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Excitatory/Inhibitory Balance in the Basal Nuclei Circuit in Treatment-Resistant Schizophrenia: A Computational Modelling Approach Using The Virtual Brain

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Abstract

Background: Schizophrenia (SZ) is a severe psychiatric disorder with a lifetime prevalence of approximately 1%. Nearly one third of the patients with SZ show little or no improvement in positive symptoms, an excess and/or distortion of typical mental functioning, such as hallucinations and delusions, with first-line antipsychotics. This condition is termed treatment resistant schizophrenia (TRS). Compared with treatment responsive patients (non-TRS), those with TRS have lower quality of life, poorer cognitive and social functioning and higher risk of substance abuse. The clinical heterogeneity motivates the central question of this thesis: whether TRS reflects a distinct pattern of circuit-level dysfunction, rather than simply a more severe version of SZ.

Objectives: This thesis had two aims. The first aim was to establish whether the resulting circuit-level parameters, global coupling (G), local inhibitory coupling (J_i), local excitatory NMDA mediated coupling (J_{NMDA}), and recurrent excitation ($w+$), could distinguish schizophrenia patients from healthy controls (HC), and TRS from non-treatment resistant (non-TRS) patients. The second aim was to test whether these same parameters, together with treatment resistance status, could predict symptom severity, measured using Positive and Negative Syndrome Scale (PANSS) scores, within the SZ group. These parameters were obtained using The Virtual Brain (TVB) to model a basal nuclei circuit and characterise its excitatory/inhibitory (E/I) balance, the relative strengths of excitatory versus inhibitory signalling. The circuit was expanded beyond standard basal nuclei parcellations to include dentate nuclei, cerebellar structures not typically included in basal nuclei parcellations.

Methods: The final sample comprised 76 participants. Thirty-three were patients with SZ and 43 were healthy controls. Subject-specific models of the basal nuclei circuit were built for each participant and its brain dynamics were simulated using the Wong-Wang neural mass model in TVB.

Results: None of the four basal nuclei circuit parameters, nor of the two fit indices (PCC, KS), or the overall cost function, differed significantly between SZ patients and HCs. The same finding was obtained when comparing TRS, non-TRS, and HCs. When we tested the ability of these parameters to predict symptom severity using multiple regression, treatment resistance status emerged as a consistent predictor of PANSS total, negative and disorganisation scores. Moreover, J_i significantly predicted disorganisation symptom severity at an uncorrected threshold.

Conclusion: Taken together, these findings do not establish a new biomarker of treatment resistance in SZ. However, they do provide a preliminary basis for future work relating basal nuclei circuit dynamics to the clinical heterogeneity of SZ. Independent of these findings, the dentate-inclusive parcellation developed in this work constitutes a methodological contribution in its own right.

Keywords: Schizophrenia, Treatment Resistant Schizophrenia, The Virtual Brain, Basal Nuclei, Dentate Nucleus

Introduction

Schizophrenia (SZ) is a severe psychiatric disorder with a lifetime prevalence of approximately 1% of the population (McCutcheon et al., 2019; Wada et al., 2022). It typically emerges in early adulthood and is associated with a substantial healthcare burden. Annual costs in the United States alone exceed \$150 billion. The number is driven largely by the long-term social and occupational impairments that follow its early age of onset (McCutcheon et al., 2019). The disorder also carries a considerable personal cost, with affected individuals having a mean life expectancy around 15 years shorter than the general population, as well as a 5-10% lifetime risk of death by suicide (McCutcheon et al., 2019).

Clinically, SZ is characterised by three symptom domains. They are positive symptoms (e.g., delusions, hallucinations), negative symptoms (e.g., lack of motivation, avolition, blunted affect, social withdrawal), and cognitive symptoms (e.g., deficits in working memory, executive function, and processing speed). Positive symptoms are usually what brings a patient to clinical attention and respond comparatively well to antipsychotic medication. Negative and cognitive symptoms, though less visible, account for a large share of the long-term disability associated with the disorder. They typically respond poorly, or not at all, to antipsychotic treatment (McCutcheon et al., 2019). Cognitive and negative symptoms often precede the first psychotic episode, sometimes by years, suggesting that the underlying neurobiological changes begin well before the disorder becomes clinically apparent.

Not all patients respond equally to treatment. Nearly one-third of patients with SZ show little or no improvement in positive symptoms with first-line, non-clozapine antipsychotics. This condition

is collectively termed treatment-resistant schizophrenia (TRS). It is formally defined as persistence of positive symptoms despite two or more adequate trials of antipsychotic treatment at adequate dose, duration, and adherence (Wada et al., 2022). Compared to patients with non-TRS, those with TRS have lower quality of life, poorer cognitive and social functioning and higher risk of suicidal ideation and of substance abuse (Wada et al., 2022). Clozapine remains the gold-standard treatment for TRS, but even among those who receive it, roughly half show a poor response, highlighting that TRS itself is not a uniform category (Wada et al., 2022).

The leading aetiological account of SZ, the dopamine hypothesis, attributes positive symptoms to hyperactive dopaminergic signalling in the striatum (Wada et al., 2022). However, this hypothesis does not hold uniformly across all patients. Those with TRS show reduced dopamine synthesis capacity relative to non-TRS patients, opposite of what a single hyperdopaminergic mechanism would predict. This heterogeneity has shifted how the field frames dopamine dysfunction. Now, it is less of a standalone chemical imbalance, and more a downstream expression of a broader cortico-limbic-striatal disturbance (Wada et al., 2022). Current framing motivates the modelling of basal nuclei as part of an interconnected circuit, rather than looking at striatal dopamine in isolation.

These findings frame the central question of this thesis: whether TRS reflects a distinct pattern of circuit-level dysfunction rather than simply a more severe version of standard SZ. The thesis addresses this question using TVB, a computational modelling framework that simulates whole brain activity from individual structural and functional MRI data. The first chapter reviews the dopaminergic and basal nuclei circuitry implicated in SZ. It also addresses the biological basis for distinguishing treatment responders from non responders, and the rationale for incorporating the

cerebellar dentate nuclei into the basal nuclei circuit. The second chapter details the imaging and modelling methods underlying this approach. It introduces the MRI acquisition and processing technique used to generate the structural and functional data. This is followed by an overview of TVB, the modelling framework used to simulate circuit activity from this data. Third chapter presents the experimental study, from the participant sample, data acquisition, and preprocessing pipeline used to build circuit specific connectivity data. It closes with an explanation of the statistical approach used to compare groups and test symptom associations, results, and a discussion of the resulting findings. Chapter four closes the thesis with its broader conclusions and implications.

Chapter 1: **Theoretical framework**

1.1 Schizophrenia

SZ is a heterogeneous psychiatric disorder whose clinical presentation, diagnostic boundaries, and underlying neurobiology are reviewed in this chapter, beginning with its core symptomatology. Not all symptoms of SZ respond equally to treatment. This divide tracks three domains recognised across current diagnostic and research frameworks: positive, negative, and cognitive. Each has a distinct clinical course and treatment response (McCutcheon et al., 2019). Positive symptoms consist primarily of hallucinations (most commonly auditory) and persecutory or referential delusions. They are typically what prompts a patient to first seek clinical care, and they show the best response to antipsychotic medication (McCutcheon et al., 2019). Negative symptoms, by contrast, are harder to treat and easier to overlook, and cover a narrower but more disabling set of deficits. These include avolition, blunted affect, anhedonia, alogia, and social withdrawal. Due to their nature, negative symptoms rarely prompt the same urgency as an acute psychotic episode, yet they account for much of the disorder's long-term functional cost (McCutcheon et al., 2019). Cognitive symptoms include impairments in working memory executive function, processing speed, and verbal memory (Tranfa et al., 2023). They follow a similar pattern of treatment resistance and disability. Both negative and cognitive symptoms can appear years before the first psychotic episode. This timing suggests that a neurobiological change is already happening long before the disorder is typically diagnosed (McCutcheon et al., 2019).

Diagnosis is made on clinical grounds, most commonly using DSM-5 criteria. The patient must show at least two core symptoms for one month or longer. Core symptoms include: delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour, and negative symptoms. At least one of the two symptoms present must be delusions, hallucinations, or

disorganised speech. This must be accompanied by a decline in functioning, in work, relationships, or self-care since onset. Some signs of disturbance must persist for at least six months, including at least one month of active-phase symptoms (McCutcheon et al., 2019).

Beyond this three-domain framework, factor analytic work on PANSS items had identified disorganisation (including conceptual disorganisation and disorganised behaviour) as an additional, partly separable symptom dimension (Wallwork et al., 2012). This domain overlaps conceptually with the disorganised speech and disorganised behaviour criteria used in DSM-5 diagnosis described above. However, it is treated in PANSS based research, and in this thesis, as a distinct outcome from positive symptoms. Disorganisation severity has also been linked specifically to cerebellar structure, in a sex dependent manner. Among individuals at clinical high risk for psychosis, smaller cerebellar cortex volume correlated with more severe disorganisation symptoms in females. At the same time, the relationship was reversed in males with larger cerebellar cortex volume associated with greater disorganisation severity (Sefik et al., 2022).

These clinical features map onto two broad classes of neurobiological alteration. Cognitive and negative symptoms are linked to cortical E/I imbalance, involving reduced dendritic spine density, GABAergic interneuron dysfunction, and disrupted gamma-band neural oscillations. Together, they impair the coordination of large-scale functional brain networks (McCutcheon et al., 2019). Positive symptoms, by contrast, are linked to subcortical dopamine dysregulation with molecular imaging studies showing elevated striatal dopamine synthesis and release capacity in patients relative to controls (McCutcheon et al., 2019). Structural and functional connectivity are altered more broadly, including reduced sensorimotor network connectivity linked specifically to verbal memory impairment in SZ (Tranfa et al., 2023).

1.2 Treatment-resistant schizophrenia

TRS affects a substantial minority of patients. Independent estimates converge on approximately one third of individuals with chronic SZ showing this pattern (McCutcheon et al., 2019; Wada et al., 2022). The concept of TRS was introduced in 1988 when clozapine was shown to be effective in patients who had failed to respond to other antipsychotics, establishing that a subset of SZ patients is resistant to most available treatments (Howes et al., 2017).

Because early studies used inconsistent criteria to define resistance, a working group later established a consensus definition (Howes et al., 2017). Under this framework, TRS requires three elements: a confirmed diagnosis of SZ, adequate pharmacological treatment, and persistence of significant symptoms despite this treatment. Adequate treatment is defined as at least two antipsychotic trials with different drugs. Each trial has to last a minimum six weeks at a therapeutic dosage for a combined minimum of twelve weeks. Persistent symptoms are defined as at least moderate severity on a standardised rating scale, with less than 20% symptomatic improvement over the treatment period, with at least moderate functional impairment (Howes et al., 2017).

Compared to non-TRS patients, those with TRS have lower quality of life, poorer cognitive and social functioning, and higher risk of suicidal ideation and substance abuse (Wada et al., 2022). Clozapine remains the gold-standard treatment for TRS, but even among patients that receive it, roughly half show a poor response. This is formally recognised as clozapine-resistant schizophrenia (Wada et al., 2022; Howes et al., 2017), highlighting that TRS itself is not a uniform category. Lower striatal dopamine synthesis capacity, higher glutamate concentration in the anterior cingulate cortex, and more pronounced grey matter changes have all been associated with

treatment resistance (McCutcheon et al., 2019). The neurobiological basis of observed heterogeneity is examined in the sections that follow.

1.3 Dopaminergic system in schizophrenia

The dopamine hypothesis is one of the most widely accepted explanations for the aetiology of SZ. It argues that hyperactive dopaminergic signalling in the striatum underlies positive symptoms (Wada et al., 2022). This is supported by convergent PET evidence: presynaptic dopamine function (release, synthesis, and storage) is consistently elevated in the striatum of patients relative to controls. The elevation is not uniform across the striatum but is most pronounced in the associative subdivision specifically (Wada et al., 2022). Amphetamine-induced dopamine release in this subregion correlates directly with positive symptom severity. Synthesis capacity is elevated even before illness onset and persists throughout the disease course (Wada et al., 2022). Vano et al. (2024) added clearer details to the anatomical picture. Using neuromelanin-sensitive MRI as a marker of long-term dopamine function in the midbrain, they found elevated neuromelanin signalling in the substantia nigra/ventral tegmental area (SN-VTA) of patients. This correlated directly with striatal dopamine synthesis capacity, most strongly between the ventral SN-VTA and the associative striatum specifically. The new data positions a defined mesostriatal loop, rather than the striatum in isolation, as the anatomical locus of dopaminergic dysfunction.

Critically, this hyperexcitation does not hold for all patients. When patients are stratified by treatment response, those with TRS typically show decreased dopamine synthesis capacity relative to non-TRS patients (Wada et al., 2022). Moreover, Jauhar et al. (2018) found that dopamine synthesis capacity in the associative striatum was significantly higher in treatment-responders than

in both non-responders and controls. Also, non-responders did not show a statistically significant difference in synthesis capacity as compared to healthy controls. This is the central biological heterogeneity finding that highlights the single-mechanism dopamine model. Rather than a treatment response producing these divergent dopaminergic phenotypes, the reverse is more likely. A pre-existing difference in dopamine function more likely determines how a patient responds to treatment in the first place.

Heterogeneity observed in SZ has shifted the field's view of dopamine dysfunction in this disorder. It is no longer an isolated chemical imbalance, but part of a larger disturbance spanning connected brain regions. Wada et al. (2022) describe glutamatergic dysfunction in the medial prefrontal cortex and hippocampus that appears to precede striatal dopamine changes. This positions dopamine dysregulation as the downstream expression of a cortico-limbic-striatal imbalance rather than its origin.

1.4 Multi-neurotransmitter account of schizophrenia

As discussed in Section 1.3, the dopamine hypothesis attributes positive symptoms to hyperactive dopaminergic signalling in the striatum (Wada et al., 2022). An alternative view suggests that dopaminergic dysfunction is not an isolated chemical imbalance, but just one component of a broader multi-neurotransmitter disturbance. McCutcheon et al. (2019) propose that cognitive and negative symptoms arise from a cortical E/I imbalance. The imbalance involves reduced dendritic spine density, GABAergic interneuron dysfunction, and disrupted gamma oscillation. These occur alongside subcortical dopamine dysregulation rather than as a direct consequence of it. Wada et al. (2022) similarly report glutamatergic dysfunction in the medial prefrontal cortex and hippocampus that precedes striatal dopamine changes. This finding suggests that two systems are

more interdependent than a dopamine-only account implies. Direct evidence for coordinated dysfunction across neurotransmitter systems comes from Bojesen et al. (2025). They found that the relationship between dopamine synthesis in the nucleus accumbens and GABA levels in the anterior cingulate cortex is reversed in antipsychotic-naïve patients relative to controls. The degree of this reversal predicted treatment response. In unison, these findings suggest that a single-neurotransmitter account may not fully capture the disorder's symptom profile.

1.5 The basal nuclei circuit: structure, function, and dopaminergic modulation

The basal nuclei comprise the striatum (caudate, putamen, and ventral striatum/nucleus accumbens), the external (GPe) and internal (GPi) segments of the globus pallidus, the substantia nigra (pars compacta, SNc, and pars reticulata, SNr), and the subthalamic nucleus (STN) (Haber, 2016). The striatum is the main input structure. It receives topographically organised projections from the cortex, thalamus, and brainstem dopaminergic cells. Specifically, dorsolateral striatum receives sensorimotor cortical input, central striatum receives associative cortical input, and ventromedial striatum receives limbic input (Haber, 2016). The GPi and SNr are the main output structures, projecting to the thalamus, which in turn projects back to the cortex, closing the loop (Haber, 2016).

Information flows through the circuit via three parallel pathways. In the direct pathway, striatal projection neurons inhibit the GPi/SNr directly. The inhibition pauses their tonic inhibitory output and disinhibits the thalamus, facilitating movement or behaviour. In the indirect pathway, a separate population of striatal neurons inhibits the GPe. This disinhibits the STN, which in turn excites the GPi/SNr, increasing inhibitory output to the thalamus and suppressing movement or

behaviour (Lanciego et al., 2012). The direct and indirect pathways are therefore an opposed function: one facilitates voluntary movement, while the other inhibits it (Lanciego et al., 2012). A third, faster route (hyperdirect pathway) allows the frontal cortex to excite the STN directly. It bypasses the striatum entirely, providing a rapid braking mechanism on basal nuclei output that precedes and shapes the slower direct/indirect pathway signals (Haber, 2016; Lanciego et al., 2012).

Dopamine modulates this system via two receptor families expressed on largely separate populations of striatal projection neurons. Direct-pathway neurons predominantly express D1 receptors. Dopamine binding in these receptors is excitatory, reinforcing the "go" signal. Indirect-pathway neurons, by contrast, predominantly express D2 receptors, where the dopamine binding is inhibitory, suppressing the "stop" signal (Lanciego et al., 2012). Because the two pathways pull in opposite directions, this difference in the receptor type lets a single dopamine signal push the "go" pathway forward and suppress inhibition at the same time. This allows the action or cognitive/motivational operation the circuit is currently selecting to be amplified.

This architecture is not a single circuit but a set of parallel loops that are largely separate from one another. Each one processes a different domain of behaviour while sharing the same basic direct/indirect/hyperdirect layout. Alexander, DeLong, and Strick's (1986) original formulation described five of such basal nuclei-thalamocortical circuits: motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate. These circuits are organised by the cortical territory from which each originates and returns to. In the simplified three-way scheme, these correspond to motor (sensorimotor cortex and putamen), associative/cognitive (dorsolateral prefrontal cortex and associative striatum), and limbic (orbitofrontal and anterior cingulate cortex,

hippocampus, and amygdala input to the ventral striatum loops) (Alexander et al., 1986; Haber, 2016). This parallel, loop-segregated organisation makes it reasonable for the dysfunction in SZ to be localised in the associative loop specifically (see Section 1.3), rather than the basal nuclei being uniformly affected.

1.6 Alterations in the basal nuclei dopaminergic system in schizophrenia

The mesostriatal pathway, specifically the dopaminergic projections from the SN-VTA to the striatum, is the anatomical backbone of this dysfunction. Vano et al. (2024) demonstrated that SN-VTA neuromelanin signal correlates with striatal dopamine synthesis capacity. The strongest relationship is seen specifically between the ventral SN-VTA and the associative striatum. It is the same subregion where presynaptic dopamine elevation is most pronounced in SZ generally (Wada et al., 2022). This gives the "associative-striatum specificity", described in more detail in Section 1.3, a plausible upstream source, meaning that dysfunction doesn't start in the striatum itself but in the nigral input to it.

As for brain iron specifically, Vano et al. (2025) used quantitative susceptibility mapping (a direct MRI marker of tissue iron, distinct from the neuromelanin measure mentioned above) and found that SN-VTA iron was significantly lower in patients than controls. Furthermore, they also found that lower iron correlated with higher striatal dopamine synthesis capacity, independently of neuromelanin and myelin content. Since iron is a required cofactor for dopamine synthesis, this suggests reduced midbrain iron may be a contributor to (rather than just a correlate of) striatal hyperdopaminergia, and is proposed as a candidate treatment target in its own right.

Concerning the corticostriatal connectivity, White et al. (2016) found that treatment-resistant patients showed reduced functional connectivity between the ventral striatum and substantia nigra as compared to non-TRS patients. They have also found that altered corticostriatal connectivity more broadly was more widespread in TRS. This is the clearest evidence that the circuit-level disruption, not just the neurochemical one, differs by treatment-response subgroup.

Differences in lateralisation are also noteworthy, and He et al. (2021) provided direct structural evidence for it. They used diffusion tensor imaging (DTI) and volumetric MRI in the basal nuclei (caudate, putamen, pallidum, thalamus) to compare chronic SZ patients and controls. They found schizophrenia-specific increases in volume in the pallidum and dorsal caudate only in the left hemisphere. Several thalamic subregions showed the opposite pattern, with reduced volume specifically in the left hemisphere, meaning a shift toward the right. The degree of this thalamic change correlated with positive symptom severity, with a greater rightward shift in the posterior parietal thalamus associated with worse positive symptoms. Notably, they found no corresponding group difference in functional connectivity laterality. This is a specific structural/volumetric asymmetry finding that does not extend (at least in their data) to functional connectivity strength. This is consistent with earlier reports of higher blood flow in the left pallidum and functional hyperactivity of the left caudate in SZ (Early et al. 1989). Together, these findings suggest that basal nuclei dysfunction in SZ is not just circuit-specific and localised to associative regions, but it is also asymmetric across hemispheres in a way that is consistent with clinical presentation.

1.7 Effects of antipsychotic treatment on the basal nuclei dopaminergic system

Antipsychotic treatment does not normalise presynaptic dopamine synthesis. Jauhar et al. (2019) scanned first-episode patients before and after at least 5 weeks of antipsychotic treatment and

found no significant change in striatal, thalamic, or midbrain dopamine synthesis capacity. Additionally, there was no relationship between observed changes in dopamine synthesis capacity and symptom improvement. This has led the authors to conclude that therapeutic response is not mediated by changes in presynaptic dopaminergic function.

It seems that treatment changes the relationship between neurotransmitter systems rather than their absolute levels. Jauhar et al. (2023) measured striatal dopamine synthesis capacity and anterior cingulate glutamate levels, in the same patient population, before and after treatment. Neither measure changed significantly by itself. However, the relationship between the two measures changed significantly. This dopamine-glutamate relationship differed from healthy controls at baseline, but became indistinguishable from controls at follow-up. This represents a clean demonstration of dopamine-glutamate circuit reorganisation independent of any change in either DA or glutamate neurotransmitters' absolute levels.

Functional connectivity and spontaneous regional brain activity both change with treatment. However, findings across studies are inconsistent with respect to direction and circuit specificity. Sarpal et al. (2015) followed first-episode patients through 12 weeks of second-generation antipsychotic treatment and found that striatal functional connectivity with prefrontal and limbic regions (anterior cingulate and dorso-lateral prefrontal cortex - DLPFC) increased as psychotic symptoms improved. Therefore, corticostriatal dysconnectivity has been interpreted as state-dependent and reversible with treatment response. Hu et al. (2024), however, studied early-onset, drug-naïve patients over 8 weeks of antipsychotic treatment and found results inconsistent with this pattern. Functional Connectivity (FC) between the putamen and frontal/parietal regions (inferior frontal gyrus, middle frontal gyrus, supramarginal gyrus, inferior parietal lobule)

decreased further after treatment. This worsened FC reductions already present at baseline with respect to controls. Across both studies, treatment-related connectivity change appears circuit and subregion-specific rather than a uniform "normalisation" in one direction. These findings do not necessarily contradict each other (different striatal subregions, different patient ages/illness stages), but they should not be presented as a single clean finding.

Spontaneous regional brain activity also shifts with treatment, but not toward the pattern seen in healthy controls. Hu, et al. (2016) followed treatment-naïve first-episode patients through 8 weeks of risperidone treatment and found that patients already showed elevated functional Amplitude of Low-Frequency Fluctuations (fALFF, a measure of spontaneous low-frequency activity) in the left caudate before treatment. After treatment, fALFF further increased in the bilateral putamen and right caudate, with higher regional homogeneity in the right caudate and left putamen. Critically, fALFF in patients with a larger treatment-related increase in left putamen correlated with less improvement in positive symptoms. This means that the medication-induced striatal hyperactivity was counter-therapeutic. Due to this, authors suggest that at least part of the "abnormal" spontaneous striatal activity seen in chronic patients reflects a medication effect layered on top of the illness itself, not purely a marker of the disorder.

Finally, Wei et al. (2024) followed first-episode, drug-naïve patients through 12 weeks of risperidone treatment and found that left nucleus accumbens volume decreased while left pallidum volume increased over treatment. The decreased volume in nucleus accumbens (NAcc), central for reward and motivational processing, correlated with cognitive improvement: larger baseline NAcc volume predicted greater cognitive gains from treatment.

1.8 Treatment responders and non-responders: a biological distinction

One of the clearest biological distinctions between treatment responders and non-responders lies in baseline dopamine synthesis capacity. Jauhar et al. (2018) found that dopamine synthesis capacity in the associative striatum was significantly higher in responders than in both non-responders and controls. Non-responders were statistically indistinguishable from controls. Higher baseline synthesis correlated with greater improvement in Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) positive, negative, and total scores.

Frontostriatal structural connectivity differentiates the groups further. Shin et al. (2022) measured white matter connectivity (fractional anisotropy) between DLPFC and associative striatum alongside dopamine synthesis capacity in TRS, non-TRS, and controls. They found a significant negative correlation between this connectivity and striatal dopamine synthesis in non-TRS patients specifically ($r = -0.629$). This means a weaker prefrontal regulation of the striatum was associated with higher dopamine synthesis, but the relationship was entirely absent in TRS and in controls.

D2/3 receptor binding potential also predicts outcome, in the opposite direction initially expected. Wulff et al. (2015) found that lower baseline striatal D2/3 binding potential, indicating higher endogenous dopamine already occupying the receptors, predicted better treatment response. Patients who went on to respond had significantly lower baseline D2/3 binding potential (BPp) than non-responders. At follow-up, higher receptor blockade correlated with lower Global Assessment of Functioning-Functional score (GAF-F). This suggests that, at a certain point, dopamine suppression stops improving symptoms and instead impairs functioning.

GABA-dopamine coupling is the most direct evidence that treatment response has a distinct neurochemical signature. Bojesen et al. (2025) measured dopamine synthesis in the nucleus accumbens alongside GABA in the ACC in antipsychotic-naïve patients and controls. Controls showed the expected negative relationship (more GABA, less dopamine synthesis, normal inhibitory regulation). However, patients showed a positive relationship instead, and the degree of this abnormality predicted treatment response. This finding is in contrast with Wada et al. (2022), who reported no clear evidence for GABAergic distinction in TRS. The discrepancy likely reflects that Bojesen et al. (2025) tested neurotransmitter interrelations directly, whereas earlier evidence (Wada et al., 2022) had only examined GABA in isolation.

Corticostriatal and striato-nigral connectivity disruption provides more evidence of circuit-level distinction between subgroups. White et al. (2016) found that corticostriatal and striato-nigral connectivity disruption is more pervasive and distributed in TRS than in non-TRS patients. It suggests a broader and less anatomically localised pattern of circuit disruption in TRS. This is consistent with a distinct pathophysiology rather than a more severe variant of the same disorder.

Taken together, these findings suggest that treatment response and treatment resistance reflect qualitatively distinct neurobiological profiles, rather than differences in severity alone. Firstly, responders and non-responders differ in baseline dopamine synthesis capacity (Jauhar et al., 2018). They also differ in the relationship between prefrontal structural connectivity and striatal dopamine synthesis (Shin et al., 2022). Dopamine receptor availability and its relationship to functional outcome (Wulff et al., 2015) fits within this same straightforward dopamine level count. Lower baseline D2/3 receptor binding potential, indicating higher presynaptic dopamine, predicted better treatment response. This account is complicated, however, by evidence on the coordination

between dopaminergic and GABAergic signalling (Bojesen et al., 2025). They found that treatment response depended not on the dopamine level alone, but on how it aligned with GABA levels. Patients whose dopamine and GABA levels were both high, or both low, showed better outcomes, a pattern single-neurotransmitter dopamine model does not capture. Lastly, at the circuit level, TRS is further distinguished by more widespread corticostriatal and striato-nigral disruption than non-TRS (White et al., 2016). Collectively, this evidence supports treatment resistance as a distinct neurochemical and circuit-level phenotype, rather than a more advanced form of treatment-responsive illness.

1.9 Cerebellar involvement and the role of the dentate nuclei

The cerebellum is anatomically and functionally interconnected with the same circuits implicated above. The cerebellum, striatum, and thalamus communicate via monosynaptic and polysynaptic connections, forming cortico-striatal-thalamic-cerebellar (CSTC) loops. Associative subdivisions of these loops show consistent bidirectional connectivity changes in SZ, such as hyperconnectivity with sensory cortices and hypoconnectivity with the association cortex, that are associated with cognitive impairment (Faris et al., 2024). Connectivity between the cerebellum and basal nuclei is itself altered in SZ, as is cerebellar connectivity with regions involved in reward processing (Faris et al., 2024).

The dentate nucleus specifically (one of the deep cerebellar nuclei, DCN) has a direct anatomical relationship with the dopaminergic midbrain. The cerebellum sends monosynaptic glutamatergic projections to both dopaminergic and non-dopaminergic neurons of the substantia nigra pars compacta (Washburn et al., 2024). Additionally, DCN output regulates both the VTA (Carta et al.,

2019) and substantia nigra directly (Washburn et al., 2024). In rodent work by Mittleman et al., (2008), electrical stimulation of the Purkinje layer and the dentate nucleus specifically evokes a sustained increase in prefrontal cortex dopamine release. Moreover, the cerebellum is described as having a "triple relationship" with the dopaminergic system: it produces dopamine locally, receives dopaminergic innervation (largely from the VTA), and regulates brainstem/basal nuclei dopamine systems in turn (Mittleman et al., 2008).

This bidirectionality is disrupted in SZ, specifically at the cerebellum-midbrain interface. Resting-state fMRI in first-episode patients showed decreased functional connectivity between midbrain dopaminergic regions and both the dorsal striatum and cerebellum at baseline (Hayward et al., 2023). More broadly, cerebellar alterations in SZ included reduced cerebellar volume (grey and white matter) and microcircuit-level changes (reduced cell density, altered Purkinje cell dendritic branching). It also included reduced connectivity with PFC, basal nuclei, and VTA, reduced functional activation during cognitive tasks, and dopaminergic/GABAergic/glutamatergic dysfunction within the cerebellum itself (see Faris et al., 2024).

1.10 Rationale for the present study

This thesis characterises E/I balance within a dentate-inclusive basal nuclei circuit in SZ, using TVB. The circuit incorporates the cerebellar contributions outlined in Section 1.9 alongside the corticostriatal circuit reviewed in Sections 1.5 to 1.8. Together, these sections establish that this circuitry is implicated in SZ through dopaminergic, striatal, and cerebellar alterations, and that these alterations differ biologically between TRS and non-TRS patients. Despite this evidence, to our knowledge, no prior study has modelled these circuit dynamics computationally within a basal

nuclei network. This thesis addresses that gap and pursues two aims. First is to test whether the resulting circuit parameters distinguish SZ patients from HCs, and TRS from non-TRS patients, building on the biological distinction between these two groups established in Section 1.8. The second is to test whether these parameters relate to symptom severity within the patient group. This follows from evidence that baseline dopamine synthesis capacity and striatal D2/3 receptor availability already predict symptom improvement and functional outcome (Section 1.8). Because the dopaminergic tone is known to regulate E/I balance within the basal nuclei (Wada et al., 2022), these parameters may capture a downstream signature of the same processes.

Chapter 2: Methods

2.1.1 Physical Principles of MRI

Magnetic Resonance Imaging (MRI) is a non-invasive neuroimaging technique that enables the acquisition of high-resolution quantitative and anatomical information from biological tissue in any plane or volume (Holdsworth & Bammer, 2008). MRI is particularly well-suited to brain imaging because biological tissue is rich in hydrogen, as the human body is approximately 60% water, and the brain over 70%.

A hydrogen nucleus consists of a single proton carrying a positive charge that rotates continuously around its own axis. This property is known as spin. The spinning charge generates a magnetic field, causing the proton to behave like a small bar magnet with a north and south pole (Currie et al., 2013). The magnetic moment μ is proportional to the intrinsic angular momentum P and the gyromagnetic ratio γ , a nucleus-specific constant:

$$\mu = \gamma P$$

In the absence of an external magnetic field, the magnetic moments of hydrogen protons are randomly oriented and their net sum is zero. When a subject is placed inside the scanner and exposed to the static external magnetic field B_0 , the protons begin to precess around the direction of B_0 at the Larmor frequency ω_0 .

$$\omega_0 = \gamma B_0$$

Because it is energetically more favourable to align parallel to B_0 than anti-parallel, a small excess of spins orients parallel to the field, producing a net longitudinal magnetisation M_0 . The vectorial sum of all magnetic moments per unit volume defines the magnetisation vector M , which, in equilibrium, aligns with B_0 .

To generate a measurable signal, the system must be displaced from this equilibrium. This is achieved by applying a radiofrequency (RF) pulse $B_1(t)$. It oscillates at the Larmor frequency and is oriented orthogonally to B_0 . When the protons absorb energy at their resonant frequency, the magnetisation vector M is tipped away from the longitudinal axis toward the transverse plane, generating a transverse magnetisation M_{xy} (Currie et al., 2013). When a 90° RF pulse is applied, the entire net magnetisation is transferred into the transverse plane, where the rotating M_{xy} induces a voltage in a receiver coil, constituting the raw MRI signal. When the RF pulse is switched off, the system returns to equilibrium through a process called relaxation. During relaxation, the transverse magnetisation M_{xy} decays and the longitudinal magnetisation M_z recovers.

2.1.2 Relaxation

As the transverse magnetisation decays and the system returns to equilibrium, it induces a signal known as the Free Induction Decay (FID) that can be recorded with a receiver coil. The relaxation process involves two independent mechanisms: longitudinal relaxation (T_1) and transverse relaxation (T_2) (Mastrogiacomo et al., 2019).

Longitudinal relaxation, also known as spin-lattice relaxation, describes the exponential recovery of the longitudinal magnetisation M_z toward its equilibrium value M_0 (Cercignani et al., 2018). This occurs through energy exchange between excited protons and the surrounding molecular environment, or lattice, increasing molecular vibration. The recovery follows the following function:

$$M_z(t) = M_0(1 - e^{-(t/T_1)})$$

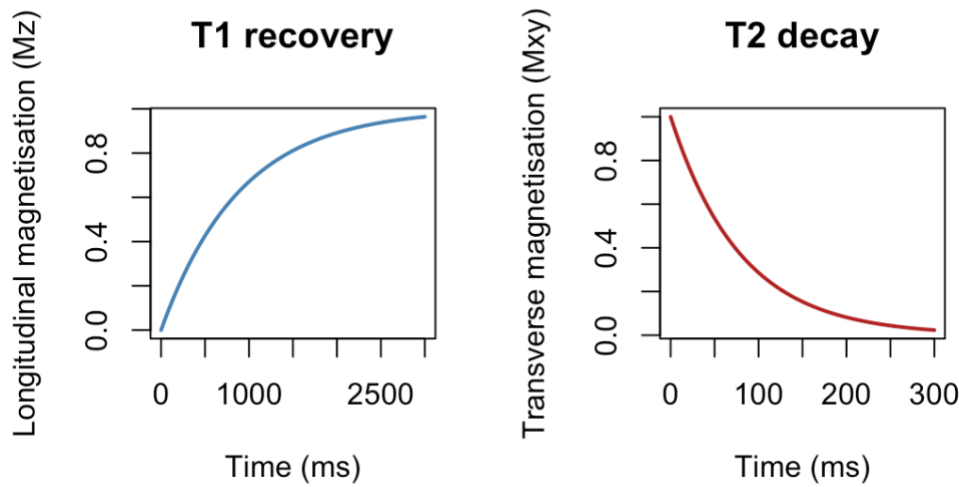


Figure 1: Simulated T1 recovery and T2 decay curves.

T1 is defined as the time required for M_z to recover to 63% of M_0 . T1 is tissue-dependent; fat-based tissues have short T1 values (100–150 ms), water-based tissues have intermediate T1 values (400–1200 ms), and liquids such as cerebrospinal fluid have long T1 values (1500–2000 ms).

Transverse relaxation, also known as spin-spin relaxation, describes the exponential decay of the transverse magnetisation M_{xy} due to interactions between neighbouring spins. This decay is caused by progressive dephasing of the spins (Cercignani et al., 2018). T2 is defined as the time needed for M_{xy} to decay to 37% of its initial value.

$$M_{xy}(t) = M_{xy}(0)e^{-(t/T_2)}$$

T2 is always shorter than T1 for any given tissue. In practice, local inhomogeneities in B_0 accelerate dephasing further, resulting in a faster apparent decay reflected by T_2^* .

$$1/T_2^* = \gamma\Delta B + 1/T_2$$

$\gamma\Delta B$ reflects the additional dephasing introduced by field inhomogeneities. The signal decaying under T_2^* is the FID. To recover signal lost to field inhomogeneities, a 180° refocusing RF pulse can be applied after a time $TE/2$. This rephases the spins and produces a spin echo at time TE , which reflects pure T_2 decay, independent of inhomogeneity effects.

2.1.3 Image Reconstruction and Spatial Encoding

MRI data are not acquired directly in image space but are instead stored in the spatial frequency domain, commonly referred to as k-space (Hansen & Kellman, 2015). K-space is a two-dimensional data matrix with two orthogonal axes. The first one is k_x , associated with the frequency-encoding direction, and the second is k_y , associated with the phase-encoding direction. The centre of k-space contains low spatial frequencies that define overall image contrast and signal amplitude. The edges encode higher spatial frequencies that contribute fine structural detail. Once k-space is fully sampled, the Fourier Transform (FT) is applied to convert the frequency-domain data into the final spatial image (Moratal et al., 2008). The relationship between k-space and the reconstructed image is illustrated in Figure 2.

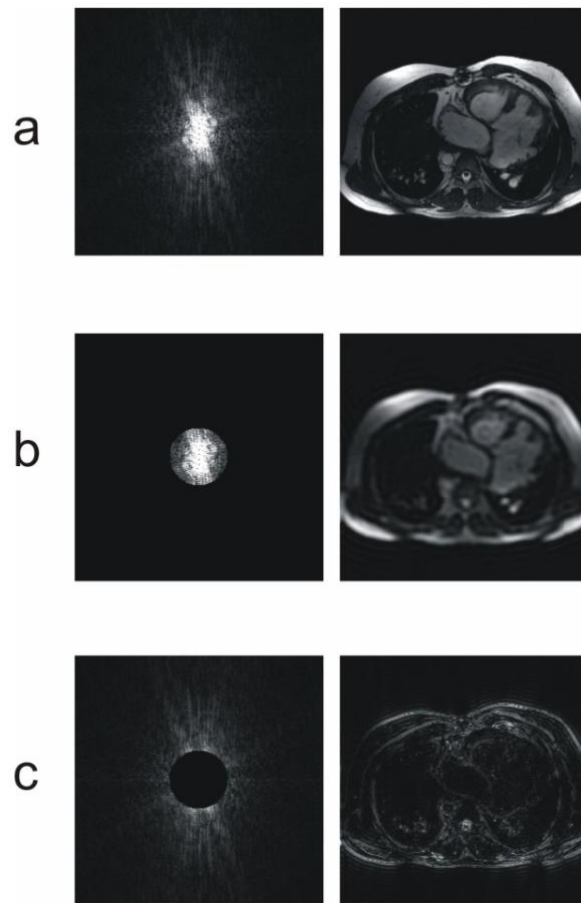


Figure 2: Effect of k -space filtering on image contrast and detail. (a) Original k -space and its reconstructed image. (b) Low passing filtering, retaining only the centre of k -space, preserves image contrast but removes fine detail and contour. (c) High-pass filtering, retaining only the periphery of k -space, preserves detail and edges but removes contrast (Moratal et al., 2008).

Spatial encoding is the process of assigning signals to specific locations within the body. It is achieved through three independently applied magnetic field gradients: a slice selection gradient (G_z), a phase encoding gradient (G_y), and a frequency encoding gradient (G_x) (Van Geuns et al., 1999).

Slice selection is achieved by applying a gradient along the z-axis simultaneously with the RF pulse. Because the Larmor frequency depends on the local magnetic field strength, only protons within a narrow frequency band corresponding to a specific slice are excited. By adjusting the central frequency of the RF pulse, the position of the selected slice can be shifted.

Phase encoding is applied briefly along the y-axis between the RF pulse and signal readout, introducing position-dependent phase shifts in the precessing spins. By repeating acquisitions with different phase-encoding gradient amplitudes, signals from different y-positions accumulate unique phase histories that can be spatially resolved.

Frequency encoding is applied along the x-axis during signal readout, causing spins at different x-positions to precess at slightly different frequencies. This frequency variation encodes position along the x-axis. Later, Fourier Transform is used to disentangle the composite signal into its spatial components. Together, these three gradients allow the acquisition and reconstruction of three-dimensional images with millimetre-scale spatial resolution.

2.1.4 Pulse Sequences and Imaging Contrasts

A major advantage of MRI lies in the flexibility to manipulate tissue contrast through the design of pulse sequences. Pulse sequences are a series of RF pulses and magnetic field gradients timed to emphasise specific tissue properties (Mugler, 1999). The intrinsic tissue parameters that determine MRI contrast are proton density (PD), T1, and T2. These cannot be modified by the operator. However, by adjusting the repetition time (TR) and the echo time (TE) the image weighting can be tailored to highlight different tissue characteristics (Bitar et al., 2006).

T1-weighted images are acquired with short TR and short TE, exploiting differences in longitudinal relaxation. Tissues with shorter T1, such as fat and white matter, recover more rapidly and appear brighter. Tissues with longer T1, such as cerebrospinal fluid, appear darker. T1-weighted images are used as anatomical references, providing strong grey/white matter contrast. T2-weighted images are acquired with long TR and long TE, emphasising differences in transverse relaxation. Tissues with longer T2, such as water and oedema, retain more signal and appear brighter, while those with shorter T2 appear darker. T2-weighted images are particularly useful for detecting pathological changes involving water accumulation or demyelination.

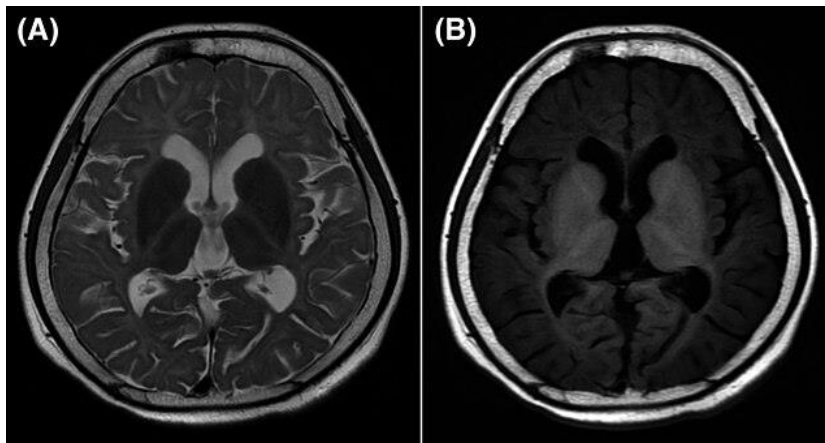


Figure 3: T2 weighted (A) and T1 weighted (B) axial MRI images. Adapted from Wang et al. (2022), licensed under CC BY 4.0.

2.2.1 Diffusion MRI

Diffusion-weighted MRI (DWI) is an application of MRI that exploits the random Brownian motion of water molecules within biological tissue to generate contrast sensitive to tissue

microstructure (Soares et al., 2013). In a free unstructured medium, water molecules undergo isotropic diffusion. It means they move randomly and equally in all directions, and the displacement probability follows a spherical distribution. The root mean square displacement increases proportionally to the square root of the observation time, as described by the following equation:

$$\text{RMSD} = \sqrt{2nDt}$$

Where RMSD is the root mean square displacement, n is the number of dimensions, D is the diffusion coefficient, and t is the observation time.

In structured biological tissue, molecular diffusion is restricted, or hindered, by physical boundaries such as cell membranes, myelin sheaths, and axonal walls. When these barriers constrain movement preferentially along one direction, such as in white matter tracts, where water diffuses more freely along the axonal axis than perpendicular to it, diffusion becomes anisotropic and the displacement distribution takes an ellipsoidal shape (Baliyan et al., 2016). Because the true free diffusion coefficient cannot be measured directly in such constrained environments, the measured value is referred to as the Apparent Diffusion Coefficient (ADC).

To sensitise the MRI signal to diffusion, pairs of diffusion-encoding gradients are incorporated within a spin echo sequence. When a molecule does not move between the two gradient pulses, the second gradient cancels out the effect of the first, and the signal is preserved. When a molecule has moved between the two gradient applications, rephasing is incomplete and the signal is attenuated in proportion to the degree of diffusion (Figure 4).

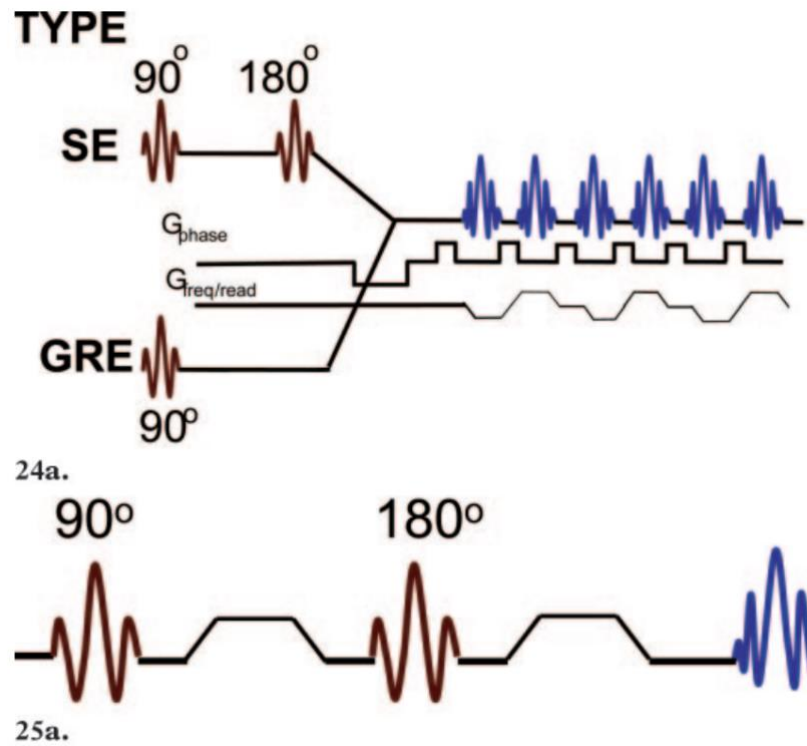


Figure 4. Diffusion weighted imaging pulse sequence diagram. A pair of diffusion-encoding gradient pulses is incorporated into a spin echo sequence, one before and one after the 180° refocusing pulse (Bitar et al., 2006).

This relationship is described by the Stejskal-Tanner equation:

$$S(b)/S(0) = \exp(-bD)$$

$S(b)$ is the diffusion-weighted signal, $S(0)$ is the signal without diffusion weighting, and b is the b-value encoding the strength and duration of the diffusion gradients.

$$b = (\gamma G \delta)^2 (\Delta - \delta/3)$$

Because the ADC is not rotationally invariant, its value depends on the orientation of the applied gradient relative to the tissue. Because of that, a complete characterisation of diffusion directionality requires measurement in at least six non-collinear directions. Diffusion Tensor

Imaging (DTI) allows the computation of the full diffusion tensor D as a 3×3 symmetric matrix that describes the magnitude and direction of diffusion in three-dimensional space (Cercignani et al., 2018). Diagonalisation of D yields three eigenvectors (e_1, e_2, e_3), representing the principal diffusion directions, and three eigenvalues ($\lambda_1, \lambda_2, \lambda_3$), representing diffusion magnitudes along each direction.

Several rotationally invariant scalar indices can be derived from the tensor eigenvalues. Mean Diffusivity (MD) reflects the average magnitude of diffusion within a voxel and is sensitive to cellular density and membrane barriers (Grover et al., 2015).

$$\mathbf{MD} = (\lambda_1 + \lambda_2 + \lambda_3) / 3$$

Fractional Anisotropy (FA) quantifies the degree to which diffusion is directionally asymmetric, ranging from 0 (perfectly isotropic) to 1 (perfectly anisotropic) (Vandermosten et al., 2012).

$$\mathbf{FA} = \sqrt{3/2} \times \sqrt{[(\lambda_1 - \mathbf{MD})^2 + (\lambda_2 - \mathbf{MD})^2 + (\lambda_3 - \mathbf{MD})^2]} / \sqrt{(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}$$

FA is high in organised white matter tracts such as the corpus callosum, and lower in grey matter or regions with crossing fibres. It is widely used as a sensitive biomarker of white matter integrity and has been shown to decrease in conditions involving demyelination or axonal damage. Two additional derived measures offer further microstructural specificity. Axial diffusivity (DI), which is equal to the largest eigenvalue and reflecting diffusion along the primary fibre axis, and radial diffusivity ($D_{\perp}$), calculated as the mean of the two minor eigenvalues and reflecting diffusion perpendicular to the fibre axis. Radial diffusivity ($D_{\perp}$) has been associated with demyelination, with increased values reflecting loss of myelin integrity. At the same time, axial diffusivity (DI)

has been linked to axonal injury, with decreased values reflecting damage along the fibre axis (O'Donnell & Westin, 2011).

These metrics can be extracted from the full brain or from specific regions of interest (ROIs) to perform statistical comparisons. ROI-based analysis defines specific brain areas through manual segregation or automated segmentation, and extracts average parameter values from enclosed voxels. While this approach offers high sensitivity to focal changes, it requires strong anatomical hypotheses and does not provide full-brain coverage (Soares et al., 2013).

2.2.2 Tractography

Tractography is a computational technique that uses the directional information encoded in the diffusion tensor to reconstruct white matter fibre pathways in vivo (O'Donnell & Westin, 2011). By following the principal eigenvector from voxel to voxel, streamline-based tractography algorithms generate trajectories representing estimated fibre pathways. These streamlines can be used to delineate specific tracts, extract microstructural metrics within them, and construct structural connectivity matrices describing the anatomical wiring between brain regions.

A fundamental limitation of classical tensor-based tractography is its inability to resolve voxels containing multiple crossing fibre populations, since only a single principal diffusion direction is estimated per voxel. To address this, constrained spherical deconvolution (CSD) models the full fibre orientation distribution within each voxel, enabling identification and tracking of multiple crossing fibre populations (Tournier et al., 2012). CSD-based tractography is particularly important for recovering anatomically correct connections involving fibre crossings and

decussations, such as those in the cerebellum, which would otherwise be missed. Anatomically constrained tractography (ACT) further improves biological accuracy by incorporating tissue segmentation to ensure that streamlines originate in white matter and terminate in grey matter, reducing anatomically implausible connections (Smith et al., 2012). An example of whole brain tractography reconstruction is shown in Figure 5.

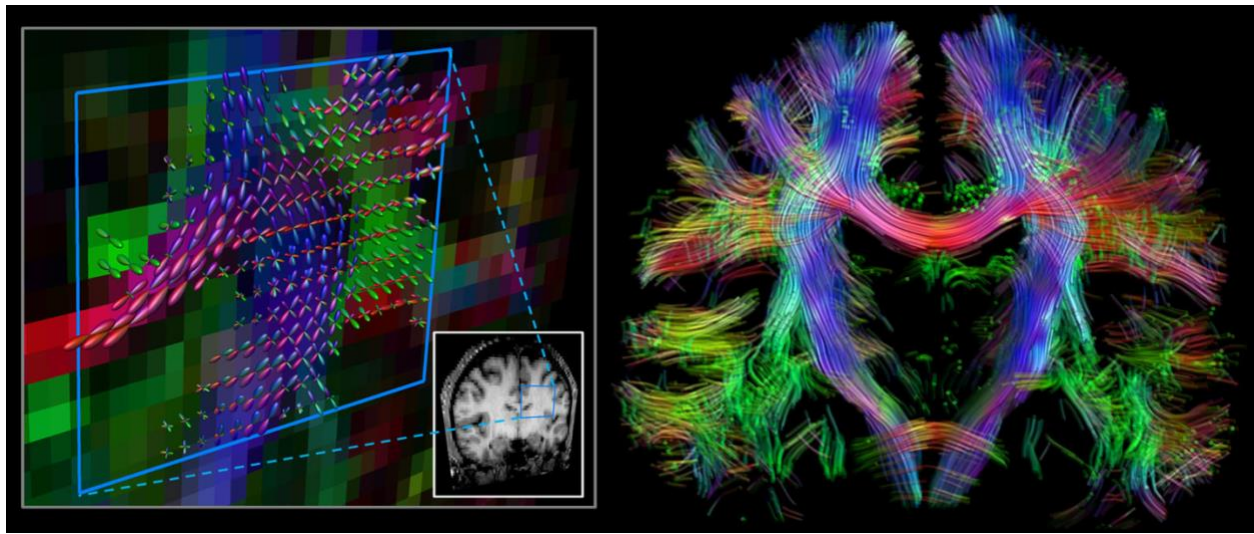


Figure 5: Whole brain tractography reconstruction, coloured by fibre orientation (reproduced from Tournier et al., 2011).

2.3.1 Functional MRI

Functional magnetic resonance imaging (fMRI) is a neuroimaging technique that measures brain activity indirectly through changes in blood oxygenation. It does so by exploiting the different magnetic properties of oxygenated and deoxygenated haemoglobin (Bush & Cisler, 2013). Unlike structural MRI, which produces a single static image, fMRI acquires a time series of whole-brain volumes enabling the study of dynamic brain activity over time.

The basis of the fMRI signal is the Blood Oxygen Level-Dependent (BOLD) effect, which arises from the magnetic susceptibility difference between the two forms of haemoglobin. Oxyhaemoglobin is diamagnetic and does not disturb the local magnetic field. Deoxyhaemoglobin is paramagnetic and distorts surrounding field homogeneity, accelerates $T2^*$ dephasing, and reduces signal intensity in $T2^*$ -weighted images (Cercignani et al., 2018). When neural activity increases in a region, local oxygen consumption rises, producing an initial increase in deoxyhaemoglobin concentration. However, through neurovascular coupling, this metabolic demand rapidly triggers a proportionally larger increase in cerebral blood flow, delivering an oversupply of oxygenated blood to the active region (Wager & Lindquist, 2015). The net result is a reduction in local deoxyhaemoglobin concentration, which decreases $T2^*$ dephasing and produces a positive increase in BOLD signal. It is important to note that fMRI does not measure neural activity directly. It measures the haemodynamic consequence of that activity (Hillman, 2014).

The temporal profile of the BOLD response follows a characteristic shape known as the Haemodynamic Response Function (HRF) shown below.

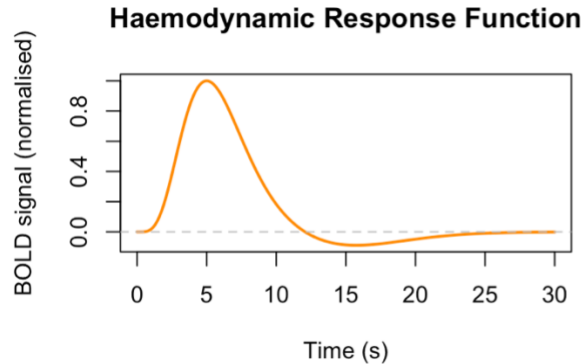


Figure 6: Simulated Haemodynamic Response Function curve.

Following a brief neural event, the signal shows an initial small dip (0–2 seconds) reflecting early oxygen consumption, followed by a pronounced positive overshoot peaking at approximately 4–6 seconds as oxygenated blood arrives, a subsequent decline, and a post-stimulus undershoot before returning to baseline, with a total duration of approximately 20–30 seconds. The post-stimulus undershoot occurs because cerebral blood flow returns to baseline faster than blood volume, producing a temporary relative increase in deoxyhaemoglobin until full vascular recovery is achieved. This temporal lag between neural activity and the measured BOLD signal is a fundamental constraint of fMRI study design.

2.3.1.1 Resting-State fMRI

Resting-state fMRI (rs-fMRI) acquires BOLD time series while participants lie still without performing any explicit task. Although no directed cognitive demand is imposed, the brain exhibits

spontaneous low-frequency BOLD fluctuations (below 0.1 Hz). These are spatially correlated between anatomically and functionally related regions (Lee et al., 2013). These correlated fluctuations define resting-state networks (RSNs). RSNs are sets of brain regions whose spontaneous activity is temporally synchronised, reflecting their functional organisation. Consistently identified RSNs include the default mode network, sensorimotor, visual, frontoparietal, and attentional networks, all of which have been shown to exhibit characteristic alterations in neurological and psychiatric disorders (Lee et al., 2013). RSNs can be identified through data-driven methods such as independent component analysis (ICA), which maximises the independence of spatially distinct signal components, or through seed-based correlation analysis, which examines the temporal correlation between a predefined region of interest and the rest of the brain.

Functional connectivity between each pair of regions is quantified as the Pearson correlation coefficient (PCC) between their BOLD time series, producing a symmetric matrix in which each element $FC(i,j)$ reflects the strength of the functional connection between region i and region j .

These pairwise coefficients populate a functional connectivity matrix in which each row and column represents a brain region (node) and each element represents the strength of the functional connection (edge) between a pair of regions.

2.4 The Virtual Brain

The Virtual Brain (TVB) is a neuroinformatic platform designed to simulate large-scale brain dynamics by combining biologically realistic structural connectivity with computational models of neural activity (Ritter et al., 2013; Sanz-Leon et al., 2013). By incorporating subject-specific

neuroimaging data, TVB enables the construction of personalised brain network models. This provides a means of studying brain function and dysfunction at the individual level across both healthy and clinical populations. TVB links microscopic neuronal activity to macroscale signals such as fMRI through a hierarchical modelling framework that integrates mesoscale representations of neural dynamics within an empirically constrained whole-brain network (D’Angelo & Jirsa, 2022). Rather than describing which brain regions show abnormal activation at the group level, TVB asks how individual brain circuits behave dynamically. Doing so enables the extraction of neurophysiological parameters, most notably excitatory/inhibitory balance, that cannot be measured directly through neuroimaging alone.

2.4.1. Brain parcellation and connectivity inputs

TVB represents the brain as a network of nodes and edges. Nodes correspond to brain regions defined by a parcellation atlas, which assigns each grey matter voxel to a labelled anatomical region. Several standard atlases exist, constructed by combining structural/functional data across large groups of subjects. Edges encode the anatomical or functional connections between regions and are drawn from two complementary sources. The structural connectivity (SC) matrix is derived from whole-brain tractography and weighted by the normalised number of diffusion streamlines between each pair of regions, reflecting the anatomical wiring of the brain. The empirical functional connectivity (FC) matrix is derived from rs-fMRI and reflects the PCC between regional BOLD time series. The SC matrix provides the anatomical backbone of the simulation, while the empirical FC matrix serves as the optimisation target, the pattern of large-scale activity that the model is iteratively tuned to reproduce (Monteverdi et al., 2023).

2.4.2. The Wong-Wang neural mass model

At each network node, local neuronal dynamics are simulated using the Wong-Wang neural mass model (Deco et al., 2014; Wong & Wang, 2006). This model represents the collective activity of a local population of interconnected excitatory and inhibitory neurons. They were originally developed to simulate decision-making tasks and were subsequently adapted for large-scale resting-state simulations. In TVB, each node is modelled as a local network of an excitatory and an inhibitory population interconnected via NMDA, AMPA, and GABA synaptic receptors. The model describes the average synaptic gating variable S , reflecting the proportion of open NMDA channels and serving as a proxy for local neural activity:

$$dS_i/dt = -S_i/\tau_s + \gamma(1 - S_i)H(x_i) + \sigma\eta_i(t)$$

τ_s is the synaptic time constant, γ is a kinetic parameter, $H(x_i)$ is the neuronal transfer function (population firing rate), σ is the noise amplitude, and $\eta_i(t)$ is Gaussian white noise. The transfer function takes the form:

$$H(x_i) = (ax_i - b) / (1 - \exp(-d(ax_i - b)))$$

The total synaptic input x_i to each node combines local recurrent excitation, long-range inputs from structurally connected regions scaled by the global coupling parameter G , and a background external input I_0 :

$$x_i = wJ_N S_i + J_N G \sum_j C_{ij} S_j + I_0$$

where w is the local excitatory recurrence weight, J_N is the synaptic coupling strength representing NMDA-mediated excitation, C_{ij} is the structural connectivity weight between

regions i and j , and G is the global coupling parameter, a scalar controlling the overall influence of the structural connectome on network dynamics and the primary free parameter tuned during optimisation.

Four key parameters must be optimised to align the model with empirical data: the global coupling strength G , the excitatory synaptic coupling mediated by NMDA receptors (J_{NMDA}), the inhibitory synaptic coupling (J_{i}), and the local recurrent excitation weight (w_{+}). Together, these parameters control how spontaneous neural fluctuations propagate across the large-scale network and define the circuit-level excitatory/inhibitory balance that is the primary outcome variable of this thesis (Monteverdi et al., 2023; Deco et al., 2014).

2.4.3. From neural activity to BOLD signal

The simulated synaptic activity at each node is converted into a predicted BOLD signal through the Balloon-Windkessel haemodynamic model (Stephan et al., 2007). This model captures the neurovascular coupling process by translating changes in neural activity into changes in cerebral blood flow, blood volume, and deoxyhaemoglobin concentration, ultimately producing a simulated BOLD time series directly comparable to empirical rs-fMRI recordings.

2.4.4. Model optimisation

Parameters are iteratively adjusted to minimise the discrepancy between simulated and empirical brain dynamics (Monteverdi et al., 2023). Two complementary measures of model fit are

computed. First, static functional connectivity fit is assessed by computing the PCC between the simulated FC matrix (simFC) and the empirical FC matrix (empFC). Second, dynamic functional connectivity fit is assessed using the Kolmogorov-Smirnov (KS) distance between the distributions of simulated and empirical Functional Connectivity Dynamics (FCD) matrices (Hansen et al., 2015).

The FCD captures how functional connectivity changes over time. It is constructed by computing FC over a sliding window of fixed duration shifted incrementally by one repetition time, generating a series of windowed FC matrices. Each windowed FC is vectorised using its upper triangular entries, and all vectorised windows are correlated with one another to generate a time-by-time FCD matrix, whose entries quantify how similar the connectivity pattern at each moment is to every other moment (Hansen et al., 2015; Battaglia et al., 2020). The KS distance between empirical and simulated FCD distributions measures how well the model reproduces the temporal dynamics of large-scale connectivity; lower KS values indicate a better match.

To simultaneously maximise static and dynamic fit, an overall cost function is defined as:

$$(1 - \text{PCC}) + \text{KS}$$

Lower values indicate a closer correspondence to both static and dynamic empirical data (Kong et al., 2021). Parameters are adjusted across multiple initial conditions to ensure robust convergence. The result is a subject-specific set of optimal model parameters (including G , J_{NMDA} , J_i , and w^+) that best characterise each individual's large-scale circuit dynamics.

Chapter 3: The experimental study

This chapter describes the experimental study conducted for this thesis. It applies the imaging and modelling methods introduced in Chapter 2 to the study sample. Section 3.1 describes the participants and how their MRI data were acquired. Section 3.2 describes how those data were processed, from the raw images to the structural connectivity matrix, and the BOLD time series that serve as the inputs to the virtual brain models of the basal nuclei circuit, including the step that integrates the dentate nuclei. Section 3.3 describes the statistical analyses used to compare E/I balance across the three groups (i.e., TRS, non-TRS, and HC), and to relate circuit parameters to symptom severity. Section 3.4 reports the results of these analyses. Section 3.5 discusses their interpretation, methodological advancements, clinical implications, limitations, and directions for future work.

3.1 Participants and data acquisition

The study was conducted on a cohort of 76 participants recruited at the Department of Advanced Biomedical Sciences and the Outpatient Clinic for Treatment-Resistant Psychoses (Department of Neuroscience, Reproductive Sciences and Odontostomatology), University of Naples "Federico II". Data were acquired between March 2019 and July 2020. Patients were divided into two groups. The first group included TRS (N = 16, 3 female, 13 male; mean age 37.3941 years). The second group consisted of non-TRS patients (N = 17, 8 female, 9 male; mean age 39.0566 years). An additional group of healthy controls (N = 43, 21 female, 22 male; mean age 39.2807 years) was also recruited. Patients were diagnosed according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Classification of treatment-resistant was assigned on the basis of failure to respond to at least two adequate antipsychotic trials, after which clozapine was adopted as treatment (Howes et al., 2017).

Patients were eligible if they were between 18 and 60 years of age, had an illness duration exceeding two years, had received stable medication over the preceding six months, and showed no recent worsening of psychiatric or neurological symptoms. HC were excluded in the presence of any psychiatric, neurological, or systemic condition. History of substance or alcohol dependence, or any lifetime use of psychotropic medication, was also taken into consideration. Participants were additionally screened for family psychiatric history, and individuals with a first-degree relative affected by a mental disorder were not enrolled. The study complied with the relevant ethical standards and was approved by the competent ethics committee, and all participants gave written informed consent in accordance with the Declaration of Helsinki (revised Hong Kong, 1989).

All participants were scanned on a 3 T scanner (Magnetom Trio, Siemens Healthineers) equipped with an 8-channel head coil. The protocol comprised three sequences. A T1-weighted anatomical reference was acquired with a 3D magnetisation-prepared rapid gradient-echo (MPRAGE) sequence (TR = 1900 ms, TE = 3.4 ms, TI = 900 ms, flip angle = 9° , voxel size = $1 \times 1 \times 1 \text{ mm}^3$, 160 axial slices). Diffusion-weighted images were obtained with a spin-echo echo-planar imaging (EPI) sequence (TR = 7400 ms, TE = 88 ms, flip angle = 90° , isotropic voxel size = 2.2 mm^3 , 60 slices), sampling 64 directions at $b = 1000 \text{ s/mm}^2$ together with 9 non-diffusion-weighted ($b = 0 \text{ s/mm}^2$) volumes, and were used to reconstruct structural connectivity. Resting-state functional images were acquired with a T2*-weighted gradient-echo EPI sequence (TR = 2500 ms, TE = 50 ms, voxel size = $3 \times 3 \times 4 \text{ mm}^3$, inter-slice gap = 1 mm, 200 volumes, 30 axial slices) for the analysis of functional connectivity.

Clinical severity was assessed using the Positive and Negative Syndrome Scale (PANSS). Data were collected within one month of the MRI scan, as part of the same clinical evaluation protocol described by Tranfa et al. (2023) for the same patient cohort. Age of illness onset was recorded as part of the same clinical evaluation. PANSS data were unavailable for one SZ patient, and for one more patient the positive and negative symptom subscale scores were missing . These two cases were excluded from the regression models (see Section 3.3).

3.2 Preprocessing pipeline and atlas generation

Anatomical, diffusion, and functional data of each participant were preprocessed to produce the three inputs required to perform the simulations. There are two structural connectivity matrices of the basal nuclei circuit (one representing connection weights and the other representing tract lengths), and the corresponding empirical functional connectivity (FC) matrix. Quality control was performed at each stage by visually inspecting atlas registration and dentate-nuclei integration in FSLeys. In the context of this thesis, a T1-weighted structural scan is used to define individual brain anatomy, support tissue segmentation, and serve as the anatomical reference to which diffusion and functional images are co-registered.

Anatomical and diffusion preprocessing. T1-weighted images were corrected for intensity non-uniformity using FreeSurfer and skull-stripped with FSL's BET tool. Diffusion data were denoised and corrected for eddy-current and head-motion distortions. Using the co-registered T1-weighted volume, white matter, grey matter, subcortical grey matter, and cerebrospinal fluid (CSF) were segmented within MRtrix3.

Tractography. In this thesis, whole-brain tractography using CSD-based probabilistic methods is used to generate subject-specific structural connectivity matrices, which serve as the anatomical input to The Virtual Brain modelling framework. Fibre orientation distributions were estimated through constrained spherical deconvolution, and whole-brain anatomically constrained probabilistic tractography was then performed in MRtrix3 (Monteverdi et al., 2022), generating 10 million streamlines.

Functional MRI preprocessing. Resting-state fMRI data were preprocessed using a custom MATLAB pipeline combining SPM12, FSL, and MRtrix3 commands. The pipeline comprised Marchenko–Pastur PCA denoising, slice-timing correction, realignment, co-registration to the T1-weighted volume, polynomial detrending, nuisance regression of 24 motion parameters and the CSF signal (Friston et al., 1996), and temporal band-pass filtering (0.008–0.09 Hz) (Monteverdi et al., 2022).

Atlas construction and dentate-nuclei integration. An anatomical atlas in Montreal Neurological Institute (MNI) space was built by combining 93 cerebral regions from the Automated Anatomical Labelling (AAL) atlas with 31 cerebellar regions from the SUIT atlas (Diedrichsen et al., 2009). It was segmented and registered to each subject's anatomical image. In its standard form, this atlas does not include the dentate nuclei, the principal output nuclei of the cerebellum. Despite their relevance, they are small, deep structures rarely represented in the parcellation atlases used in neuroimaging studies (Faris et al., 2024). To include them, the dentate nuclei were segmented in each subject's native diffusion space from the diffusion signal using a convolutional neural network (Gaviraghi et al., 2020). The resulting segmentation was spatially constrained using the dentate labels of the SUIT cerebellar atlas (Diedrichsen et al., 2009). Atlas-

defined masks were warped into subject space, dilated, and intersected with the network output. The final left and right dentate combined the subject-specific, diffusion-based segmentation with the anatomical prior of the atlas. The two nuclei were then assigned distinct labels and merged into the subject's parcellation, yielding the complete atlas used to construct the connectivity matrices for the basal nuclei network. This dentate-inclusive parcellation constitutes a central methodological contribution of the present work, recovering a cerebellar component of the basal nuclei circuit that standard parcellation schemes usually discard.

Structural and functional connectivity. Applying the grey-matter parcellation of the complete atlas to the whole-brain tractography yielded, for each subject, a whole-brain structural connectivity (SC) matrix. Nodes of the matrix were the cortical, subcortical, and cerebellar regions of the atlas and edges were the normalised streamline counts between them. From this whole-brain matrix, the nodes and connections defining the circuit of interest were extracted to obtain the circuit-specific SC matrix used as input for the simulations (Hansen et al., 2015). The basal nuclei circuit comprised 29 nodes: the principal structures of the basal nuclei and associated subcortical structures (nucleus accumbens, caudate, putamen, pallidum, subthalamic nucleus, substantia nigra - SNc and SNr -, and thalamus), together with the olfactory tubercle, the precentral gyrus, and a set of cerebellar regions defined on the SUIT atlas (lobules I–IV, V, and VIIIb, together with the vermis VIIIb and including the bilaterally integrated dentate nuclei). All regions, except the vermis one, were segmented in each hemisphere. While the circuit is centred on the basal nuclei, it therefore also incorporates thalamic, motor-cortical, and cerebellar nodes that participate in the same dopaminergic and motor loops.

From the resting-state data, empirical static and dynamic functional connectivity (empFC and empFCD) were reconstructed. To preserve the smallest regions of the parcellation when sampling the functional signal, the atlas was kept in native anatomical (T1) space. The functional volumes were resampled to it, rather than projecting the atlas onto the lower-resolution functional grid. Downsampling the parcellation to the coarser fMRI resolution would have otherwise caused very small regions, such as the olfactory tubercle, to disappear entirely, leaving missing time series for those nodes. The empFC matrix was then obtained by extracting the mean BOLD time course of each node and computing the PCC between every pair of regions. The resulting values were Fisher-transformed and thresholded (≈ 0.1206). The empFCD, which captures the temporal evolution of functional connectivity, was computed over a 40-second sliding window shifted by one repetition time. Upper-triangular entries of each windowed matrix were vectorised and correlated with one another to produce a time-versus-time matrix (Monteverdi et al., 2022).

Virtual brain modelling. Subject-specific models of the basal nuclei circuit were built and their neural activity simulated using TVB. The local activity of each node was generated using the Wong-Wang neural mass model (Deco et al., 2014; Monteverdi et al., 2022). Four parameters were optimised: the global coupling (G), a scaling factor for the overall strength of connections between nodes (i.e., long-range connectivity); the excitatory local coupling (J_{NMDA}), reflecting NMDA-mediated synaptic excitation; the inhibitory local coupling (J_i), reflecting GABAergic synaptic inhibition, and the recurrent excitation (w^+), reflecting the circuit's self-excitation. The simulated neural activity was converted into resting-state BOLD signals, from which simulated static and dynamic functional connectivity (simFC and simFCD) were computed. Model parameters were tuned iteratively to maximise the PCC between simFC and empFC and to minimise the Kolmogorov–Smirnov (KS) distance between simFCD and empFCD. The two criteria were

combined into a single cost function $((1 - \text{PCC}) + \text{KS})$ whose minimisation identifies the parameter set that best reproduces both the static and the dynamic features of the empirical data (Kong et al., 2021). The simulations were run with a custom Python script on a Linux workstation. The resulting optimised set of parameters (G , J_{NMDA} , J_i , w^+) describes the connectivity strength and E/I balance of the basal nuclei circuit in each participant. These parameters, particularly those reflecting the balance between excitatory and inhibitory influences within basal nuclei circuits, are the primary neurophysiological output of the modelling procedure. They form the basis for the group comparisons and symptom-severity analysis reported in this thesis.

3.3 Statistical analysis

Statistical analyses were performed in R (version 4.4.3; R Core Team, 2025) using RStudio (version 2024.12.1+563; Posit team, 2024). The variables of interest were the optimised TVB parameters of the basal nuclei circuit (G , J_i , J_{NMDA} , w^+), together with the fit indices of the simulations (PCC, KS, and the cost function). For each comparison, one TVB parameter or fit index was compared across groups (SZ vs. HC for the two-group comparison, or TRS vs. non-TRS vs. HC for the three-group comparison, see below). This was done using between-group tests (t-tests/ANOVAs, or their non-parametric equivalents, depending on distributional assumptions). Before performing group comparisons, the distribution of each parameter was assessed for normality using the Shapiro–Wilk test to determine whether a parametric or a non parametric test was needed. Homogeneity of variance across groups was checked through Levene's test. Welch's correction was applied by default for the parametric tests, regardless of the outcome.

Two sets of comparisons were performed. First, the full SZ group (including both TRS and non-TRS patients) was compared with the healthy control group. Independent-sample t-tests were used for normally distributed parameters. Mann–Whitney U tests were used for the non-normally distributed parameters. Then the three groups (TRS, non-TRS, and HC) were also compared. Normally distributed parameters were analysed with a one-way Welch’s ANOVA. Non-normally distributed parameters were analysed with a Kruskal-Wallis test. The significance threshold was set at $p = 0.05$.

To examine whether basal nuclei network parameters related to symptom severity, four multiple regression models were fitted in the SZ subgroup. In each model, one PANSS score (total, positive, negative, or disorganisation) was treated as the dependent variable. G , J_i , J_{NMDA} , w^+ , were used as predictors of interest, while treatment resistance status (TRS vs non-TRS), and age at onset were included as covariates. Overall model fit was assessed with an F-test, and the significance of individual predictors was assessed with Type II ANOVA (car package; Fox & Weisberg, 2019). It tests the partial effect of each predictor while holding all other terms in the model constant. For example, the model for disorganisation symptoms was specified as: PANSS disorganisation score from $G + J_i + J_{NMDA} + w^+ + \text{TRS status} + \text{age at onset}$. Neuropsychological data were incomplete for a few patients (see 3.1). PANSS total and disorganisation models were fitted on 32 out of the 33 SZ patients, and positive and negative symptoms models on 31 patients. False discovery rate correction (Benjamini & Hochberg, 1995) was applied across the four circuit parameters of interest (G , J_i , J_{NMDA} , w^+) for the positive, negative and disorganised subscales. These were treated as three separate symptom dimensions for the purposes of the correction (12 tests in total). PANSS total was excluded from this corrected family, and reported separately at uncorrected significance. PANSS total is defined as the sum of positive, negative, and general psychopathology traits (Kay

et al., 1987), while the disorganisation dimension used here is a factor-analytically derived subscale (Wallwork et al., 2012), drawing on items from across all three of these original subscales. For this reason, PANSS total was treated as a global severity index rather than as a fourth distinct symptom dimension. It was excluded from the corrected family on conceptual rather than purely statistical grounds. Treatment resistance status and age at onset, as covariates rather than variables of interest, were not included in the correction. Results are reported both before and after correction.

3.4 Results

3.4.1 Comparison between schizophrenia patients and healthy controls

Before comparing groups, the distribution of each basal nuclei network parameter (G , J_i , J_{NMDA} , w^+) and each goodness of fit index (PCC, KS, and the overall cost function) was assessed for normality within each group. Three parameters (J_{NMDA} , w^+ , and PCC) were normally distributed in both groups (all p s > 0.05). The remaining four parameters deviated significantly from normality in at least one group. G was not normally distributed in the SZ group ($W = 0.84$, $p < 0.001$), whereas it was in the HC ($W = 0.96$, $p = 0.153$). J_i deviated from the normal distribution in both groups (SZ: $W = 0.90$, $p = 0.005$; HC: $W = 0.94$, $p = 0.029$), while KS deviated from normality in the SZ group ($W = 0.46$, $p < 0.001$), but not in the HC group ($W = 0.98$, $p = 0.804$). Lastly, cost function deviated from normality in the SZ group ($W = 0.78$, $p < 0.001$), but not in the HC one ($W = 0.96$, $p = 0.109$). Levene's test indicated homogeneity of variance across groups for all seven parameters (all p s > 0.05).

Accordingly, group differences were assessed using Wilcoxon rank-sum test for G , J_i , KS , and cost function. Independent sample Welch's t -tests were used for J_{NMDA} , w^+ , and PCC , instead. None of the parameters differed significantly between the SZ and HC groups (e.g., $J_{NMDA} : t(70.71) = 0.39, p = 0.695$), as reported in Table 1. Figure 7 shows the corresponding violin plots.

Table 1.

Parameter	SZ Mean	HC Mean	Test Statistic	<i>p-value</i>
G	0.94	0.77	$W = 893$	0.183
J_i	2.39	2.23	$W = 849$	0.373
J_{NMDA}	0.148	0.146	$t = 0.39$	0.695
w^+	1.46	1.47	$t = -0.21$	0.835
PCC	0.25	0.27	$t = -0.91$	0.365
KS	0.10	0.09	$W = 725.5$	0.743
Cost function	0.85	0.82	$W = 866$	0.290

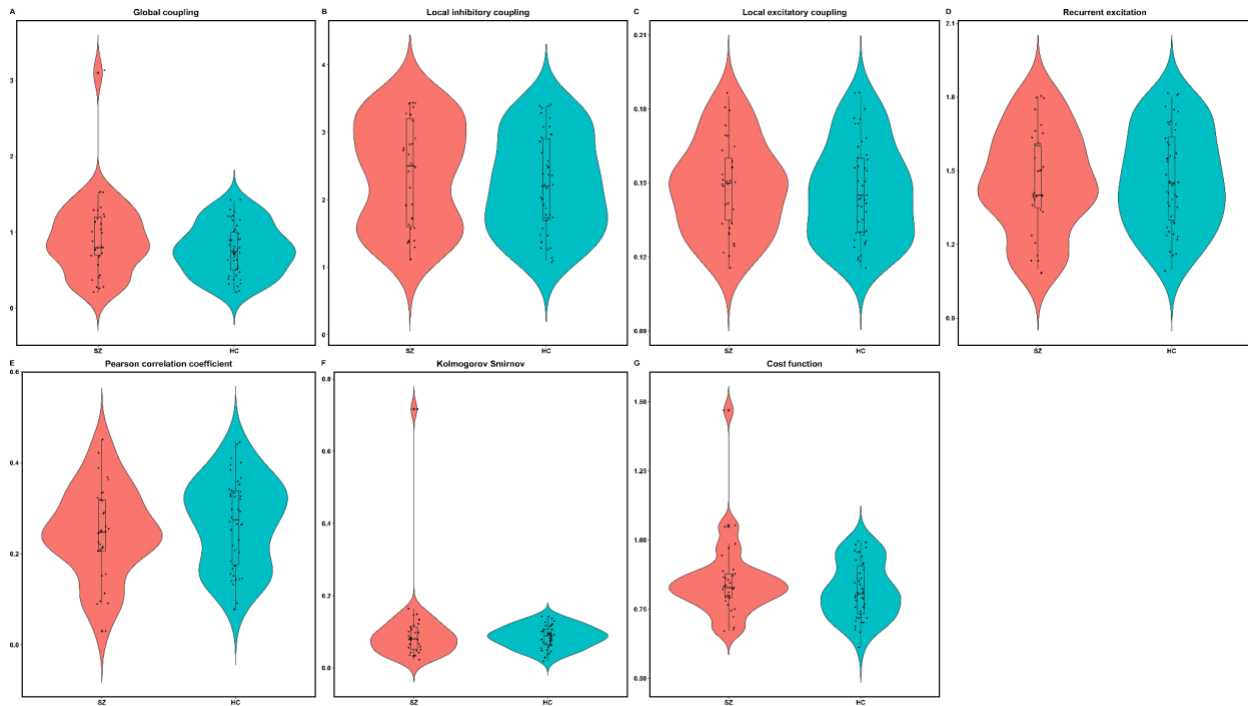


Figure 7. Comparison of basal nuclei network parameters between SZ and HC. Violin plots show the full distribution of each parameter by group, with individual data points and overlaid boxplots. (A) Global coupling, (B) Local inhibitory coupling, (C) Local excitatory coupling, (D) Recurrent excitation, (E) Pearson correlation coefficient, (F) Kolmogorov-Smirnov, (G) Cost Function.

3.4.2 Comparison between TRS, non-TRS, and healthy controls

To assess possible differences between clinical subgroups, the same seven parameters were then compared across the two clinical subgroups (TRS, non-TRS) and HCs. G , J_i , KS , and the cost function deviated from normality in at least one subgroup, most consistently, in the TRS subgroup (e.g., G : $W = 0.81$, $p = 0.004$; KS : $W = 0.50$, $p < 0.001$; cost function: $W = 0.79$, $p = 0.002$). Instead, J_{NMDA} , w^+ , and PCC were normally distributed across TRS, non-TRS, and HC (all p s > 0.05). Levene's test indicated homogeneity of variance across all three groups for all parameters

(all p s > 0.05). Kruskal-Wallis tests were therefore used to assess differences between groups for G , J_i , KS , and cost function. Welch's one-way ANOVAs were used for J_{NMDA} , $w+$, and PCC .

As shown in Table 2, and consistent with the two-group comparison, no parameter differed significantly across TRS, non-TRS, and HC. Figure 8 shows the corresponding violin plot.

Table 2.

Parameter	Test statistic	<i>p-value</i>
G	$X^2 = 1.79$	0.409
J_i	$X^2 = 0.86$	0.652
J_{NMDA}	$F = 1.16$	0.327
$w+$	$F = 0.57$	0.573
PCC	$F = 0.97$	0.389
KS	$X^2 = 3.22$	0.200
Cost function	$X^2 = 4.51$	0.105

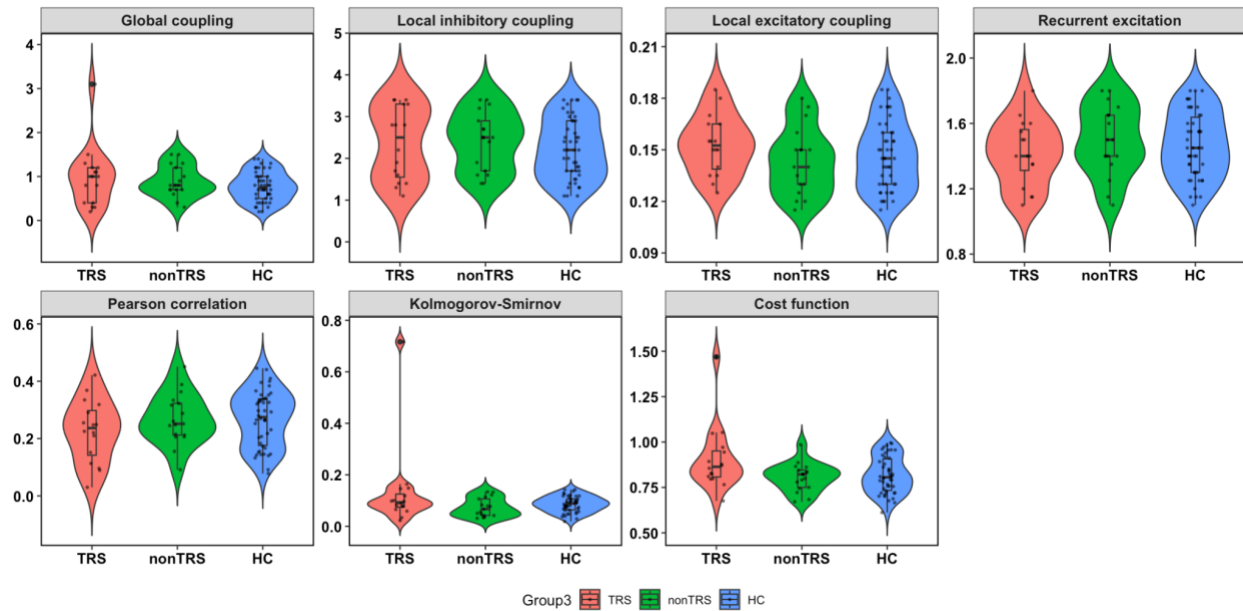


Figure 8. Violin plots show the full distribution of each parameter by group with individual data points and overlaid boxplots.

3.4.3 Relationship between basal nuclei network parameters and symptom severity

Results of the regression analysis examining the association between basal nuclei network parameters and PANSS symptom severity are reported below (see section 3.3 for model specifications). Model fit statistics for all four outcomes are shown in Table 3. None of the models' F statistics were statistically significant.

Table 3. Overall model fit for the four PANSS regression models.

Outcome	<i>F</i>	<i>p-value</i>	R^2	Adjusted R^2
PANSS total	2.45	0.053	0.37	0.22
Positive symptom	0.82	0.569	0.17	-0.04
Negative symptoms	2.22	0.076	0.36	0.20
Disorganisation	1.93	0.115	0.32	0.15

Across all four models, treatment-resistance status was the only consistent predictor (see Figure 9 for mean scores in each subgroup). TRS patients scored significantly higher than non-TRS patients on PANSS total ($\beta = 21.98$, $F(1,25) = 10.41$, $p = 0.003$), negative symptoms ($\beta = 9.94$, $F(1,24) = 10.59$, $p = 0.003$), and disorganisation ($\beta = 8.47$, $F(1,25) = 6.89$, $p = 0.015$). The positive symptom scores did not show statistically significant differences between groups ($\beta = 5.01$, $F(1,24) = 2.35$, $p = 0.139$).

Notably, although the corresponding model was not statistically significant, the parameter J_i was a significant predictor of disorganisation symptom severity ($\beta = 4.14$, $F(1,25) = 4.25$, $p = 0.0497$, see Figure 10): higher J_i values were associated with more severe disorganisation symptoms. This was the only network parameter to significantly predict any symptom outcome. None of the other parameters (G , J_{NMDA} , and w^+) could predict PANSS total, positive, negative, or disorganisation scores significantly in any model (all p s > 0.18).

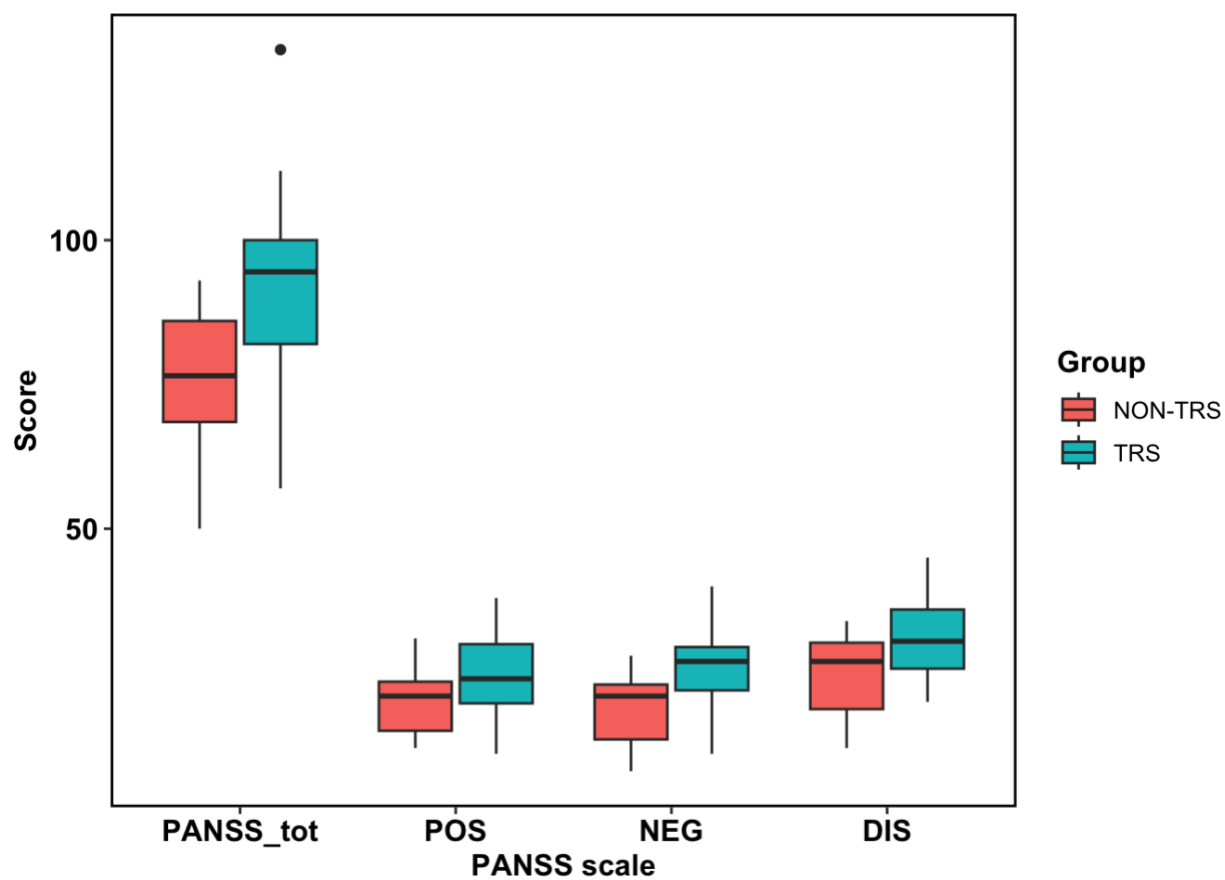


Figure 9. PANSS total, positive, negative, and disorganisation symptom scores by treatment resistance status (TRS vs non-TRS).

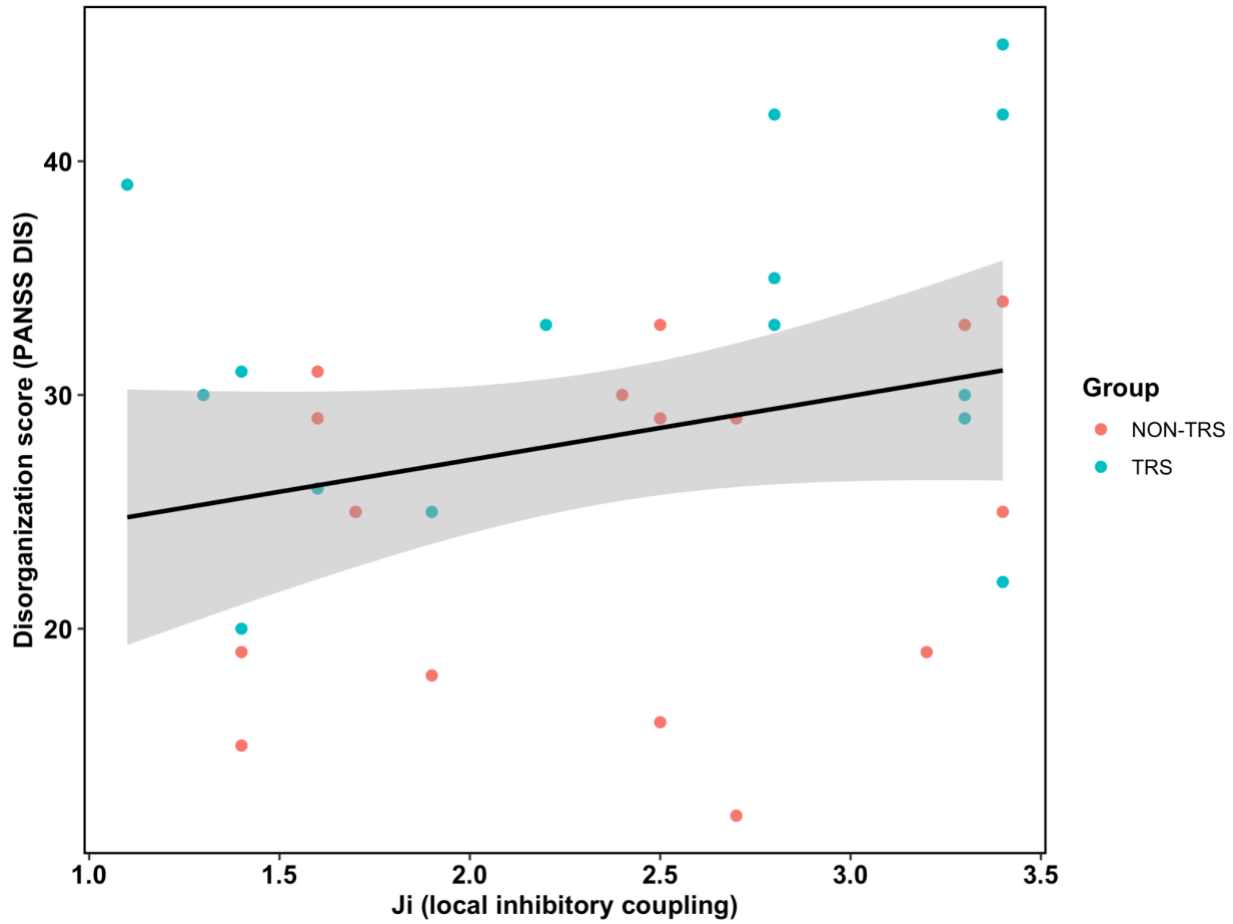


Figure 10. Association between J_i and disorganisation symptom severity (PANSS DIS), by treatment resistance status. The line and shaded band show the unadjusted linear relationship between J_i and PANSS DIS, without accounting for other variables. They are presented alone, for visualisation purposes. The regression coefficient reported in the text ($\beta = 4.14$, $F(1,25) = 4.25$, $p = 0.0497$) comes from the full regression model. It reflects the association between J_i and PANSS DIS, after controlling for G , J_{NMDA} , w^+ , treatment resistance status and age at onset.

After applying FDR correction (see Section 3.3), none of the parameters G , J_{NMDA} , or w^+ was a significant predictor of any PANSS score neither before nor after applying the correction. Association between J_i and disorganisation did not remain significant after the correction was applied (FDR- $p = 0.564$).

3.5 Discussion

This thesis aimed to characterise excitatory/inhibitory (E/I) balance within a basal nuclei circuit using The Virtual Brain (TVB), pursuing two main aims. The first was to establish whether the resulting circuit level parameters (G , J_i , J_{NMDA} , w^+) could distinguish SZ patients from healthy controls, and treatment-resistant (TRS) from non-treatment-resistant (non-TRS) patients. The second was to test whether these same parameters could predict symptom severity, as measured by the PANSS scores, within the SZ group. Focusing on the basal nuclei circuit specifically reflects this network's implicated role in SZ pathophysiology, given evidence of dopaminergic (Vano et al., 2024), and striatal (He et al., 2021) dysfunction within it. To our knowledge, these questions have not previously been examined within the basal nuclei network, representing a novel application of this approach. This thesis also makes two related but distinct methodological contributions. First, the basal nuclei circuit was built from scratch, rather than relying on predefined resting-state networks, allowing it to be tailored specifically to basal nuclei anatomy. Second, the circuit incorporated dentate nuclei, cerebellar structures not typically included in basal nuclei parcellations, adding a further valuable dimension to the present work.

3.5.1 Group comparisons

None of the seven variables of interest (G , J_i , J_{NMDA} , w^+ , PCC, KS, and the overall cost function) differed significantly between the SZ and HC groups, nor across the TRS, non-TRS, and HC subgroups. It is also worth noting that the two fit indices (PCC and KS) did not differ between groups either. This indicates that the model achieved comparable fit to the empirical data in patients and controls. It makes it unlikely that the null result for the E/I parameters themselves reflects poorer model convergence in one group. Our results suggest that the E/I balance within

this circuit shows no detectable alterations in SZ. However, the modest sample size limits the generalisability of our findings. Therefore, replication in larger samples is needed to detect potentially small but significant differences between groups. Indeed, molecular imaging studies using PET measures of striatal dopamine synthesis capacity have consistently differentiated treatment responders from non-responders (Jauhar et al., 2018; see Section 1.8). Given that dopaminergic tone is known to regulate E/I balance within basal nuclei, some corresponding alteration in NMDA mediated neurotransmission might have been expected here as well (Wada et al., 2022). It is worth noting that PET studies index dopamine synthesis *in vivo*, whereas the present circuit parameters reflect *in silico* glutamatergic and GABAergic activity. It is a related but distinct level of measurement, which may partly explain why a comparable distinction was not detected here. It is possible that circuit-level E/I parameters are simply less sensitive to this biological distinction than direct measures of dopamine function. These parameters reflect GABAergic and NMDA-mediated synaptic balance within the basal nuclei circuit, rather than dopaminergic transmission itself. This circuit's activity is heavily shaped by dopaminergic modulation, but the model does not include direct parameters for dopamine. Emerging extensions of the TVB framework that incorporate dopaminergic parameters directly may help address this limitation in future work (Preti et al., 2026; see Section 3.5.6). The other possibility is that our sample was underpowered to detect an effect of comparable magnitude. It is also worth noting that this is, to the best of our knowledge, the first application of TVB modelling to a dentate-inclusive basal nuclei circuit in SZ, so there is no directly comparable prior finding against which to benchmark the present null result.

A further observation from the normality testing preceding these comparisons is worth noting. Several parameters, including G , J_i , KS , and the overall cost function, deviated from normality

specifically within the TRS subgroup. At the same time, these parameters were normally distributed in HC. This difference may be due to the discrepancy in the group size. With only 16 TRS patients compared to more than twice as many HC participants, a single extreme value carries proportionately more influence on the Shapiro-Wilk statistic in the smaller group. Therefore, this deviation from normality could simply be a statistical artefact of unequal group size. However, another non-mutually exclusive interpretation is consistent with the broader premise, established in Chapter 1 that TRS is not a biologically uniform category, even among patients who fail to respond to standard antipsychotic treatment (Wada et al., 2022). A wider or skewed distribution within the TRS subgroup specifically, even without a detectable shift in central tendency, may reflect this underlying heterogeneity. This possibility would be worth examining directly in a larger TRS sample, for example through measures of within-group variance or subtyping analyses.

3.5.2 Symptom severity associations

When assessing the ability of basal nuclei circuit parameters to predict PANSS scores in the SZ group we observed two patterns. The most prominent observation is that treatment-resistance status was the most consistent predictor across models. TRS patients scored significantly higher than non-TRS patients on PANSS total, negative symptoms, and disorganisation. This finding is expected, although TRS status was assigned independently of PANSS, on the basis of a failure to respond to at least two antipsychotic trials. Therefore, a heavier residual symptom burden in the TRS group is consistent with its classification criterion. The effect of treatment-resistance status on positive symptoms was not significant. This is expected as antipsychotics are quite effective in addressing positive symptomatology (McCutcheon et al., 2019). As both TRS and non-TRS patients are treated with antipsychotics, and positive symptoms tend to respond comparatively well

to these medications regardless of the treatment resistance status (Wada et al., 2022), the two groups would be expected to differ less on this domain than on negative or disorganisation symptoms. This asymmetry likely reflects the predominant mechanism of conventional antipsychotics, blockade of D2 receptors, whose altered activity is implicated in the pathophysiology of positive symptoms specifically (McCutcheon et al., 2019). Negative and cognitive symptoms, by contrast, have been hypothesised to arise from alterations in other neurotransmitter systems. These include glutamatergic, GABAergic, and cholinergic signalling, which are not directly targeted by conventional antipsychotics (Howes et al., 2024). Notably, none of the four circuit parameters (G , J_{NMDA} , J_i , w^+) predicted these outcomes as consistently as TRS status itself did. This suggests that what distinguishes TRS from non-TRS clinically is not fully captured by the circuit-level E/I parameters modelled here. This is broadly consistent with the view presented in Chapter 1 (see Section 1.8) that treatment resistance reflects a qualitatively distinct neurobiological profile rather than a simple severity gradient (White et al., 2016; Wada et al., 2022). At the same time, several features of the present model likely limit its ability to capture this distinction fully. The relatively small sample size constrains the precision with which any true effect of treatment resistance status on circuit parameters could be detected. The model also does not explicitly represent dopaminergic modulation, despite dopamine's role in TRS pathophysiology. Finally, its biophysical granularity is limited in that it does not distinguish between purely excitatory and purely inhibitory connections between regions: the model represents structural connectivity as undirected streamline-based weights rather than signed E/I edges. Any of these factors might explain why the specific circuit parameters examined here do not, on their own, fully capture the distinction between TRS and non-TRS

Moreover, the local inhibitory coupling parameter (J_i), reflecting GABAergic synaptic inhibition within the basal nuclei circuit, predicted disorganisation symptom severity, although the association did not survive correction for multiple comparisons . As this result emerged from a single exploratory model of a newly defined circuit, it is discussed below although its interpretation is treated with caution, rather than dismissed outright.

This finding is consistent with the known behavioural profile of disorganisation symptoms that comprise disorganised speech and behaviour, representing the most overtly behavioural and motor domain of SZ's symptomatology (Wallwork et al., 2012). This is in contrast with the perceptual character of positive symptoms or the affective and agentic character of negative symptoms. The basal nuclei circuit modelled here is itself fundamentally an action-selection system in which the balance between direct- and indirect-pathway outputs governs whether a given movement or behaviour is facilitated or suppressed (Lanciego et al., 2012; see Section 1.5). An increase in local inhibitory tone could plausibly disrupt this balance. It would bias the circuit toward the kind of dysregulated behavioural output reflected specifically by disorganisation symptoms. However, this interpretation should be treated as exploratory, as it emerged from a relatively small sample using a newly defined circuit parcellation with no directly comparable prior finding to corroborate it.

3.5.3 Methodological advancements

This thesis incorporates two methodological advancements relative to prior approaches to modelling basal nuclei circuits in SZ. The first is the integration of the dentate nuclei into the basal nuclei parcellation. Standard atlases used in neuroimaging studies rarely include the dentate nuclei, given their small size and deep cerebellar location (Faris et al., 2024). As a result, despite

having direct, reciprocal anatomical connections to the dopaminergic midbrain (Washburn et al., 2024; Carta et al., 2019) and a demonstrated capacity to modulate prefrontal dopamine release (Mittleman et al., 2008), dentate nuclei are typically excluded from basal nuclei circuit investigation. The inclusion of these nuclei allows the model to capture the full cerebello-basal nuclei-thalamic loop. Comparable connectomic studies, including whole brain analysis conducted on the same patient cohort (Tranfa et al., 2023), have not modelled this specific cerebello-basal nuclei-thalamic loop. This represents a genuine methodological contribution independent of the specific findings reported here. The absence of significant group differences should not be interpreted as evidence that including dentate nuclei in the circuit was unnecessary. Rather, they indicate that, within the present sample, this expanded circuit did not yield parameter-level distinctions detectable at this sample size.

The second advancement is the circuit-specific, rather than whole-brain, scope of the model. The basal nuclei circuit examined here comprised 29 nodes centred on the basal nuclei. It included subcortical, subthalamic, motor-cortical, and cerebellar regions participating in the same loops (Section 3.2), rather than the full cortical and subcortical connectome. As noted above, this network was selected for its implicated role in the SZ pathophysiology, and because it has not been modelled in this way. Extracting it as a dedicated circuit, rather than embedding it within a whole brain model, allowed parameters to be estimated specifically from basal nuclei connectivity and dynamics, rather than being diluted across a much larger network. This is consistent with the view reported in Chapter 1 that basal nuclei dysfunction in SZ concerns specific, parallel cortico-striato-thalamic loops, rather than being distributed uniformly across the brain (Alexander et al., 1986; Haber, 2016). It also means, however, that the model cannot capture potential contributions from regions outside this circuit that have themselves been implicated in SZ and treatment resistance,

such as prefrontal and hippocampal glutamatergic dysfunction (Wada et al., 2022) and the widespread cortical structural and functional connectivity alterations reported using whole-brain approaches in the same patient sample (Tranfa et al., 2023). A circuit-specific model is, by construction, blind to any signal that might reside outside the modelled circuit, and any interaction between this circuit and other, unmodelled networks cannot be assessed with the present approach.

3.5.4 Clinical implications

The present findings carry two implications for clinical practice and future biomarker development, which should be viewed simply as suggestions, rather than mandates. Firstly, the null group-level comparisons indicate that, at least as currently modelled and with limited sample size, the GABAergic and glutamatergic E/I coupling parameters examined here do not yet constitute a usable biomarker for distinguishing TRS from non-TRS, or patients from healthy controls. This does not undermine the broader premise that TRS reflects a distinct neurobiological subtype (Section 1.8). Since treatment-resistance status remained the most consistent predictor of symptom severity in the regression analyses reported here, for now, treatment-response history rather than a circuit-derived marker remains the more practical basis for identifying TRS clinically.

Secondly, and more speculatively, although the association between the local inhibitory coupling parameter (J_i) and disorganisation symptom severity is not robust, it is broadly consistent with a growing body of evidence implicating GABAergic signalling in treatment response and symptom expression in SZ. This includes evidence for a specific role of GABAergic coordination with dopaminergic tone (Bojesen et al., 2025). Disorganisation symptoms, alongside negative and cognitive symptoms, respond poorly to first-line antipsychotic treatment (see Intro), which is thought to act primarily through dopaminergic mechanisms (McCutcheon et al., 2019). If a circuit-

level marker of local inhibitory tone was shown to reliably track disorganisation symptom severity in a larger and independent sample, this could eventually support a different treatment rationale. Rather than relying solely on dopamine-targeting antipsychotics, alternative or additional treatments could specifically target GABAergic function in patients with prominent disorganisation symptoms. This remains a speculative hypothesis that would require replication and validation before any such clinical application could be considered.

More broadly, the dentate-inclusive circuit modelling approach developed in this thesis points to a broader direction for the field. Individualised, biophysically grounded brain models can move beyond group-level comparisons toward characterising circuit function at the level of the single patient (D'Angelo & Jirsa, 2022). This has clear relevance for a disorder highly clinically and biologically heterogeneous as SZ (see Intro).

3.5.5 Limitations

Several limitations should be considered when interpreting these findings. Firstly, subgroup sizes were modest, particularly for the SZ subgroups (16 TRS, 17 non-TRS patients). This limited statistical power to detect small effects and constraining the precision of the regression coefficient estimates reported in Section 3.4.3. Secondly, the study design was cross-sectional. Clinical severity and circuit parameters were both assessed at a single time point. Therefore, it is not possible to determine whether the association observed between J_i and disorganisation symptoms reflects a stable, trait-like feature of the circuit, a state that fluctuates with illness course or treatment, or a marker with prognostic value for future symptom trajectories. A longitudinal design would be required to distinguish between these possibilities. Thirdly, this is, to our knowledge, the first study to apply this dentate-inclusive basal nuclei parcellation within a TVB framework to SZ.

Therefore, the present findings, particularly the weak Ji-disorganisation association, have not yet been tested in an independent sample and should be treated as preliminary until replicated.

3.5.6 Future directions

The limitations outlined above point to several concrete directions for future work. One direction is that higher statistical power is required to detect small effects. The centre (University of Naples “Federico II”) has additional eligible patients of this type who were not included in the present sample and could be used to extend it as a possible short-term goal. It could allow for detecting group-level effects that may have gone undetected here, and would allow better precision in the estimation of the regression models reported in Section 3.4.3. Additionally, a larger, ideally multi-site sample would allow external validation of the results. A second direction would be a longitudinal extension of this research which would follow the patients along the illness course or capture a change of treatment. This would make it possible to determine whether the Ji-disorganisation association reflects a stable trait, a state that tracks clinical fluctuation, or has prognostic value. The present cross-sectional data cannot establish any of these. A third direction, given that this is the first application of this dentate-inclusive basal nuclei parcellation to SZ, would be to pursue independent replication in a separate cohort. It would help establish whether the present findings generalise beyond this sample, and the modelling approach itself is appropriate for this population.

A further direction follows directly from the literature reviewed in Chapter 1. Several biological markers, distinct from those examined here, have been shown to predict subsequent treatment response when measured at baseline. They include striatal dopamine synthesis capacity (Jauhar et al., 2018), D2/3 receptor availability (Wulff et al., 2015), and cortico-striatal GABA-dopamine

coupling (Bojesen et al., 2025). This raises two possibilities for prospective testing. One possibility, relating to these markers, is that circuit-level E/I parameters, and J_i in particular, could be measured at baseline and tested as predictors of subsequent treatment response, for instance, in patients transitioning to clozapine after failing standard antipsychotic trials. Alternatively, and more directly related to the present findings, a prospective design could test whether baseline J_i predicts subsequent course of disorganisation symptoms. If J_i proved to be predictive under either design, it would move from being a cross-sectional correlate to representing a marker with genuine clinical utility.

A related direction concerns the modelling framework itself. Recent work has extended TVB to embed patient-specific dopaminergic parameters into whole brain models. Simulation-based inference was used to estimate these parameters from individual neuroimaging data and simulate the effects of antipsychotic treatment (Preti et al., 2026). Applying this dopamine inclusive approach to the present basal nuclei circuit would allow circuit parameters to capture dopaminergic transmission directly, rather than only its downstream effects on GABAergic and glutamatergic balance. It could also offer a more sensitive means of detecting the group level differences that were not observed here.

Chapter 4: Conclusions

This thesis aimed to characterise excitatory/inhibitory balance within a dentate-inclusive basal nuclei circuit in SZ. It also tested whether the resulting circuit parameters could differentiate SZ patients from HCs, and, within the patient group, TRS from non-TRS patients, and predict symptom severity within the patient group. No parameter differentiated the groups in either the two or three group comparison. The null result is therefore best interpreted in light of the modest subgroup sizes rather than as evidence against circuit-level dysfunction in SZ. Within the patient group, however, treatment-resistance status consistently predicted symptom severity across multiple PANSS domains. The local inhibitory coupling parameter, J_i , was associated with disorganisation symptom severity, although the association was not robust. As it has plausible mechanistic grounding in the basal nuclei's role in action selection, it requires replication before it can be considered genuine.

Independent of these specific findings, the dentate-inclusive parcellation developed in this work constitutes a methodological contribution in its own right. It considers a cerebellar component of the basal nuclei circuit that standard approaches typically overlook. This component has a well-established, yet underexplored, anatomical relationship to the dopaminergic system central to schizophrenia's pathophysiology.

Taken together, these findings do not establish a new biomarker of treatment resistance. However, they do provide a preliminary, hypothesis-generating basis for future work relating basal nuclei circuit dynamics to the clinical heterogeneity of SZ, particularly with respect to disorganisation symptoms and treatment response.

Beyond these specific findings, the basal nuclei circuit developed in this thesis carries broader relevance for future, more clinically oriented modelling work. TVB based approaches have already

demonstrated an ability to generate personalised, subject specific models in other neuropsychiatric and neurodegenerative populations (Monteverdi et al., 2022, 2023). More recently this framework has been extended to capture dopaminergic transmission directly, rather than only its downstream circuit effects (Preti et al., 2026; see Section 3.5.6). Incorporating this kind of extension into the present circuit would move it closer to brain digital twins, which are patient specific simulations capable of predicting individualised treatment response and directly informing clinical decision-making. Framed this way, the dentate-inclusive basal nuclei circuit developed here is not only a methodological contribution to the study of SZ, but a concrete starting point toward that longer-term goal.

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