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# **Biophysical modeling of excitation/inhibition balance and conversion to psychosis in the clinical high risk syndrome**

## **Running title:**

E/I imbalance and conversion to psychosis

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## **Abstract**

### **Background**

Reduced mismatch negativity (MMN) and P300 event-related potential (ERP) components are widely replicated in schizophrenia and are also observed in individuals at clinical high risk for psychosis (CHR-P) who subsequently convert to psychosis. It is unknown whether they reflect changes in excitatory and/or inhibitory synaptic function, both implicated in schizophrenia and considered potential drug targets.

### **Methods**

We analyzed baseline MMN and P300 ERPs from the NAPLS2 study, asking whether altered synaptic excitation, inhibition, or both could explain amplitude reductions in CHR-P (n=583). CHR-P participants who converted to psychosis (CHR-Converters; n=77) or remitted by 24-month follow-up (CHR-Remitters; n=94) were compared on MMN evoked by pitch+duration double-deviant tones and P300 elicited by target tones from passive and active auditory oddball paradigms, respectively. Biophysical modeling was used to infer (excitatory) pyramidal cell and (inhibitory) interneuron function from both MMN and P300 ERPs.

### **Results**

MMN and P300 amplitude reductions in future CHR-Converters relative to CHR-Remitters were best explained by reduced pyramidal cell excitability (posterior probability  $P > .95$  of a group-by-condition interaction effect). In simulations, reduced pyramidal cell excitability suppressed deviant and target ERPs. Within CHR-Converters, more severe positive symptoms were associated with disinhibition of pyramidal cells ( $P > .99$ ).

### **Conclusions**

Results mirror previous findings in schizophrenia and suggest that reduced pyramidal cell excitability is present at baseline in future CHR-Converters, consistent with the hypothesis that hypofunction of pyramidal cells is a primary pathology in schizophrenia, rather than a consequence of chronic illness. Positive symptoms among CHR-Converters may reflect compensatory downregulation of inhibition.

**Key words:** Clinical high risk for psychosis, dynamic causal modeling, biophysical modeling, MMN, P300, E/I balance

## Introduction

The onset of psychotic disorders like schizophrenia is commonly preceded by a prodrome marked by attenuated psychotic symptoms of sub-threshold severity, duration, and/or conviction (1,2). Individuals meeting criteria for this “attenuated psychosis syndrome” are considered at clinical high risk for psychosis (CHR-P) (3). Meta-analytic estimates suggest that approximately 26% of CHR-P individuals develop a psychotic disorder within 2-3 years (4), while one of the largest scale studies conducted to date reported a smaller 2-year conversion rate of 16% (5,6). About 46% remit over the same period (7). Crucially, no preventive treatments for CHR-P are available at present – a limitation attributed to the lack of mechanistic models of psychosis onset in CHR-P (8).

Two electroencephalography (EEG)-based measures have emerged as potential biomarkers of psychotic disorders: the mismatch negativity (MMN) and P300 components of auditory event-related potentials (ERPs). Both reflect neural responses to infrequent deviant stimuli relative to frequent standard stimuli. The MMN is evoked in response to deviant sounds in the absence of attention, with participants typically instructed to ignore the sounds and focus on an incidental visual task (9), and is thought to reflect auditory echoic memory and pre-attentive prediction error signaling (9–14). In contrast, the P300, which can be divided into P3a and P3b subcomponents, reflects attention-dependent responses to infrequent stimuli (10). P3a is elicited by ‘novel’ task-irrelevant distractor stimuli and reflects exogenous bottom-up attention switching, while P3b is elicited by infrequent task-relevant ‘target’ stimuli requiring a response and is related to endogenous top-down attentional allocation (15,16).

Reduced MMN (effect size  $[ES]=0.95-0.99$ ) (11,17,18) and P3b ( $ES=0.74-0.85$ ) (19,20) amplitudes are among the most robust findings in schizophrenia. They are also observed in CHR-P individuals (21,22) and have been associated with clinical outcomes in CHR-P (23–31). In the largest longitudinal CHR-P study to date (764 CHR-P, 280 healthy controls [HC]), Hamilton et al. (25,28) found reduced MMN and P3b amplitudes in CHR-P participants who converted to psychosis within 2 years (CHR-Converters). MMN reductions distinguished future CHR-Converters from non-converters (including those with persistent symptoms [CHR-Persistent] and those who remitted from the CHR-P syndrome [CHR-Remitters]) and HC (25). P3b responses were decreased in CHR-Converters and CHR-Persistent relative to CHR-Remitters, who were indistinguishable from HC (28).

An imbalance between excitatory and inhibitory (E/I) circuit function may be a fundamental pathophysiology in psychosis (32,33) and may also underlie MMN and P300 reductions in psychosis spectrum disorders (34,35). Hypofunction of NMDA receptors, induced via NMDA receptor antagonism, reduces MMN (36–40) and P300 (37,40–43) amplitudes. In people with schizophrenia, MMN reductions are associated with lower brain glutamate and GABA levels assessed using proton-magnetic resonance spectroscopy (MRS) (44), potentially implicating both reduced excitation and reduced inhibition. Nevertheless, the most direct evidence for disruptions in both excitatory and inhibitory function derives from post-mortem (45–47) and genetic (48,49) studies, as measuring E/I in humans *in vivo* remains challenging (50,51). Understanding how and when these excitatory and inhibitory dysfunctions arise – and whether one precedes or drives the other – is essential for developing effective preventive interventions.

Biophysical (neural mass) models and dynamic causal modeling (DCM) can, in principle, infer excitatory and inhibitory cell function at the individual level from EEG data (52), making it possible to study the synaptic pathology underlying MMN and P300 reductions non-invasively (34,35). This is achieved by specifying how the activity of neuronal populations maps to the EEG signal and inverting this mapping to estimate model parameters from the recorded data. A recent DCM study of >100 people with schizophrenia found reduced pyramidal cell excitability across four EEG and functional magnetic resonance imaging (MRI) paradigms (53). Interestingly, *disinhibition* correlated with abnormal auditory percepts. These findings suggest a primary hypofunction of excitatory cells, with compensatory downregulation of inhibition – to restore E/I balance – that leads to positive symptoms (32,33,45,53). It is unknown, however, whether these changes occur in CHR-P or are unique to the chronic stage of psychosis due to progressive synaptic loss (54). If this mechanistic account is true, pyramidal cell hypoexcitability should be present in CHR-P individuals, at least in those at greatest risk for conversion.

Here, we apply a new model designed for estimating excitatory and inhibitory cell function (55) to a large CHR-P dataset from the North American Prodrome Longitudinal Study 2 (NAPLS2) (56). We compare CHR-Converters to CHR-Remitters, a distinction crucial for identifying mechanisms of resilience and transition to psychosis. While comparisons with HC help characterize the CHR-P state, the imperative is to find predictors that distinguish clinical outcomes among CHR-P individuals; especially given low conversion rates (4,5). We model two biomarkers that distinguish CHR-Converters and CHR-Remitters across passive (MMN) and active (P3b) auditory oddball paradigms (25,28) to probe the underlying synaptic mechanisms. CHR-Persistent participants exhibited a mixed biomarker profile – with MMN responses resembling CHR-Remitters and P3b responses more like CHR-Converters (25,28) – and were excluded to ensure consistent group comparisons across paradigms. We hypothesized that CHR-Converters would exhibit reduced pyramidal cell excitability – reflecting early excitatory dysfunction as a key driver of illness onset – but a positive relationship between disinhibition and positive symptoms.

## Methods

### *Participants*

Participants were recruited from 8 university-based outpatient programs as part of the multisite, case-control NAPLS2 study (56,57). A total of n=764 individuals meeting criteria for the CHR-P syndrome based on the Structured Interview for Psychosis-Risk Syndromes (1) were followed for 24 months or until they converted to psychosis, with clinical assessments every 6 months. Symptoms were assessed using the Scale of Psychosis-Risk Symptoms (SOPS; (1)), with CHR-Converters meeting Presence of Psychotic Symptoms criteria. Participants who completed the study but no longer met CHR-P criteria at the 24-month assessment were classified as CHR-Remitters. Participants who showed persistent symptoms without meeting conversion criteria at the 24-month assessment (CHR-Persistent) were excluded from this report, which focused on differences between the more ‘extreme’ outcomes: conversion and remission. Additional analyses including CHR-Persistent participants, and comparisons between CHR-Converters and age and sex matched HC, are provided in the **Supplement**.

Among n=583 CHR-P participants who provided usable MMN and/or P300 data (see (25,28) for enrollment details and inclusion criteria), 266 non-converter participants did not complete the 24-month follow-up and could not be assigned to outcome groups with confidence. The final sample included n=77 CHR-Converters and n=94 CHR-Remitters for the MMN paradigm, and n=73 CHR-Converters and n=89 CHR-Remitters for the P300 paradigm (for demographics/clinical characteristics, see **Table 1**). At baseline, 23 CHR-Converters (29.9%) and 16 CHR-Remitters (17.9%) were receiving antipsychotic medication but were included because their clinical history indicated that symptoms were within the CHR-P range (but not psychotic) at the time medication was started (57). To account for medication effects, group-level analyses were repeated 1) excluding medicated individuals and 2) including antipsychotic use at baseline as a covariate (**Supplement**).

### ***Stimuli and task***

Full descriptions of the experimental paradigms are reported elsewhere (25,28). Briefly, the MMN paradigm consisted of infrequent deviant – including duration (633 Hz, 100 ms, 5%), pitch (1000 Hz, 50 ms, 5%), and duration+pitch double-deviant (1000 Hz, 100 ms, 5%) – tones presented in a pseudorandom sequence among frequent standard tones (633 Hz, 50 ms duration, 85%). Participants were asked to ignore the auditory stimuli and engage in a visual oddball task. Only the MMN evoked by double-deviant tones was analyzed in this report, as it was the best predictor of conversion to psychosis, relative to the other deviant types (25).

The P300 paradigm consisted of frequent standard tones (500 Hz, 80%) and randomly interspersed infrequent target tones (1,000 Hz, 10%) and task-irrelevant novel sounds (10%). Participants were instructed to respond only to the target tones by pressing a button with their preferred hand. Response accuracy was high (>98%) after excluding 4 CHR-P participants (1 CHR-Converter) who performed below chance levels (28). Only the P300 evoked by target stimuli (P3b) was analyzed in the current report, as it distinguished conversion from remission outcomes, whereas the P300 to novel stimuli (P3a) showed similar reduction in CHR-P relative to HC participants irrespective of clinical outcome (28).

### ***Data acquisition and preprocessing***

EEG was collected using a BioSemi ActiveTwo high-impedance recording system with a 32-channel or a 64-channel electrode cap (4 study sites each) and digitized at 1024 Hz. For preprocessing, see **Supplement** and (25,28). Averaged ERP waveforms were exported into SPM and downsampled to 250 Hz for sensor-level analyses. For modeling, data were further downsampled to 125 Hz to match the empirical residual autocorrelation with the residual autocorrelation assumed by the model, a procedure shown to improve model recovery (58).

### ***Sensor-level analysis***

This study investigated the neurobiological mechanisms underlying MMN and P3b deficits, rather than the presence of previously established group effects (25,28). Prior sensor-level analyses of this dataset found significantly reduced P3b and MMN amplitudes in CHR-Converters compared to CHR-Remitters (25,28), although the MMN effect did not survive correction for multiple comparisons. For ease of reading, we illustrate sensor-level effects and the time window over which they were expressed using t-tests per timepoint (uncorrected) and report group differences assessed with independent sample t-tests ( $\alpha=0.05$ , two-tailed, uncorrected). MMN was quantified at 6 frontocentral electrodes (F3, Fz, F4, C3, Cz, C4) by subtracting the standard from the double-deviant ERP and computing the mean amplitude 90-170 ms post-stimulus (25). P300 was quantified at electrode Pz by subtracting the standard from the target ERP and computing the mean amplitude 235-400 ms post-stimulus (15,28). Software details are reported in the **Supplement**.

### ***Excitation/inhibition model***

We modeled both paradigms using a canonical microcircuit model designed to estimate excitatory and inhibitory function (55). This neural mass model characterizes the evolution of neuronal populations (voltage, current) over time, with each source consisting of superficial and deep pyramidal cells, spiny stellate cells and inhibitory interneurons (53,59,60). Importantly, Hauke et al. (55) introduced two intrinsic connectivity parameters expressing the difference in E/I between experimental conditions:  $B^{gee}$  and  $B^{gii}$  (**Figure 1**). These parameters determine the synaptic gain or ‘excitability’ of excitatory ( $B^{gee}$ ) and inhibitory ( $B^{gii}$ ) cells, modeled implicitly through inhibitory self-connections. Since these connections are inhibitory, decreased  $B^{gee}$  or  $B^{gii}$  correspond to greater excitatory or inhibitory neuron excitability, respectively.

We assumed that group differences were not due to condition-specific changes in extrinsic (between-source) connections, which were fixed to the grand mean posterior, but instead reflected changes in the condition-specific rebalancing of E/I implicit in intrinsic (within-source) synaptic connections. Notably,  $B^{gee}$  and  $B^{gii}$  were constrained to be global (i.e., equal across regions) to reflect broadly distributed cortical pathology – based on post-mortem studies (54,61–63), structural MRI findings (64–66), and the polygenic nature of schizophrenia (48) – as well as reduce overfitting and obtain more efficient estimates of cortex-wide E/I balance. Additional parameters, including deep pyramidal and spiny stellate excitability, were fixed to reduce the number of free parameters, maximize parameter identifiability and focus on the most likely pathology (55).

We modeled two different task-specific auditory and attention-related networks, including bilateral primary auditory cortex, superior temporal gyrus (STG) and inferior frontal gyrus for the MMN; and STG, inferior frontal junction and intraparietal sulcus for the P300 (**Figure 1C**). Priors over parameters are reported in **Table 2**. For inversion procedures, see **Supplement**.

### ***Model diagnostics***

Model fit (i.e., accuracy) was evaluated using the Pearson correlation ( $r$ ) between observed and predicted responses to standard and deviant or target tones, and the percentage variance explained

( $R^2$ ), both Fisher's  $r$ -to- $z$  transformed for statistical testing (**Figures S1A and S1B**). Due to non-normal distributions indicated by Kolmogorov-Smirnov tests, group differences in Fisher  $z$ -transformed  $r$  and  $R^2$  values were assessed using Mann-Whitney U tests.

Both  $B^{gee}$  and  $B^{gii}$  were recoverable in analyses reported elsewhere (55). To evaluate parameter identifiability, we computed Pearson correlations between  $B^{gee}$  and  $B^{gii}$ . High correlations ( $r > |0.6|$ ) (67) between parameters can reflect the model's inability to disentangle their distinct contributions; in contrast, low correlations suggest that the model is able to estimate each parameter's unique effect (i.e., disentangle or resolve conditional dependencies).

### ***Second-level analysis***

We used parametric empirical Bayes (PEB) (68,69) to test for second-level (between-subject) effects on synaptic parameters. PEB is a Bayesian general linear model that takes both the expectation and covariance of each participant's individual (first-level) parameter estimate into account. We explain variance in first-level E/I parameters ( $B^{gee}$  and  $B^{gii}$ ) across participants with variables of interest (group or symptom severity) and covariates (age, study site, antipsychotic medication). Age-by-group interactions were tested and excluded from the PEB analysis due to lack of significance (**Figure S2**). We report the Bayesian posterior probability (P) for each effect, which quantifies the probability that the effect is present (i.e., non-zero), given the data and model. A  $P > 0.95$  is interpreted as strong evidence for an effect (70).

### ***Posterior predictive checks***

To explore the contribution of  $B^{gee}$  and  $B^{gii}$ , we conducted simulations using posterior parameter estimates from the grand mean inversion (**Supplement**). In each simulation, a single parameter was systematically varied while all the other parameters were held constant at their posterior to evaluate its effect on ERP amplitude. This (sensitivity) analysis discloses the contribution of each parameter to the data features being explained; in this instance the MMN and P300.

## **Results**

### **CHR-Converters show reduced MMN and P300 amplitudes compared to CHR-Remitters**

We analyzed baseline ERP data from passive and active auditory oddball paradigms (**Figure 1A**) in CHR-P participants who converted to psychosis within two years and those who remitted. MMN amplitude (90-170 ms (25)) was significantly reduced in CHR-Converters compared to CHR-Remitters ( $t_{169} = -2.22$ ,  $p = .028$ ). Timepoint-wise t-tests (uncorrected) identified the most prominent effects around 130-160 ms post-stimulus (**Figure 1B, left**). Amplitude of the P3b subcomponent (235-400 ms (28)) was also reduced in CHR-Converters compared to CHR-Remitters ( $t_{160} = -3.22$ ,  $p = .002$ ). Timepoint-wise t-tests

(uncorrected) showed that this deficit extended to the slow wave following the P3b peak (400-630 ms; **Figure 1B, right**).

### **Excitation/inhibition model captures individual variability in MMN and P300**

Our computational model (**Figure 1C**) adequately fit most participants' MMN (**Figure 1D**) and P300 (**Figure 1E**) data, with mean (SD) correlations between observed and predicted responses of  $r=0.78$  (0.12) for the deviant-standard difference waveform and  $r=0.81$  (0.11) for the target-standard difference waveform. Mean  $R^2$  was 0.61 (0.18) for the deviant-standard and 0.67 (0.16) for the target-standard difference waveform. Model fit did not differ significantly between groups (all  $p>0.05$ ).

Correlations between parameter estimates across subjects were un concerning ( $r=-0.04$  for MMN,  $r=0.20$  for P300; **Figures S1C and S1D**), indicating good parameter identifiability.

### **Computational modeling indicates a loss of pyramidal cell excitability in CHR-Converters**

Across both paradigms, we found a consistent condition-specific increase in pyramidal self-inhibition (i.e., decreased excitability) in deviant relative to standard trials ( $P>.99$ ) and target relative to standard trials ( $P>.95$ ) in CHR-Converters compared to CHR-Remitters (**Figures 2A and 2B**). The evidence for these effects remained strong when omitting age and site covariates, and robust to the inclusion of antipsychotic-use covariates (**Figures S4A and S4B**). In the unmedicated subsample ( $n=54$  CHR-Converters,  $n=78$  CHR-Remitters), the evidence for a group difference in pyramidal self-inhibition remained strong for the active ( $P>.95$ ; **Figure S4D**) but not the passive ( $P=.68$ ; **Figure S4C**) oddball.

### **Positive symptoms are associated with increased, rather than decreased, pyramidal cell excitability**

Within CHR-Converters, more severe baseline positive symptoms were associated with decreased pyramidal self-inhibition (i.e., disinhibition) across both tasks (MMN:  $P>.95$ , P300:  $P>.99$ ; **Figures 2C and 2D**), and decreased self-inhibition of interneurons during the MMN paradigm ( $P>.95$ ; **Figure 2C**). These associations were unaltered when analyses were restricted to unmedicated CHR-Converters ( $n=54$ ; **Figures S4E and S4F**). Within CHR-Remitters, more severe baseline positive symptoms were associated with decreased interneuron excitability in the P300 ( $P>.99$ ) but not the MMN paradigm (**Figure S5**).

### **Posterior predictive checks confirm that reduced pyramidal cell excitability explains ERP deficits**

Across both paradigms, two parameter changes led to smaller ERP amplitudes in simulations: reduced pyramidal excitability and increased interneuron excitability. Reducing pyramidal excitability produced smaller MMN (**Figure 3A, top**) and P300 (**Figure 3B, top**) amplitudes due to a strong suppression of the deviant/target ERP and weakly increased standard ERPs, whereas increasing

interneuron excitability had minimal effects on MMN amplitude (**Figure 3A, bottom**) and produced smaller P300 amplitudes (**Figure 3B, bottom**) due to a strong suppression of the target ERP and no change in the standard ERP. Notably, we found no evidence of increased interneuron excitability in CHR-Converters compared to CHR-Remitters, suggesting that only reduced pyramidal excitability can explain the empirical effects.

Note that the E/I parameters model the difference between conditions and thus have opposite effects on the standard and deviant/target by design. However, here, we assessed – through simulations – which synaptic effect could explain MMN and P300 reductions. The observed effects were robust to variation in priors on synaptic gain and cell coupling (**Figures S7-S10**). Additional simulations exploring the interaction between pyramidal and interneuron excitability are reported elsewhere (55).

## Discussion

In the largest longitudinal study of CHR-P individuals to date, previously established ERP deficits in CHR-Converters compared to CHR-Remitters – across two auditory oddball paradigms (25,28) – were best explained by reduced pyramidal cell excitability in future CHR-Converters. For both passive (MMN) and active (P3b) oddball paradigms, baseline positive symptom severity within CHR-Converters was associated with the opposite circuit change: pyramidal cell disinhibition. This is consistent with the hypothesis that, in the early stages of psychotic illness, a primary loss of pyramidal cell excitability is compensated by an allostatic downregulation of inhibition (33,45) – thereby restoring E/I balance. Under this hypothesis, secondary downregulation may precipitate psychotic symptoms.

Crucially, our findings provide evidence that pyramidal cell hypoexcitability – previously observed in chronic schizophrenia (53) and, more recently, in two of three transdiagnostic biotypes composed of people with schizophrenia, bipolar, and schizoaffective disorder (71) – is already present in youth at CHR-P who develop psychosis within 2 years. We observed this deficit in CHR-Converters compared to CHR-Remitters, suggesting that excitatory dysfunction is not merely a general feature of psychosis risk. This also supports the idea that excitatory dysfunction precedes conversion to psychosis, rather than being a consequence of chronic psychotic illness.

Although 17% of CHR-Remitters and 30% of CHR-Converters were taking antipsychotics at baseline, our results were unaltered when antipsychotic use was included as a covariate (cf. (53)), indicating that the observed deficits were unlikely to be driven by medication effects. Antipsychotic use was higher in CHR-Converters, and we cannot exclude the possibility that prior exposure influenced these results, but antipsychotics have generally been found to have small effects on MMN and P300 amplitudes (72–75), consistent with our finding. Analyses restricted to unmedicated participants showed pyramidal hypoexcitability in CHR-Converters compared to CHR-Remitters during the active, but not the passive, oddball task; possibly due to a loss of power or because this subsample underrepresents more severe cases (76–78). Additional analyses revealed an interaction between group and antipsychotic use on pyramidal excitability during the passive oddball task.

Reduced condition-specific pyramidal excitability in CHR-Converters may reflect hypofunction of NMDA receptors and their signaling cascade – and a disproportionate effect of this on the larger oddball waveforms – as NMDA receptor antagonism has consistently been shown to reduce MMN (36,38,40,79,80) and P300 (40–43) amplitudes. While this change in synaptic efficacy could also reflect increased inhibition via parvalbumin-positive (PV) interneurons, postmortem studies suggest that PV interneurons are *hypoactive*, rather than hyperactive, in schizophrenia (81–83). We found no evidence of such a reduction in PV function in CHR-Converters. Our findings challenge the hypothesis that interneuron abnormalities are a primary mechanism in schizophrenia and point to pyramidal cell NMDA receptor hypofunction as a more plausible explanation. This aligns with recent work suggesting that PV interneuron deficits are secondary to reduced excitatory drive (32,45) and evidence that, in rodents, NMDA receptor knockout on pyramidal cells reproduces electrophysiological changes typically observed in schizophrenia (84).

While reduced pyramidal excitability distinguished CHR-Converters from CHR-Remitters, a somewhat paradoxical finding was that greater symptom severity was associated with disinhibition. This mirrors previous findings in chronic schizophrenia: across EEG and functional MRI paradigms, people with schizophrenia showed reduced pyramidal excitability compared to controls, but positive (auditory) symptoms correlated with disinhibition in auditory areas (53). At the sensor-level, 40 Hz power and phase-locking in the auditory steady-state paradigm are reduced in schizophrenia, yet they correlate positively with auditory symptoms (85,86). Similarly, a mega-analysis of MRS studies found reduced levels of glutamate in people with schizophrenia, but a positive correlation between glutamate and positive symptoms (87). These findings are consistent with a compensatory disinhibition hypothesis in which secondary downregulation of inhibition (33,45), and not the primary glutamatergic dysfunction, drives psychotic symptoms.

Our study is not without limitations. First, the design limits our ability to draw causal inferences regarding the role of E/I (im)balance. Although we stratified CHR-P participants by clinical outcome, longitudinal studies are needed to track E/I balance across illness stages and determine whether disinhibition emerges later in the illness trajectory as a compensatory response to earlier reductions in pyramidal excitability, as proposed here. While 1-year and 2-year EEG follow-up data were available in NAPLS2, most conversions occurred within the first year, limiting their utility for understanding pre-conversion changes. Studies with shorter follow-up intervals (88–90) may help address this. This would be particularly informative in genetically at-risk individuals, where E/I balance could be studied before the onset of prodromal symptoms.

Longitudinal designs will also be key for establishing the test-retest reliability of connectivity and synaptic efficacy estimates, for instance by assessing the impact of measurement error and state vs trait-like effects (91). Additionally, animal studies with causal perturbations of excitatory/inhibitory function are needed to validate the parameter estimation. These are critical steps toward translating these parameters into mechanistically informative biomarkers of risk in CHR-P individuals with potential to guide novel treatment development and treatment selection.

Identifying the optimal time window for capturing early neurophysiological changes remains challenging, and complementary approaches using animal (92,93) and induced pluripotent stem cell (94,95) models should also be pursued. Further progress may be achieved by integrating genetic data with biophysical modelling, for instance by relating pyramidal excitability to polygenic risk scores or

variation in genes linked to NMDA receptor function (e.g., *GRIN2A*) (48,49), to clarify whether reduced pyramidal excitability reflects inherited liability. Moreover, studies with clinical control groups are needed to determine the specificity of our findings, as potential comorbidities associated with conversion to psychosis (e.g., mood symptoms, substance use, sleep disturbance) could have contributed to our findings but could not be controlled for given the relatively small sample of CHR-Converters. Future work should also aim to better characterize the CHR-Persistent group.

Lastly, our model was designed to estimate excitatory (superficial pyramidal) and inhibitory (interneuron) function (55). Deep pyramidal and spiny stellate excitability were fixed, and excitability parameters were constrained to be equal across all modelled regions. This limits the potential regional specificity of the results but reduces overparameterization. In this framework, a single parameter explained MMN and P300 deficits in CHR-Converters, reflecting global (rather than region-specific) reductions in pyramidal excitability, and higher positive symptom severity was associated with global cortical disinhibition. This aligns with structural and functional MRI studies in NAPLS2 and 3 cohorts, which found broadly distributed neuroanatomical and connectivity abnormalities in CHR-Converters, including accelerated cortical thinning in prefrontal, temporal and parietal cortex (96–98), and aberrant connectivity within auditory, frontoparietal and attentional networks (99). However, the equality constraint could be relaxed to model gradients of E/I balance across the brain, and studies incorporating positron emission tomography data may help identify regional variability. Similarly, deep pyramidal and spiny stellate excitability could be estimated to evaluate alternative microcircuit mechanisms, for instance granular layer dynamics or thalamocortical input.

In conclusion, biophysical modeling of two auditory oddball paradigms revealed two key findings: a consistent reduction in superficial pyramidal cell excitability in CHR-Converters compared to CHR-Remitters, and an association between positive symptom severity and disinhibition in CHR-Converters. This is consistent with our hypothesis that excitatory hypofunction is a major and primary neurobiological risk factor for psychotic illness, especially schizophrenia, although more work is needed to establish whether it distinguishes diagnosable disorders from persisting subthreshold symptoms. Conversely, disinhibition in cortical circuits may be a compensatory response to pyramidal cell dysfunction contributing to the emergence of psychotic symptoms. These findings have important implications for treatment, particularly during the prodrome, as one might hypothesize the more effective strategy ought to be to target the primary dysfunction (i.e., increase pyramidal excitability) rather than trying to dampen compensatory disinhibition, even if the latter is more directly linked to psychotic symptoms.

### **Code availability**

The analysis code will be made publicly available at [https://github.com/juliarodsan/napls\\_ei](https://github.com/juliarodsan/napls_ei) upon acceptance of the paper. The model code will be made publicly available at [https://github.com/daniel-hauke/dcm\\_ei](https://github.com/daniel-hauke/dcm_ei) (Hauke et al., 2025) upon acceptance of the paper.

### **Data availability**

Access to NAPLS2 EEG data can be arranged through a formal collaboration with the NAPLS2 PIs. Contact Dr. Daniel Mathalon to inquire about such collaborations.

### **Competing Interests**

The authors declare no competing interests.

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## Figure Legends

**Figure 1. Dynamic causal modeling (DCM) of auditory oddball event-related potentials (ERP).** (A) Simplified representations of the passive (top) and active (bottom) auditory oddball paradigms. Difference waves were computed by subtracting the ERP response to standard tones from the response to deviant or target tones. (B) Deviant-standard (left) and target-standard (right) ERP difference waves (mean  $\pm$  SEM), plotted at 6 frontocentral electrodes (F3, Fz, F4, C3, Cz, C4) and at Pz, respectively, for participants at clinical high risk for psychosis who subsequently converted (CHR-Converter, light green) and those who remitted (CHR-Remitter, dark green). Vertical lines indicate the temporal windows used to measure mismatch negativity (MMN) and P300 components. Group differences in amplitude, computed using t-tests at each time point (uncorrected), are indicated below the difference waves. (C) Canonical microcircuit model for estimating E/I balance (53) used to analyze the two ERP paradigms. Bilateral sources in the primary auditory cortex (A1), superior temporal gyrus (STG) and inferior frontal gyrus (IFG) were used for the passive oddball paradigm. Bilateral sources in the STG, inferior frontal junction (IFJ) and intraparietal sulcus (IPS) were used for the active oddball paradigm. Each source consists of interacting populations of superficial and deep pyramidal cells, spiny stellate cells and inhibitory interneurons interconnected according to anatomical constraints. (D) Box and scatter plots showing the distribution of correlation coefficients across CHR-Converter and CHR-Remitter groups for standard tones (left), deviant tones (middle) and the deviant-standard difference wave (right). Each dot represents an individual participant. Group differences were tested using Mann-Whitney U tests applied to Fisher z-transformed correlation coefficients (n.s., not significant). Displayed values are untransformed for ease of interpretation. (E) Same as (D) for standard tones, target tones and the target-standard difference wave in the P300 analysis.

**Figure 2. Group-level analysis of mismatch negativity (MMN) and P300 model parameters.** Panels (A) and (B) show group differences in condition-specific modulation of superficial pyramidal cell self-inhibition ( $B^{gee}$ ) and inhibitory interneuron self-inhibition ( $B^{gii}$ ) in clinical high risk for psychosis (CHR-P) participants who subsequently converted to psychosis (CHR-Converter) compared to CHR-P participants whose symptoms remitted at follow-up (CHR-Remitter) for (A) the MMN paradigm and (B) the P300 paradigm. Asterisks (\*) indicate a significant group effect with a posterior probability of  $P > .95$ . In the microcircuit diagram, parameter increases are illustrated with thick lines. Panels (C) and (D) show condition-specific microcircuit parameters associated with Scale of Psychosis-Risk Syndromes (SOPS; (1)) positive symptoms in (C) the MMN paradigm and (D) the P300 paradigm. Asterisks indicate a significant correlation with a posterior probability of (\*)  $P > .95$  or (\*\*)  $P > .99$ . In the microcircuit diagram, negative associations are illustrated with dotted lines. Across all panels, error bars represent the 95% Bayesian confidence intervals.

**Figure 3. Microcircuit parameter sensitivity analyses.** This figure shows simulations derived from the grand mean model illustrating the effects of varying superficial pyramidal cell self-inhibition ( $B^{gee}$ , top) and inhibitory interneuron self-inhibition ( $B^{gii}$ , bottom) on (A) the deviant-standard difference waveform at 6 frontocentral electrodes (F3, Fz, F4, C3, Cz, C4) and (B) the target-standard difference waveform at electrode Pz. Each line represents a different simulation, in which the connectivity strength of the self-connection was scaled by  $\pm 50\%$  around the posterior estimate ( $E_p$ ), which is shown in black. Warmer colors indicate parameter increases, and cooler colors represent reductions.

## Tables

**Table 1. Demographic and clinical characteristics.**

| Demographic                         | CHR-Converter<br>(n=77) | CHR-Remitter<br>(n=94) | Statistical analysis                    |
|-------------------------------------|-------------------------|------------------------|-----------------------------------------|
| Age (MMN) [mean (SD)]               | 19 (3.6)                | 19 (4.4)               | t=0.00, p=.987                          |
| Age (P300) [mean (SD)]              | 18 (3.6)                | 19 (4.5)               | t=0.09, p=.769                          |
| Female [n (%)]                      | 29 (37.7)               | 47 (50.0)              | $\chi^2=2.61$ , p=.106                  |
| CHR-P syndrome [n (%)] <sup>a</sup> |                         |                        |                                         |
| APSS                                | 73 (94.8)               | 88 (93.6)              | $\chi^2=0.11$ , p=.742                  |
| BIPS                                | 8 (10.4)                | 1 (1.1)                | <b><math>\chi^2=7.38</math>, p=.007</b> |
| GRDS                                | 14 (18.2)               | 11 (11.7)              | $\chi^2=1.42$ , p=.233                  |
| Current antipsychotic use [n (%)]   | 23 (29.9)               | 16 (17.0)              | <b><math>\chi^2=3.97</math>, p=.046</b> |
| SOPS [mean (SD)]                    |                         |                        |                                         |
| Positive                            | 13.1 (4.0)              | 9.4 (4.6)              | <b>t=29.58, p&lt;.001</b>               |
| Negative                            | 12.3 (6.3)              | 10.9 (6.0)             | t=2.02, p=.157                          |
| Disorganization                     | 6.1 (3.9)               | 4.2 (2.9)              | <b>t=13.74, p&lt;.001</b>               |
| General                             | 9.5 (4.3)               | 7.8 (4.4)              | <b>t=6.60, p=.011</b>                   |

T-tests were used to assess group differences in age and Scale of Psychosis-Risk Symptoms (SOPS; (1)) ratings;  $\chi^2$  tests were used to assess group differences in sex, clinical high risk for psychosis (CHR-P), medication and available data between clinical high risk for psychosis participants who subsequently converted to psychosis (CHR-Converter) and clinical high risk for psychosis participants whose symptoms remitted during follow-up (CHR-Remitter). Values are reported as mean (standard deviation [SD]) for continuous variables and as count [n] (percentage [%]) for categorical variables. <sup>a</sup>Criteria for attenuated psychotic symptom syndrome (APSS), brief intermittent psychotic syndrome (BIPS), and genetic risk and deterioration syndrome (GRDS) are not mutually exclusive.

**Table 2. Prior expectation and precision for each model parameter.**

| Param.                       | Description                                                                     | MMN<br>prior mean                                                            | P300<br>prior mean                                                             | Prior precision |
|------------------------------|---------------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------|
| <b>Neuronal source model</b> |                                                                                 |                                                                              |                                                                                |                 |
| <b>A{1}</b>                  | Average extrinsic connectivity<br>(forward, SP to SS)                           | 200                                                                          | 200                                                                            | 1/16            |
| <b>A{2}</b>                  | Average extrinsic connectivity<br>(forward, SP to DP)                           | 25                                                                           | 25                                                                             | 1/16            |
| <b>A{3}</b>                  | Average extrinsic connectivity<br>(backward, DP to SP)                          | 50                                                                           | 50                                                                             | 1/16            |
| <b>A{4}</b>                  | Average extrinsic connectivity<br>(backward, DP to II)                          | 100                                                                          | 100                                                                            | 1/16            |
| <b>B</b>                     | Condition-specific extrinsic<br>connectivity                                    | 0                                                                            | 0                                                                              | 1/8             |
| <b>C</b>                     | Input strength                                                                  | 32                                                                           | 32                                                                             | 1/32            |
| <b>G</b>                     | Average intrinsic connectivity:<br>[ $g_{ee}$ and $g_{ii}$ ]                    | 800                                                                          | 800                                                                            | 1/32            |
| <b>B<sup>g</sup></b>         | Condition-specific intrinsic<br>connectivity: [ $B^{g_{ee}}$ and $B^{g_{ii}}$ ] | 0                                                                            | 0                                                                              | 1/8             |
| <b>T</b>                     | Synaptic time constant:<br>[SS SP II DP]                                        | [16 32 2 128] ms                                                             | [32 128 2 2] ms                                                                | 1/32            |
| <b>D</b>                     | Neuronal delays (all sources):<br>[intrinsic extrinsic]                         | [1 8] ms                                                                     | [1 8] ms                                                                       | 1/64            |
| <b>S</b>                     | Slope of output firing rate<br>function                                         | -1                                                                           | -1                                                                             | 1/64            |
| <b>R</b>                     | Stimulus: [onset dispersion]                                                    | [68 16] ms                                                                   | [100 16] ms                                                                    | 1/1024          |
| <b>Forward model</b>         |                                                                                 |                                                                              |                                                                                |                 |
| <b>Lpos</b>                  | Source locations<br>[MNI coordinates]                                           | [-42 -22 7;<br>46 -14 8;<br>-61 -32 8;<br>59 -25 8;<br>-46 20 8;<br>46 20 8] | [-61 -32 8;<br>59 -25 8;<br>-56 7 29;<br>50 8 30;<br>-33 -42 64;<br>33 -42 64] | 0               |
| <b>L</b>                     | Dipole orientation                                                              | 0                                                                            | 0                                                                              | 64              |
| <b>J</b>                     | Neuronal populations<br>contributing to the EEG:<br>[SS SP II DP]               | [0 1 0 0]                                                                    | [0 1 0 0]                                                                      | 0               |

DP, deep pyramidal neurons; II, inhibitory interneurons; SP, superficial pyramidal neurons; SS, spiny stellate cells.

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