Cognitive dysmetria' as an integrative theory of schizophrenia: A dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophrenia Bulletin*. 1998;24(2):203–18.
101. Rikhye RV, Wimmer RD, Halassa MM. Toward an Integrative Theory of Thalamic Function. *Annual Review of Neuroscience*. 2018;41:163–83.
102. Anticevic A, Halassa MM. The thalamus in psychosis spectrum disorder. *Frontiers in Neuroscience*. 2023;17
103. Pergola G, Selvaggi P, Trizio S, Bertolino A, Blasi G. The role of the thalamus in schizophrenia from a neuroimaging perspective. *Neuroscience and Biobehavioral Reviews*. 2015;54:57–75.
104. Pinault D. The thalamic reticular nucleus: structure, function and concept. *Brain Res Brain Res Rev*. 2004;46(1):1–31.
105. Halassa MM, Acsady L. Thalamic Inhibition: Diverse Sources, Diverse Scales. *Trends Neurosci*. 2016;39(10):680–93.
106. Crabtree JW. Functional Diversity of Thalamic Reticular Subnetworks. *Front Syst Neurosci*. 2018;12:41.

107. Halassa MM, Sherman SM. Thalamocortical Circuit Motifs: A General Framework. *Neuron*. 2019;103(5):762–70.
108. Sherman SM. Functioning of Circuits Connecting Thalamus and Cortex. *Compr Physiol*. 2017;7(2):713–39.
109. Guillery RW, Sherman SM. Thalamic relay functions and their role in corticocortical communication: generalizations from the visual system. *Neuron*. 2002;33(2):163–75.
110. Giraldo-Chica M, Woodward ND. Review of thalamocortical resting-state fMRI studies in schizophrenia. *Schizophrenia Research*. 2017;180:58–63.
111. Harris JA, Mihalas S, Hirokawa KE, Whitesell JD, Choi H, Bernard A, et al. Hierarchical organization of cortical and thalamic connectivity. *Nature*. 2019;575(7781):195–202.
112. Halassa MM, Kastner S. Thalamic functions in distributed cognitive control. *Nat Neurosci*. 2017;20(12):1669–79.
113. Cronenwett WJ, Csernansky J. Thalamic pathology in schizophrenia. *Curr Top Behav Neurosci*. 2010;4:509–28.
114. Ramsay IS. An Activation Likelihood Estimate Meta-analysis of Thalamocortical Dysconnectivity in Psychosis - PubMed. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. 2019;4(10):859–69.
115. Welsh RC, Chen AC, Taylor SF. Low-frequency BOLD fluctuations demonstrate altered thalamocortical connectivity in schizophrenia. *Schizophrenia Bulletin*. 2010;36(4):713–22.
116. Wu G, Palaniyappan L, Zhang M, Yang J, Xi C, Liu Z, Xue Z, Ouyang X, Tao H, Zhang J, Luo Q, Pu W. Imbalance Between Prefronto-Thalamic and Sensorimotor-Thalamic Circuitries Associated with Working Memory Deficit in Schizophrenia. *Schizophrenia Bulletin*. 2022;48(1):251–61.
117. Höflich A, Hahn A, Küblböck M, Kranz GS, Vanicek T, Windischberger C, Saria A, Kasper S, Winkler D, Lanzenberger R. Ketamine-induced modulation of the thalamocortical network in healthy volunteers as a model for schizophrenia. *International Journal of Neuropsychopharmacology*. 2015;18(9):1–11.

118. Anticevic A, Cole MW, Murray JD, Corlett PR, Wang XJ, Krystal JH. The role of default network deactivation in cognition and disease. *Trends Cogn Sci*. 2012;16(12):584–92.
119. Murray JD, Anticevic A. Toward understanding thalamocortical dysfunction in schizophrenia through computational models of neural circuit dynamics. *Schizophrenia Research*. 2017;180:70–7.
120. Mukherjee A, Lam NH, Wimmer RD, Halassa MM. Thalamic circuits for independent control of prefrontal signal and noise. *Nature*. 2021;600(7887):100–4.
121. Koziol LF, Budding D, Andreasen N, D'Arrigo S, Bulgheroni S, Imamizu H, Ito M, Manto M, Marvel C, Parker K, Pezzulo G, Ramnani N, Riva D, Schmahmann J, Vandervert L, Yamazaki T. Consensus paper: the cerebellum's role in movement and cognition. *Cerebellum*. 2014;13(1):151–77.
122. Andreasen NC, Pierson R. The Role of the Cerebellum in Schizophrenia. *Biological Psychiatry*. 2008;64(2):81–8.
123. Buckner RL, Krienen FM, Castellanos A, Diaz JC, Yeo BT. The organization of the human cerebellum estimated by intrinsic functional connectivity. *J Neurophysiol*. 2011;106(5):2322–45.
124. Schmahmann JD. The cerebellum and cognition. *Neuroscience letters*. 2019;688:62–75.
125. Schmahmann JD. Dysmetria of thought: Clinical consequences of cerebellar dysfunction on cognition and affect. *Trends in Cognitive Sciences*. 1998;2(9):362–71.
126. Guell X, Gabrieli JDE, Schmahmann JD. Triple representation of language, working memory, social and emotion processing in the cerebellum: convergent evidence from task and seed-based resting-state fMRI analyses in a single large cohort. *Neuroimage*. 2018;172:437–49.
127. Schmahmann JD. An emerging concept. The cerebellar contribution to higher function. *Archives of Neurology*. 1991;48(11):1178–87.
128. Schmahmann JD, Guell X, Stoodley CJ, Halko MA. The Theory and Neuroscience of Cerebellar Cognition. *Annual Review of Neuroscience*. 2019;42:337–64.

129. Volz H, Gaser C, Sauer H. Supporting evidence for the model of cognitive dysmetria in schizophrenia--a structural magnetic resonance imaging study using deformation-based morphometry. *Schizophr Res.* 2000;46(1):45–56.
130. Bullock WM, Cardon K, Bustillo J, Roberts RC, Perrone-Bizzozero NI. Altered expression of genes involved in GABAergic transmission and neuromodulation of granule cell activity in the cerebellum of schizophrenia patients. *Am J Psychiatry.* 2008;165(12):1594–603.
131. Yeganeh-Doost P, Gruber O, Falkai P, Schmitt A. The role of the cerebellum in schizophrenia: from cognition to molecular pathways. *Clinics.* 2011;66:71–7.
132. Bernard JA, Goen JRM, Maldonado T. A case for motor network contributions to schizophrenia symptoms: Evidence from resting-state connectivity. *Human brain mapping.* 2017;38(9):4535–45.
133. Brady RO, Jr., Gonsalvez I, Lee I, Öngür D, Seidman LJ, Schmahmann JD, Eack SM, Keshavan MS, Pascual-Leone A, Halko MA. Cerebellar-Prefrontal Network Connectivity and Negative Symptoms in Schizophrenia. *The American journal of psychiatry.* 2019;176(7):512–20.
134. Cao H, Cannon TD. Cerebellar dysfunction and schizophrenia: From “cognitive dysmetria” to a potential therapeutic target. *American Journal of Psychiatry.* 2019;176(7):498–500.
135. Goozee R, Handley R, Kempton MJ, Dazzan P. A systematic review and meta-analysis of the effects of antipsychotic medications on regional cerebral blood flow (rCBF) in schizophrenia: association with response to treatment. *Neurosci Biobehav Rev.* 2014;43:118–36.
136. Gong J, Luo C, Li X, Jiang S, Khundrakpam BS, Duan M, Chen X, Yao D. Evaluation of functional connectivity in subdivisions of the thalamus in schizophrenia. *British Journal of Psychiatry.* 2019;214(5):288–96.
137. Hua J, Blair NIS, Paez A, Choe A, Barber AD, Brandt A, Lim IAL, Xu F, Kamath V, Pekar JJ, van Zijl PCM, Ross CA, Margolis RL. Altered functional connectivity between sub-regions in the thalamus and cortex in schizophrenia patients measured by resting state BOLD fMRI at 7T. *Schizophrenia Research.* 2019;206:370–7.

138. Kim W-S, Shen J, Tsogt U, Odkhuu S, Chung Y-C. Altered thalamic subregion functional networks in patients with treatment-resistant schizophrenia. *World J Psychiatry*. 2022;12(5):693–707.
139. Müller VI, Cieslik EC, Laird AR, Fox PT, Radua J, Mataix-Cols D, Tench CR, Yarkoni T, Nichols TE, Turkeltaub PE, Wager TD, Eickhoff SB. Ten simple rules for neuroimaging meta-analysis. *Neuroscience & Biobehavioral Reviews*. 2018;84:151–61.
140. Bernard JA, Mittal VA. Dysfunctional Activation of the Cerebellum in Schizophrenia: A Functional Neuroimaging Meta-Analysis. *Clinical Psychological Science*. 2014;3(4).
141. Woodward ND, Heckers S. Mapping Thalamocortical Functional Connectivity in Chronic and Early Stages of Psychotic Disorders. *Biological Psychiatry*. 2016;79(12):1016–25.
142. Anticevic A, Haut K, Murray JD, Repovs G, Yang GJ, Diehl C, McEwen SC, Bearden CE, Addington J, Goodyear B, Cadenhead KS, Mirzakhani H, Cornblatt BA, Olvet D, Mathalon DH, McGlashan TH, Perkins DO, Belger A, Seidman LJ, Tsuang MT, van Erp TG, Walker EF, Hamann S, Woods SW, Qiu M, Cannon TD. Association of Thalamic Dysconnectivity and Conversion to Psychosis in Youth and Young Adults at Elevated Clinical Risk. *JAMA Psychiatry*. 2015;72(9):882–91.
143. Nichols TE, Das S, Eickhoff SB, Evans AC, Glatard T, Hanke M, Kriegeskorte N, Milham MP, Poldrack RA, Poline JB, Proal E, Thirion B, Van Essen DC, White T, Yeo BT. Best practices in data analysis and sharing in neuroimaging using MRI. *Nat Neurosci*. 2017;20(3):299–303.
144. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.
145. Chipchase L, Schabrun S, Cohen L, Hodges P, Ridding M, Rothwell J, Taylor J, Ziemann U. A checklist for assessing the methodological quality of studies using transcranial magnetic stimulation to study the motor system: an international consensus study. *Clin Neurophysiol*. 2012;123(9):1698–704.
146. Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA. Meta-Analysis of the Functional Neuroanatomy of Single-Word Reading: Method and Validation. *NeuroImage*. 2002;16(3, Part A):765–80.

147. Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Human Brain Mapping*. 2009;30(9):2907–26.
148. Eickhoff SB, Bzdok D, Laird AR, Kurth F, Fox PT. Activation Likelihood Estimation meta-analysis revisited. *Neuroimage*. 2012;59(3):2349–61.
149. Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *Br J Psychiatry*. 2009;195(5).
150. Smith SM, Nichols TE. Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage*. 2009;44(1):83–98.
151. Albajes-Eizagirre A, Solanes A, Vieta E, Radua J. Voxel-based meta-analysis via permutation of subject images (PSI): Theory and implementation for SDM. *NeuroImage*. 2019;186.
152. Radua J, Mataix-Cols D, Phillips ML, El-Hage W, Kronhaus DM, Cardoner N, Surguladze S. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. *European Psychiatry*. 2012;27(8):605–11.
153. Radua J, Rubia K, Canales-Rodríguez EJ, Pomarol-Clotet E, Fusar-Poli P, Mataix-Cols D. Anisotropic Kernels for Coordinate-Based Meta-Analyses of Neuroimaging Studies. *Frontiers in Psychiatry*. 2014;5:13.
154. Nichols, TE, Das, S., Eickhoff, SB, Evans, AC, Glatard, T, Hanke, M, Kriegeskorte, N, Milham, MP, Poldrack, RA, Poline, JB, Proal, E, Thirion, B, Van Essen, DC, White, T, & Yeo, BT. Best practices in data analysis and sharing in neuroimaging using MRI. *Nature Neuroscience*. 2017;20(3):299–30
155. Ahlgrén-Rimpiläinen A, Lauerma H, Kähkönen S, Rimpiläinen I. Disrupted central inhibition after transcranial magnetic stimulation of motor cortex in schizophrenia with long-term antipsychotic treatment. *ISRN Psychiatry*. 2013;876171.
156. Bagewadi VI, Mehta UM, Naik SS, Govindaraj R, Varambally S, Arumugham SS, Naveen Kumar C, Thirthalli J. Diminished modulation of motor cortical reactivity during context-based action observation in schizophrenia. *Schizophrenia Research*. 2019;204:222–9.

157. Bajbouj M, Gallinat J, Niehaus L, Lang UE, Roricht S, Meyer BU. Abnormalities of inhibitory neuronal mechanisms in the motor cortex of patients with schizophrenia. *Pharmacopsychiatry*. 2004;37(2):74–80.
158. Bridgman AC, Barr MS, Goodman MS, Zomorodi R, Rajji T, Le Foll B, Chen R, Daskalakis ZJ, George TP. Effects of varenicline on motor cortical plasticity in non-smokers with schizophrenia. *Schizophrenia Research*. 2016;178(1-3):50–5.
159. Carment L, Dupin L, Guedj L, Térémetz M, Cuenca M, Krebs MO, Amado I, Maier MA, Lindberg PG. Neural noise and cortical inhibition in schizophrenia. *Brain stimulation*. 2020;13(5):1298–304.
160. Du X, Kochunov P, Summerfelt A, Chiappelli J, Choa F-S, Hong LE. The role of white matter microstructure in inhibitory deficits in patients with schizophrenia. *Brain stimulation*. 2017;10(2):283–90.
161. Du X, Hong E. Aberrant prefronto-motor cortex connectivity explains inhibitory deficits in the motor cortex of patient with schizophrenia. *Biological Psychiatry*. 2018;83(9):S324–S5.
162. Du X, Hong LE. Test-retest reliability of short-interval intracortical inhibition and intracortical facilitation in patients with schizophrenia. *Psychiatry Research*. 2018;267:575–81.
163. Fitzgerald PB, Brown TL, Daskalakis ZJ, Kulkarni J. A transcranial magnetic stimulation study of inhibitory deficits in the motor cortex in patients with schizophrenia. *Psychiatry Research - Neuroimaging*. 2002;114(1):11–22.
164. Fitzgerald PB, Brown TL, Daskalakis JZ, Kulkarni J. A transcranial magnetic stimulation study of the effects of olanzapine and risperidone on motor cortical excitability in patients with schizophrenia. *Psychopharmacology*. 2002;162(1):74–81.
165. Fitzgerald PB, Brown TL, Daskalakis ZJ, deCastella A, Kulkarni J. A study of transcallosal inhibition in schizophrenia using transcranial magnetic stimulation. *Schizophrenia Research*. 2002;56(3):199–209.
166. Fitzgerald PB, Brown TL, Marston NAU, Oxley T, De Castella A, Daskalakis ZJ, et al. Reduced plastic brain responses in schizophrenia: a transcranial magnetic stimulation study. *Schizophrenia Research*. 2004;71(1):17–26.
167. Hare SM, Du X, Adhikari BM, Chen S, Mo C, Summerfelt A, Kvarta MD, Garcia L, Kochunov P, Elliot Hong L. Mapping local and long-distance resting connectivity

markers of TMS-related inhibition reduction in schizophrenia. *NeuroImage Clinical*. 2021;31:102688.

168. Hasan A, Schneider M, Schneider-Axmann T, Ruge D, Retz W, Rösler M, Falkai P, Wobrock T. A similar but distinctive pattern of impaired cortical excitability in first-episode schizophrenia and ADHD. *Neuropsychobiology*. 2013;67(2):74–83.

169. Hasan A, Bergener T, Nitsche MA, Strube W, Bunse T, Falkai P, Wobrock T. Impairments of motor-cortex responses to unilateral and bilateral direct current stimulation in schizophrenia. *Frontiers in psychiatry*. 2013;4:121.

170. Hasan A, Nitsche MA, Herrmann M, Schneider-Axmann T, Marshall L, Gruber O, Falkai P, Wobrock T. Impaired long-term depression in schizophrenia: a cathodal tDCS pilot study. *Brain stimulation*. 2012;5(4):475–83.

171. Hasan A, Wobrock T, Grefkes C, Labusga M, Levold K, Schneider-Axmann T, Falkai P, Müller H, Klosterkötter J, Bechdolf A. Deficient inhibitory cortical networks in antipsychotic-naïve subjects at risk of developing first-episode psychosis and first-episode schizophrenia patients: a cross-sectional study. *Biological Psychiatry*. 2012;72(9):744–51.

172. Lindberg PG, Térémetz M, Charron S, Kebir O, Saby A, Bendjemaa N, Lion S, Crépon B, Gaillard R, Oppenheim C, Krebs MO, Amado I. Altered cortical processing of motor inhibition in schizophrenia. *Cortex; a journal devoted to the study of the nervous system and behavior*. 2016;85:1–12.

173. Mehta UM, Thirthalli J, Basavaraju R, Gangadhar BN. Association of intracortical inhibition with social cognition deficits in schizophrenia: Findings from a transcranial magnetic stimulation study. *Schizophrenia Research*. 2014;158(1-3):146–50.

174. Mehta UM, Ektare A, Jakhar J, Basavaraju R, Sanjay TN, Naik SS, Syed, FA, Bhargav, PH, Reddy, PV, Kelkar, RS, Arumugham, SS, Kesavan, M, Thirthalli, J, & Gangadhar, BN. A transdiagnostic evaluation of cortical inhibition in severe mental disorders using Transcranial Magnetic Stimulation. *Journal of Psychiatric Research*. 2021;143:364–9.

175. Oxley T, Fitzgerald PB, Brown TL, de Castella A, Daskalakis ZJ, Kulkarni J. Repetitive transcranial magnetic stimulation reveals abnormal plastic response to premotor cortex stimulation in schizophrenia. *Biological Psychiatry*. 2004;56(9):628–33.

176. Roeh A, Malchow B, Levold K, Labusga M, Keller-Varady K, Schneider-Axmann T, Wobrock T, Schmitt A, Falkai P, & Hasan A. Effects of Three Months of Aerobic Endurance Training on Motor Cortical Excitability in Schizophrenia Patients and Healthy Subjects. *Neuropsychobiology*. 2018;1–8.
177. Schecklmann M, Weidler C, Eichhammer P, Hajak G, Langguth B. Increased short-interval intracortical inhibition in un-medicated patients with schizophrenia. *Brain stimulation*. 2018;11(5):1080–2.
178. Soubasi E, Chroni E, Gourzis P, Zisis A, Beratis S, Papathanasopoulos P. Cortical motor neurophysiology of patients with schizophrenia: a study using transcranial magnetic stimulation. *Psychiatry Research*. 2010;176(2-3):132–6.
179. Takahashi S, Ukai S, Kose A, Tsuji T, Iwatani J, Hashimoto T, Okumura M, Shinosaki K. Reduction in GABAergic cortical inhibition correlates with cognitive impairment in schizophrenia. *Neuroscience Research*. 2011;71:e393.
180. Tang Y, Zhang T, Edelman B, Zeng B, Zhao S, Li C, Zhuo K, Qian Z, Li H, Guo Q, Cui H, Zhu Y, Jiang L, Li C, Yu D, Wang J. Prolonged cortical silent period among drug-naïve subjects at ultra-high risk of psychosis. *Schizophrenia Research*. 2014;160(1–3):124–30.
181. Wobrock T, Schneider-Axmann T, Retz W, Rösler M, Kadovic D, Falkai P, Schneider M. Motor circuit abnormalities in first-episode schizophrenia assessed with transcranial magnetic stimulation. *Pharmacopsychiatry*. 2009;42(5):194–201.
182. Davila-Pérez P, Jannati A, Fried PJ, Mazaira JC, Pascual-Leone A. The effects of waveform and current direction on the efficacy and test-retest reliability of transcranial magnetic stimulation. *Neuroscience*. 2018;393:97–109.
183. Goodman MS, Bridgman AC, Rabin RA, Blumberger DM, Rajji TK, Daskalakis ZJ, George TP, & Barr MS. Differential effects of cannabis dependence on cortical inhibition in patients with schizophrenia and non-psychiatric controls. *Brain stimulation*. 2017;10(2):275–82.
184. Anticevic A, Cole MW, Repovs G, Murray JD, Brumbaugh MS, Winkler AM, Savic A, Krystal JH, Pearlson GD, & Glahn DC. Characterizing thalamo-cortical disturbances in schizophrenia and bipolar illness. *Cereb Cortex*. 2014;24(12):3116–30.
185. Baran B, Isik Karahanoglu F, Demanuele C, Fowler RA, Vuper TC, Seicol B, Correll D, Callahan CE, Parr E, Stickgold R, Manoach DS. Integrity of thalamocortical

circuitry is associated with sleep spindle deficits in schizophrenia. *Schizophrenia Bulletin*. 2017;43:S114.

186. Bergé D, Lesh TA, Smucny J, Carter CS. Improvement in prefrontal thalamic connectivity during the early course of the illness in recent-onset psychosis: a 12-month longitudinal follow-up resting-state fMRI study. *Psychological medicine*. 2022;52(13):2713–21.

187. Chen MH, Chang WC, Bai YM, Huang KL, Tu PC, Su TP, Li CT, Lin WC, Tsai SJ, Hsu JW. Cortico-thalamic dysconnection in early-stage schizophrenia: a functional connectivity magnetic resonance imaging study. *European Archives of Psychiatry and Clinical Neuroscience*. 2020;270(3):351–8.

188. Clos M, Diederer KMJ, Meijering AL, Sommer IE, Eickhoff SB. Aberrant connectivity of areas for decoding degraded speech in patients with auditory verbal hallucinations. *Brain Structure and Function*. 2014;219(2):581–94.

189. Ferri J, Ford JM, Roach BJ, Turner JA, van Erp TG, Voyvodic J, Preda A, Belger A, Bustillo J, O'Leary D, Mueller BA, Lim KO, McEwen SC, Calhoun VD, Diaz M, Glover G, Greve D, Wible CG, Vaidya JG, Potkin SG, Mathalon DH. Resting-state thalamic dysconnectivity in schizophrenia and relationships with symptoms. *Psychological Medicine*. 2018;48(15):2492–9.

190. Fryer SL, Ferri JM, Roach BJ, Loewy RL, Stuart BK, Anticevic A, Ford JM, Mathalon DH. Thalamic dysconnectivity in the psychosis risk syndrome and early illness schizophrenia. *Psychological Medicine*. 2022;52(13):2767–75.

191. Hua J, Choe A, Blair N, Barber A, Brandt A, Pekar J, van Zijl P, Ross C, Lim I, Xu F, Margolis R. Thalamic subregion resting state connectivity in schizophrenia measured at 7T. *Schizophrenia Bulletin*. 2018;44:S289–S90.192. Huang A, Rogers B, Sheffield J, Vandekar S, Anticevic A, Woodward N. Age and Sex Effects of Thalamocortical Functional Connectivity in Typically Developing Youth and Youth With Psychosis Spectrum Symptoms. *Biological Psychiatry*. 2021;89(9):S258.

193. Lencer R, Yao L, Reilly JL, Keedy SK, McDowell JE, Keshavan MS, Pearlson GD, Tamminga CA, Gershon ES, Clementz BA, Lui S, Sweeney JA. Alterations in intrinsic fronto-thalamo-parietal connectivity are associated with cognitive control deficits in psychotic disorders. *Human Brain Mapping*. 2019;40(1):163–74.

194. Lui S, Yao L, Xiao Y, Keedy SK, Reilly JL, Keefe RS, Tamminga CA, Keshavan MS, Pearlson GD, Gong Q, Sweeney JA. Resting-state brain function in schizophrenia and psychotic bipolar probands and their first-degree relatives. *Psychological medicine*. 2015;45(1):97–108.
195. Martino M, Magioncalda P, Yu H, Li X, Wang Q, Meng Y, Deng W, Li Y, Li M, Ma X, Lane T, Duncan NW, Northoff G, Li T. Abnormal Resting-State Connectivity in a Substantia Nigra-Related Striato-Thalamo-Cortical Network in a Large Sample of First-Episode Drug-Naïve Patients With Schizophrenia. *Schizophrenia Bulletin*. 2018;44(2):419–31.
196. Penner J, Osuch E, Schaefer B, Theberge J, Neufeld R, Menon R, Rajakumar N, Bourne JA, Williamson PC. Higher order thalamic nuclei resting network connectivity in first episode Schizophrenia and major depressive disorder. *Biological Psychiatry*. 2017;81(10):S386.
197. Ramsay I, Mueller B, Sponheim S. Thalamocortical relationships with symptoms and cognition in a transdiagnostic psychosis sample. *Neuropsychopharmacology*. 2021;46:339–47.
198. Tu PC, Lee YC, Chen YS, Li CT, Su TP. Schizophrenia and the brain's control network: Aberrant within- and between-network connectivity of the frontoparietal network in schizophrenia. *Schizophrenia Research*. 2013;147(2-3):339–47.
199. Tu P-C, Bai YM, Li C-T, Chen M-H, Lin W-C, Chang W-C, Su T-P. Identification of Common Thalamocortical Dysconnectivity in Four Major Psychiatric Disorders. *Schizophrenia Bulletin*. 2019;45(5):1143–51.
200. Wang H-LS, Rau C-L, Li Y-M, Chen Y-P, Yu R. Disrupted thalamic resting-state functional networks in schizophrenia. *Frontiers in behavioral neuroscience*. 2015;9:45.
201. Wang J, Jiang Y, Tang Y, Xia M, Curtin A, Li J, Sheng J, Zhang T, Li C, Hui L, Zhu H, Biswal BB, Jia Q, Luo C, Wang J. Altered functional connectivity of the thalamus induced by modified electroconvulsive therapy for schizophrenia. *Schizophrenia Research*. 2020;218:209–18.
202. Woodward JJ, Zamudio-Bulcock PA. Inactivation of the posterior cerebellum via dreads unveils a possible role of the cerebellum in voluntary alcohol consumption. *Alcohol Clin Exp Res*. 2016;40:149A.

203. Xie Y, Xi Y, Cui L-B, Li C, Xu Y, Zhang Y, Yan Q, Fang P, Yin H. Altered functional connectivity of the dentate nuclei in patients with schizophrenia. *Schizophrenia Research*. 2021;233:16–23.
204. Yamamoto M, Kushima I, Suzuki R, Branko A, Kawano N, Inada T, Iidaka T, Ozaki N. Aberrant functional connectivity between the thalamus and visual cortex is related to attentional impairment in schizophrenia. *Psychiatry research Neuroimaging*. 2018;278:35–41.
205. Yasuda Y, Okada N, Nemoto K, Fukunaga M, Yamamori H, Ohi K, Koshiyama D, Kudo N, Shiino T, Morita S, Morita K, Azechi H, Fujimoto M, Miura K, Watanabe Y, Kasai K, Hashimoto R. Brain morphological and functional features in cognitive subgroups of schizophrenia. *Psychiatry and clinical neurosciences*. 2020;74(3):191–203.
206. Zhang M, Palaniyappan L, Deng M, Zhang W, Pan Y, Fan Z, Tan W, Wu G, Liu Z, Pu W. Abnormal Thalamocortical Circuit in Adolescents With Early-Onset Schizophrenia. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2021;60(4):479–89.
207. Zhao W, Voon V, Xue K, Xie C, Kang J, Lin C-P, Wang J, Cheng J, Feng J. Common abnormal connectivity in first-episode and chronic schizophrenia in pre- and post-central regions: Implications for neuromodulation targeting. *Progress in neuropsychopharmacology & biological psychiatry*. 2022;117:110556.
208. Zhou L, Bi Y, Liang M, Kong Y, Tu Y, Zhang X, Song Y, Du X, Tan S, Hu L. A modality-specific dysfunction of pain processing in schizophrenia. *Human brain mapping*. 2020;41(7):1738–53.
209. Anteraper SA, Guell X, Collin G, Qi Z, Ren J, Nair A, Seidman LJ, Keshavan MS, Zhang T, Tang Y, Li H, McCarley RW, Niznikiewicz MA, Shenton ME, Stone WS, Wang J, Whitfield-Gabrieli S. Abnormal Function in Dentate Nuclei Precedes the Onset of Psychosis: A Resting-State fMRI Study in High-Risk Individuals. *Schizophrenia Bulletin*. 2021;47(5):1421–30.
210. Bang M, Park H-J, Pae C, Park K, Lee E, Lee S-K, An SK. Aberrant cerebro-cerebellar functional connectivity and minimal self-disturbance in individuals at ultra-high risk for psychosis and with first-episode schizophrenia. *Schizophrenia Research*. 2018;202:138–40.

211. Bernard JA, Dean DJ, Kent JS, Orr JM, Pelletier-Baldelli A, Lunsford-Avery JR, Gupta T, Mittal VA. Cerebellar networks in individuals at ultra high-risk of psychosis: impact on postural sway and symptom severity. *Human brain mapping*. 2014;35(8):4064–78.
212. Bernard JA, Orr JM, Mittal VA. Cerebello-thalamo-cortical networks predict positive symptom progression in individuals at ultra-high risk for psychosis. *NeuroImage Clinical*. 2017;14:622–8.
213. Cao H, Wei X, Zhang W, Xiao Y, Zeng J, Sweeney JA, Gong Q, Lui S. Cerebellar Functional Dysconnectivity in Drug-Naïve Patients With First-Episode Schizophrenia. *Schizophrenia Bulletin*. 2023;49(2):417–27.
214. Chen Y-L, Tu P-C, Lee Y-C, Chen Y-S, Li C-T, Su T-P. Resting-state fMRI mapping of cerebellar functional dysconnections involving multiple large-scale networks in patients with schizophrenia. *Schizophrenia Research*. 2013;149(1):26–34.
215. Choi SY, Ha M, Choi S, Moon S-Y, Park S, Kim M, Kwon JS. Altered intrinsic cerebellar-cerebral functional connectivity is related to negative symptoms in patients with first-episode psychosis. *Schizophrenia Research*. 2023;252:56–63.
216. Clark SV, Tannahill A, Calhoun VD, Bernard JA, Bustillo J, Turner JA. Weaker Cerebellocortical Connectivity within Sensorimotor and Executive Networks in Schizophrenia Compared to Healthy Controls: Relationships with Processing Speed. *Brain Connectivity*. 2020;10(9):490–503.
217. Guo W, Zhang F, Liu F, Chen J, Wu R, Chen DQ, Zhang Z, Zhai J, Zhao J. Cerebellar abnormalities in first-episode, drug-naïve schizophrenia at rest. *Psychiatry research Neuroimaging*. 2018;276:73–9.
218. Huang H, Zeng B, Jiang Y, Tang Y, Zhang T, Tang X, Xu L, Wang J, Li J, Qian Z, Liu X, Wang H, Luo C, Li C, Xu J, Goff D, Wang J. Aberrant resting-state functional connectivity of salience network in first-episode schizophrenia. *Brain imaging and behavior*. 2020;14(5):1350–60.
219. Orr JM, Turner JA, Mittal VA. Widespread brain dysconnectivity associated with psychotic-like experiences in the general population. *NeuroImage: Clinical*. 2015;4:343–51.

220. Park SH, Kim T, Ha M, Moon S-Y, Lho SK, Kim M, Kwon JS. Intrinsic cerebellar functional connectivity of social cognition and theory of mind in first-episode psychosis patients. *NPJ schizophrenia*. 2021;7(1):59.
221. Wang L, Zou F, Shao Y, Ye E, Jin X, Tan S, Hu D, Yang Z. Disruptive changes of cerebellar functional connectivity with the default mode network in schizophrenia. *Schizophrenia Research*. 2014;160(1):67–72.
222. Wang H, Guo W, Liu F, Wang G, Lyu H, Wu R, Chen J, Wang S, Li L, Zhao J. Patients with first-episode, drug-naïve schizophrenia and subjects at ultra-high risk of psychosis shared increased cerebellar-default mode network connectivity at rest. *Scientific reports*. 2016;6:26124.
223. Xie YJ, Xi YB, Cui L-B, Guan MZ, Li C, Wang ZH, Fang P, Yin H. Functional connectivity of cerebellar dentate nucleus and cognitive impairments in patients with drug-naïve and first-episode schizophrenia. *Psychiatry Research*. 2021;300:113937.
224. Zhou J, Guo X, Liu X, Luo Y, Chang X, He H, Duan M, Li S, Li Q, Tan Y, Yao G, Yao D, Luo C. Intrinsic Therapeutic Link between Recuperative Cerebellar Connectivity and Psychiatry Symptom in Schizophrenia Patients with Comorbidity of Metabolic Syndrome. *Life*. 2023;13(1).
225. Woodward ND. Imaging thalamocortical networks across illness stages in psychosis. *Biological Psychiatry*. 2014;75(9):160S.
226. Huang AS, Rogers BP, Sheffield JM, Vandekar S, Anticevic A, Woodward ND. Characterizing effects of age, sex and psychosis symptoms on thalamocortical functional connectivity in youth. *NeuroImage*. 2021;243:118562.
227. Ramsay IS, Mueller B, Ma Y, Shen C, Sponheim SR. Thalamocortical connectivity and its relationship with symptoms and cognition across the psychosis continuum. *Psychological medicine*. 2022:1–10.
228. Xi C, Liu Z-N, Yang J, Zhang W, Deng M-J, Pan Y-Z, Cheng Y-Q, Pu W-D. Schizophrenia patients and their healthy siblings share decreased prefronto-thalamic connectivity but not increased sensorimotor-thalamic connectivity. *Schizophrenia Research*. 2020;222:354–61.229. Kim M, Kim T, Ha M, Oh H, Moon S-Y, Kwon JS. Large-Scale Thalamocortical Triple Network Dysconnectivities in Patients With First-Episode Psychosis and Individuals at Risk for Psychosis. *Schizophrenia Bulletin*. 2023;49(2):375–84.

230. Deco G, Ponce-Alvarez A, Hagmann P, Romani GL, Mantini D, Corbetta M. How local excitation-inhibition ratio impacts the whole brain dynamics. *J Neurosci*. 2014;34(23):7886–98.
231. Lewis DA, Curley AA, Glausier JR, Volk DW. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. *Trends in Neurosciences*. 2012;35(1):57–67.
232. Gu H, Hu Y, Chen X, He Y, Yang Y. Regional excitation-inhibition balance predicts default-mode network deactivation via functional connectivity. *Neuroimage*. 2019;185:388–97.
233. Ferrarelli F, Tononi G. The Thalamic Reticular Nucleus and Schizophrenia. *Schizophrenia Bulletin*. 2011;37(2):306–15.
234. Schmitt LI, Wimmer RD, Nakajima M, Happ M, Mofakham S, Halassa MM. Thalamic amplification of cortical connectivity sustains attentional control. *Nature*. 2017;545(7653):219–23.
235. Schmahmann JD. The cerebellum and cognition. *Neurosci Lett*. 2019;688:62–75.
236. Çetin MS, Christensen F, Abbott CC, Stephen JM, Mayer AR, Cañive JM, et al. Thalamus and posterior temporal lobe show greater inter-network connectivity at rest and across sensory paradigms in schizophrenia. *NeuroImage*. 2014;97:117–26.
237. Sterzer P, Adams RA, Fletcher P, Frith C, Lawrie SM, Muckli L, et al. The Predictive Coding Account of Psychosis. *Biological Psychiatry*. 2018;84(9):634–43.
238. Hwang K, Bertolero MA, Liu WB, D'Esposito M. The Human Thalamus Is an Integrative Hub for Functional Brain Networks. *J Neurosci*. 2017;37(23):5594–607.
239. Friston K. The dysconnection hypothesis of schizophrenia: a 30-year update. *World Psychiatry*. 2026;25(2):225–6.
240. Friston K. Predictive coding, precision and synchrony. *Cogn Neurosci*. 2012;3(3-4):238–9.
241. Fletcher PC, Frith CD. Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. *Nat Rev Neurosci*. 2009;10(1):48–58.
242. Powers A, Angelos PA, Bond A, Farina E, Fredericks C, Gandhi J, et al. A Computational Account of the Development and Evolution of Psychotic Symptoms. *Biological Psychiatry*. 2025;97(2):117–27.
243. Adams R, Stephan K, Brown H, Frith C, Friston K. The Computational Anatomy of Psychosis. *Frontiers in Psychiatry*. 2013;4.

244. Butler PD, Silverstein SM, Dakin SC. Visual Perception and Its Impairment in Schizophrenia. *Biological Psychiatry*. 2008;64(1):40–7.
245. Javitt DC, Freedman R. Sensory processing dysfunction in the personal experience and neuronal machinery of schizophrenia. *Am J Psychiatry*. 2015;172(1):17–31.
246. Walther S, van Harten PN, Waddington JL, Cuesta MJ, Peralta V, Dupin L, et al. Movement disorder and sensorimotor abnormalities in schizophrenia and other psychoses - European consensus on assessment and perspectives. *Eur Neuropsychopharmacol*. 2020;38:25–39.
247. Lanyi O, Keri S, Palffy Z, Polner B. Can you believe your eyes? Positive schizotypy is associated with increased susceptibility to the Muller-Lyer illusion. *Schizophr Res*. 2024;264:327–35.
248. Joseph A, Adams RA, Gaughran F, Howes OD, Martino D, Morgante F, et al. Schizophrenia and disordered sensorimotor control: challenges, mechanisms and opportunities. *Brain*. 2026.
249. Hirjak D, Volkmer S, Pokorny V, Mittal VA. Advancing the sensori-/psychomotor domain in schizophrenia spectrum disorders: From clinical observation to translational innovation. *Schizophr Res*. 2025;285:185–95.
250. Friston KJ, Kahan J, Biswal B, Razi A. A DCM for resting state fMRI. *Neuroimage*. 2014;94(100):396–407.
251. Ziemann U. Neuropharmacology of intracortical inhibition. *Clinical neurophysiology*. 2010;121:S4.
252. Anticevic A, Lisman J. How Can Global Alteration of Excitation/Inhibition Balance Lead to the Local Dysfunctions That Underlie Schizophrenia? *Biological Psychiatry*. 2017;81(10):818–20.
253. Kaufmann T, Skåtun KC, Alnæs D, Doan NT, Duff EP, Tønnesen S, et al. Disintegration of Sensorimotor Brain Networks in Schizophrenia. *Schizophrenia Bulletin*. 2015;41(6):1326–35.
254. Hirjak D, Meyer-Lindenberg A, Sambataro F, Fritze S, Kukovic J, Kubera KM, et al. Progress in sensorimotor neuroscience of schizophrenia spectrum disorders: Lessons learned and future directions. *Prog Neuropsychopharmacol Biol Psychiatry*. 2021;111:110370.

255. Lee K, Ji JL, Helmer M, Murray JD, Krystal JH, Anticevic A. A Framework for Advancing Mechanistic Neurobehavioral Biomarkers in Psychiatry. *Biol Psychiatry*. 2026;99(10):896–908.
256. Liu SK, Fitzgerald PB, Daigle M, Chen R, Daskalakis ZJ. The Relationship Between Cortical Inhibition, Antipsychotic Treatment, and the Symptoms of Schizophrenia. *Biological Psychiatry*. 2009;65(6):503–9.
257. Cao H, Chén OY, Chung Y, Forsyth JK, McEwen SC, Gee DG, et al. Cerebello-thalamo-cortical hyperconnectivity as a state-independent functional neural signature for psychosis prediction and characterization. *Nature communications*. 2018;9(1):3836.
258. Stoodley CJ, Valera EM, Schmahmann JD. Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. *Neuroimage*. 2012;59(2):1560–70.
259. Ford J, Ferri J, Roach B, Fryer S, Stuart B, Loewy R, et al. Thalamic dysconnectivity in the psychosis risk syndrome and early illness schizophrenia. *Biological Psychiatry*. 2018;83(9):S325–S6.
260. Farzan F, Halko MA, Pousada-Casal A, Schmahmann JD, Pascual-Leone A. Modulation and assessment of the cerebello-cortical connectivity through transcranial magnetic stimulation (TMS) combined with electroencephalography (EEG). *Annals of Neurology*. 2012;72:S82–S3.
261. Basavaraju R, Ithal D, Thanki M, Arvinda HR, Thirthalli J, Pascual-Leone A, et al. Intermittent theta burst stimulation of cerebellar vermis in schizophrenia: impact on negative symptoms and brain connectivity. *Schizophrenia Bulletin*. 2019;45:S234–.
262. Csukly G, Orbán-Szigeti B, Suri K, Zsigmond R, Hermán L, Simon V, et al. Theta-burst rTMS in schizophrenia to ameliorate negative and cognitive symptoms: study protocol for a double-blind, sham-controlled, randomized clinical trial. *Trials*. 2024;25(249).
263. Hua JPY, Abram SV, Ford JM. Cerebellar stimulation in schizophrenia: A systematic review of the evidence and an overview of the methods. *Frontiers in Psychiatry*. 2022;13:1069488.
264. Adams RA, Huys QJ, Roiser JP. Computational Psychiatry: towards a mathematically informed understanding of mental illness. *J Neurol Neurosurg Psychiatry*. 2016;87(1):53–63.

265. Fox MD, Halko MA, Eldaief MC, Pascual-Leone A. Measuring and manipulating brain connectivity with resting state functional connectivity magnetic resonance imaging (fcMRI) and transcranial magnetic stimulation (TMS). *Neuroimage*. 2012;62(4):2232–43.
266. Clementz BA, Sweeney JA, Hamm JP, Ivleva EI, Ethridge LE, Pearlson GD, Keshavan MS, Tamminga CA. Identification of Distinct Psychosis Biotypes Using Brain-Based Biomarkers. *American Journal of Psychiatry*. 2018;16(2):225–36.
267. Bradley C, Nydam AS, Dux PE, Mattingley JB. State-dependent effects of neural stimulation on brain function and cognition. *Nature Reviews Neuroscience*. 2022;23(8):459–75.
268. Zrenner C, Ziemann U. Closed-Loop Brain Stimulation. *Biological Psychiatry*. 2024;95(6):545–52.
269. Poldrack RA, Baker CI, Durnez J, Gorgolewski KJ, Matthews PM, Munafo MR, et al. Scanning the horizon: towards transparent and reproducible neuroimaging research. *Nat Rev Neurosci*. 2017;18(2):115–26.
270. Nichols TE, Das S, Eickhoff SB, Evans AC, Glatard T, Hanke M, et al. Best practices in data analysis and sharing in neuroimaging using MRI. *Nat Neurosci*. 2017;20(3):299–303.
271. Powers A, Mathys C, Corlett P. Conditioned hallucinations: Toward development of computational markers for early diagnosis and personalized treatment. *Early Intervent Psychiatry*. 2018;12:65.
272. Farzan F, Barr MS, Levinson AJ, Chen R, Wong W, Fitzgerald PB, et al. Evidence for gamma inhibition deficits in the dorsolateral prefrontal cortex of patients with schizophrenia. *Brain : a journal of neurology*. 2010;133(Pt 5):1505–14.
273. Du X, Choa F-S, Chiappelli J, Wisner KM, Wittenberg G, Adhikari B, et al. Aberrant Middle Prefrontal-Motor Cortex Connectivity Mediates Motor Inhibitory Biomarker in Schizophrenia. *Biological Psychiatry*. 2019;85(1):49–59.
274. Carment L, Dupin L, Guedj L, Térémetz M, Krebs MO, Cuenca M, et al. Impaired attentional modulation of sensorimotor control and cortical excitability in schizophrenia. *Brain*. 2019;142(7):2149–64.

275. Fusar-Poli P, Salazar de Pablo G, Correll CU, Meyer-Lindenberg A, Millan MJ, Borgwardt S, et al. Prevention of Psychosis: Advances in Detection, Prognosis, and Intervention. *JAMA Psychiatry*. 2020;77(7):755–65.
276. Kraguljac NV, Lahti AC. Neuroimaging as a Window Into the Pathophysiological Mechanisms of Schizophrenia. *Frontiers in Psychiatry*. 2021;12.
277. Thibaut F, Boutros NN, Jarema M, Oranje B, Hasan A, Daskalakis ZJ, et al. Consensus paper of the WFSBP Task Force on Biological Markers: Criteria for biomarkers and endophenotypes of schizophrenia part I: Neurophysiology. *World J Biol Psychiatry*. 2015;16(5):280–90.
278. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010;167(7):748–51.
279. Kiemes A, Gomes FV, Cash D, Uliana DL, Simmons C, Singh N, et al. GABA(A) and NMDA receptor density alterations and their behavioral correlates in the gestational methylazoxymethanol acetate model for schizophrenia. *Neuropsychopharmacology*. 2022;47(3):687–95.

16. BIBLIOGRAPHY

16.1. Publications Related to the Thesis

Lányi, O., Zahemszky, D., Wenning, A. S., Engh, M. A., Molnár, Z., Horváth, A. A., Hegyi, P., & Csukly, G. (2026). Cerebello-Thalamo-Cortical Dysconnectivity in Schizophrenia Spectrum Disorders: A Resting-State Functional Magnetic Resonance Imaging Meta-Analysis. *Biological psychiatry. Cognitive neuroscience and neuroimaging*, 11(3), 329–346. <https://doi.org/10.1016/j.bpsc.2025.05.017>

Lányi, O., Koleszár, B., Schulze Wenning, A., Balogh, D., Engh, M. A., Horváth, A. A., Fehérvari, P., Hegyi, P., Molnár, Z., Unoka, Z., & Csukly, G. (2024). Excitation/inhibition imbalance in schizophrenia: A meta-analysis of inhibitory and excitatory TMS-EMG paradigms. *Schizophrenia*, 10(1), 56. <https://doi.org/10.1038/s41537-024-00476-y>

16.2. Publications not Related to the Thesis

Vass, Á., Pálffy, Z., Sörnyei, D., **Lányi, O.**, Pongrácz, M., Szabó, G., Császár, I., Csukly, G., & Farkas, K. (2026). EEG spectral power across rest, body scan, and task conditions in Autism and Schizophrenia. *Psychiatry Research: Neuroimaging*, 362, 112292. <https://doi.org/10.1016/j.psychresns.2026.112292>

Vass, Á., Farkas, K., **Lányi, O.**, Kói, T., Csukly, G., Réthelyi, J. M., & Baradits, M. (2025). Current Status of Electroencephalography Microstate in Psychiatric Disorders: A Systematic Review and Meta-Analysis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 10(10), 1015-1024. <https://doi.org/10.1016/j.bpsc.2025.04.001>

Csukly, G., Tombor, L., Hidasi, Z., Csibri, E., Fullajtár, M., Huszár, Z., Koszovác, V., **Lányi, O.**, Vass, E., Koleszár, B., Kóbor, I., Farkas, K., Rosenfeld, V., Berente, D. B., Bolla, G., Kiss, M., Kamondi, A., & Horvath, A. A. (2024). Low Functional network integrity in cognitively unimpaired and MCI subjects with depressive symptoms: Results from a multi-center fMRI study. *Translational Psychiatry*, 14(1), 179. <https://doi.org/10.1038/s41398-024-02891-2>

Lányi, O., Kéri, S., Pálffy, Z., & Polner, B. (2024). Can you believe your eyes? Positive schizotypy is associated with increased susceptibility to the Müller-Lyer illusion. *Schizophrenia Research*, 264, 327-335. <https://doi.org/10.1016/j.schres.2023.12.023>

17. ACKNOWLEDGEMENTS

I am grateful to my supervisor, Dr Gábor Csukly, for his scientific guidance, trust, and support throughout my PhD. I also thank the Department of Psychiatry and Psychotherapy and the Centre for Translational Medicine at Semmelweis University for providing the institutional support.

In addition, I am grateful to the Fulbright Program and the Hungarian-American Fulbright Commission for supporting me for 12 months as a visiting researcher at the Yale School of Medicine. I am also deeply grateful to Dr Albert Powers and the members of the Powers Lab for hosting me for a year during my PhD and for providing me the opportunity to lead my own research project in an intellectually stimulating research environment. While this work is not included as a thesis publication, the experience substantially shaped my development as a researcher and broadened my theoretical knowledge and methodological skills.