Relating glutamate, conditioned, and clinical hallucinations via 1H-MR Spectroscopy

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Word Count: 150 (Abstract) + 3867 (Abstract + text body)

20 **ABSTRACT**

21 *Background and Hypothesis:* Hallucinations may be driven by an excessive influence of prior
22 expectations on current experience. Initial work has supported that contention and implicated
23 the anterior insula in the weighting of prior beliefs.

24 *Study Design:* Here we induce hallucinated tones by associating tones with the presentation of a
25 visual cue. We find that people with schizophrenia who hear voices are more prone to the effect
26 and using computational modeling we show they overweight their prior beliefs. In the same
27 participants, we also measured glutamate levels in anterior insula, anterior cingulate,
28 dorsolateral prefrontal and auditory cortices, using magnetic resonance spectroscopy.

29 *Study Results:* We found a negative relationship between prior-overweighting and glutamate
30 levels in the insula that was not present for any of the other voxels or parameters.

31 *Conclusions:* Through computational psychiatry, we bridge a pathophysiological theory of
32 psychosis (glutamate hypofunction) with a cognitive model of hallucinations (prior-
33 overweighting) with implications for the development of new treatments for hallucinations.

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35 **Keywords:** Conditioned hallucinations, Predictive Processing, Schizophrenia, Computational
36 Psychiatry; MR Spectroscopy (MRS)

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39 Introduction

40 The predictive processing account of psychosis posits that hallucinations – percepts
41 without an external stimulus – arise when prior beliefs are over-weighted relative to sensory
42 evidence^{1–3}. If the incoming data are less precise (i.e. sensory uncertainty is overestimated),
43 inference will conform to priors and hallucinations will result¹. Participants who hallucinate tend
44 to overweight prior beliefs in experimental tasks, e.g. they can be more readily conditioned to
45 hallucinate an absent tone based on of previous learning that visual stimuli predict tones^{4–6}. Here
46 we replicate and extend this observation, testing the hypothesis that glutamate signaling
47 underwrites the association between hallucinations and strong priors.

48 Predictive processing accounts posit a hierarchy of inference that is recapitulated in the
49 anatomy and physiology of the brain⁷. Forward connections promulgate prediction errors up the
50 hierarchy via AMPA receptor signaling⁷. In contrast, backward connections mediate contextual
51 effects –priors– downwards via NMDA receptors⁷. This division of labor is supported by primate
52 data gathered from the visual system⁸. Blocking NMDA glutamate receptors – for example with
53 the non-competitive NMDA receptor antagonist ketamine – induces a state redolent of
54 endogenous psychosis⁹. It may do so by decreasing glutamatergic neurotransmission via NMDA
55 receptors (hence the NMDA hypofunction model) but in addition, NMDA blockade on GABAergic
56 interneurons increases glutamate release¹⁰ and thus, may increase transmission through AMPA
57 receptors (hyper-glutamatergic accounts)^{11–13}.

58 Proton magnetic resonance spectroscopy (MRS) studies in patients with schizophrenia
59 (SCZ) suggest low glutamate levels¹⁴, although patients with more severe symptoms may have

higher glutamate concentrations^{15–18}. A follow-up study found elevated glutamate levels in left superior temporal gyrus but reduced glutamate in anterior cingulate cortex in hallucinators compared to non-hallucinators¹⁹. We aimed toward to clarify the relationship between hallucinations, psychosis, and glutamate using methods from computational psychiatry^{20–22}.

We invited patients with SCZ, some of whom hallucinate and some of whom do not , as well as healthy control participants (CTR), to complete the conditioned hallucinations task⁴. On a separate occasion we measured glutamate levels in the auditory, anterior insular, anterior cingulate, and right dorsolateral prefrontal cortices. Previous work implicated left anterior insula in perceptual precision weighting and conditioned hallucinations: Powers and colleagues found that conditioned hallucinations engaged insula, while model-based parameters extracted from left insula were significantly greater in hallucinators, compared to non-hallucinators⁴. Based on this tripartite relation between insular activation, model parameters and hallucination status, we predicted that an alteration in glutamate levels in left anterior insula might play a role in endogenous psychosis and prior overweighting. The other three voxels were chosen based on their established link with other tasks used in the project (presented elsewhere) and were analyzed in a purely exploratory fashion.

Methods

Participants

Thirty-six SCZ and 24 CTR participated in the study (see **Table 1** for participant demographics). They were recruited across two sites: the Connecticut Mental Health Center (CMHC), at Yale University and the Maryland Psychiatric Research Center (MPRC), at the University of Maryland School of Medicine. Participants were recruited via local advertisements or referred to the study through their clinician. Exclusion criteria included: 1) any neurological disorder or head trauma resulting in loss of consciousness or sustained deficits; 2) any recreational drug or alcohol use meeting criteria for at-risk drinking (>2 drinks/day or 14 drinks/week for males, >1 drink/day or 7 drinks/week for females) for one month prior to enrollment or substance use disorder for 12 months prior to enrollment; 3) left-handedness; 4) self-reported abnormal hearing or vision; 5) any contraindication for MRI scanning; and 6) pregnancy for female participants. All SCZ were taking antipsychotic medication (**Table 1**). CTR had no family history of psychotic disorders, had not been previously diagnosed with a psychiatric disorder and had never been treated with psychotropic medications. All subjects gave written informed consent prior to the study, in accordance with the declaration of Helsinki. All procedures were approved by institutional review boards at Yale University and the University of Maryland School of Medicine.

Clinical procedures

Diagnoses were confirmed with the Structured Clinical Interview for DSM-5 (SCID-5). The Brief Psychiatric Rating Scale (BPRS) was used to assess symptom severity (**Table 1**). Item 12 of the BPRS was used to separate SCZ into hallucinators (SCZH⁺) and non-hallucinators (SCZH⁻). Hallucinators had a score larger than 1. The SCZ group comprised 18 hallucinators (11 patients

had moderate-to-severe (BPRS-12=5) or severe (BPRS-12=6) hallucinations; the majority experienced auditory hallucinations) and 17 non-hallucinators (**Figure 1C**). None of the CTR endorsed any hallucinations (BPRS-12=1).

Table 1: Participant Characteristics (mean (SD))

<i>Variables</i>	CTR (n=24)	SCZH⁻ (n=17)	SCZH⁺ (n=18)	Statistic	p value
Age	34.8 (10.3)	31.3 (9.6)	35.5 (10.7)	$F=0.86$	0.43
Gender	10/14	11/6	13/5	$\chi^2=4.42$	0.11
Race (African American/Caucasian/other/missing)	3 17 3 1	8 9 0 0	4 12 1 1	$\chi^2=8.94$	0.18
Participant Education	15.8 (1.9)	14.1 (1.2)	14.5 (1.6)	$F=6.42$	0.003
Maternal Education	14.6 (4.0)	14.5 (2.4)	13.7 (5.5)	$F=0.31$	0.73
Paternal Education	14.5 (4.6)	14.0 (4.7)	14.0 (6.9)	$F=0.05$	0.95
Neurocognitive test results					
WTAR	114.2 (13.8)	101.2 (28.5)	112.4 (9.1)	$F=1.47$	0.39
MD Processing Speed	55.2 (14.0)	42.5 (14.4)	45.2 (16.2)	$F=3.31$	0.04
MD Working Memory	55.8 (7.9)	43.1 (15.2)	46.4 (16.6)	$F=4.03$	0.02
MD Verbal Learning	49.2 (6.3)	42.9 (14.5)	42.3 (15.7)	$F=1.81$	0.19
Clinical Ratings					
BPRS Hallucinatory Behavior	1.0 (0.0)	1.0 (0.0)	4.7 (1.2)	-	-
BPRS Delusions	2.0 (0.0)	3.6 (1.8)	5.8 (1.8)	$t=3.53^1$	0.001¹
BPRS Negative Symptoms	3.3 (1.1)	6.1 (2.4)	4.9 (1.7)	$t=-1.72^1$	0.09 ¹
Duration of Illness (yrs)		8.4 (8.3)	13.4 (11.4)	$t=1.45$	0.16
Medication					
Antipsychotic (Atypical Typical)		16 1	15 3	$\chi^2=1.00$	0.32
Antipsychotic medication: CPZ equivalents (mg)		278.4 (259.5)	388.47 (208.98)	$t=0.58$	0.57
Other psychotropic medication					
Antidepressant + Benzodiazepine + Mood stabilizer		1	0		
Antidepressant+ Benzodiazepine		0	3		
Benzodiazepine		0	3		
Antidepressant		4	4		
Mood stabilizer		3	0		

WTAR=Wechsler Test of Adult Reading, measure of premorbid intelligence; MD Working Memory= Working memory domain (MATRICS); MD Processing Speed= processing speed domain (MATRICS); MD Verbal Learning=verbal learning domain (MATRICS); CPZ= chlorpromazine equivalent; BPRS Delusions=Suspiciousness+Unusual Thought Content; BPRS Negative Symptoms=Emotional Withdrawal+Motor Retardation+Blunted Affect;

¹ SCZH⁻ vs. SCZH⁺

Conditioned hallucinations task

Participants were instructed to listen for a 1 kHz tone, embedded in white noise and presented concurrently with a flashed visual stimulus (light- and dark-gray checkerboard) on a black background (**Figure 1A**). Stimulus presentation and data collection were controlled using Matlab 2017b (Mathworks, Natick, MA) and Psychtoolbox 3.0.12.

Threshold estimation was followed by 12 blocks of 30 trials. In each trial, a checkerboard flashed on the screen and a tone was played simultaneously at 25%, 50% or 75% detection-likelihood tone intensity. Importantly, the tone was omitted on some trials (no-tone condition) (**Figure 1B, left**). Trials were pseudorandomized within block. The likelihood of threshold tone presentation decreased non-linearly over blocks. The presentation of subthreshold and no-tone trials increased (**Figure 1B, right**). This distribution encouraged initial learning of audio-visual associations and then offered more opportunities for conditioned hallucinations (CH) later in the experiment. Participants were instructed to press one response button if they heard a tone and another button to indicate that they heard no tone. They also held the response button down longer to indicate higher confidence in their choice. More information about the task and the stimuli can be found in **Supplementary Methods**.

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Figure 1: The conditioned hallucinations task. (A.) Participants worked to detect a tone embedded in noise and presented concurrently with a visual checkerboard **(B.)** We estimated individual psychometric curves for tone detection and varied tone intensity over 12 blocks of 30 trials (left). High-intensity tones were more likely early and low-intensity and absent tones were more likely later (right). **(C.)** Our sample consisted of 3, demographically-matched groups: 24 healthy controls (CTR; red), 17 schizophrenia-

patients without hallucinations (SCZH⁻; dark blue) and 18 schizophrenia-patients with hallucinations (SCZH⁺; light blue).

MRS data acquisition

Twenty-one CTR, 17 SCZH⁻ and 16 SCZH⁺ of our initial CH sample also completed (on a different day) a 1H-MRS session (**Table S1**) at the Yale Magnetic Resonance Research Center or the University of Maryland Center for Brain Imaging Research. Participants were asked to stay awake and keep their eyes closed. Spectra were acquired from four voxels encompassing the anterior cingulate cortex (ACC), left anterior insula (LIN), right dorsolateral PFC (rdlPFC), and left auditory cortex (LAC) (see **Figure 4A-D**) We focused on “Glx” (Glutamate and Glutamine) which is reliably quantified with PRESS at 3T. More details about MRS can be found in the **Supplementary Methods**.

Statistical analysis

The main variables of interest were the CH rate and confidence in CH. We also computed the number of and confidence in ‘Yes’ responses for trials where the tone was present (25%, 50% and 75%), as well as the confidence ratings when responding ‘No’. No-response trials were discarded from further analysis. All the analyses were performed using the Statistics toolbox of MATLAB R2019b. Details about the statistical analysis can be found in the **Supplementary Methods**.

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156 **Hierarchical Gaussian Filter**

157 To probe the computational mechanisms underlying conditioned hallucinations, we fitted
 158 variants of the Hierarchical Gaussian Filter (HGF)^{23,24} to the behavioral data^{4,6}. The HGF toolbox
 159 (v.5.3.2) is freely available for download in the TAPAS package at
 160 <https://translationalneuromodeling.github.io/tapas>.

161 The HGF is a generic hierarchical Bayesian model for inference in volatile environments.
 162 It consists of hierarchically organized states in which learning at higher levels determines learning
 163 at lower levels, by adjusting their learning rate. The lower levels, in turn, send precision-weighted
 164 prediction errors to the higher levels, updating posterior means on a trial-by-trial basis. Our
 165 generative model consists of three hidden states (X_1 , X_2 , X_3) and an observation (U). The hidden
 166 states represent a low-level perceptual belief (X_1), audio-visual associations (X_2), and the
 167 volatility of those associations (X_3) – how rapidly they change over time. Second- and third-level
 168 states evolve as hierarchical-coupled Gaussian random walks, controlled by parameters ω_2 and
 169 ω_3 respectively (audio-visual association and volatility evolution rates). X_2 – X_3 coupling
 170 parameter κ and initial beliefs μ_{02} and μ_{03} were fixed (**Table S3**).

171 Our three-level perceptual model was paired with a Softmax decision model:

$$172 \quad P("Yes" | X_{tone}) = f(X_{tone}) = \frac{1}{1 + \exp(-\beta X_{tone})} \quad (1)$$

A sigmoid function wherein β is a positive real number that corresponds to the inverse decision temperature (determining the slope of the sigmoid) and it is a free parameter and X_{tone} is the posterior probability of a tone being present given the subject's prior belief and the sensory input (intensity of tone). Formally, this can be described as the posterior mean of a beta distribution:

$$X_{tone} = p + \frac{1}{1 + \nu} (s - p) \quad (2)$$

where s is the expected detection rate (depends on the trial-type: 0.25, 0.5 or 0.75) and p is the prior expectation regarding the presence of a tone and relies on the audio-visual association that the subject has learnt so far (it is equal to $\hat{\mu}_1^{23}$). Crucially, the relative contribution of prior p , compared to sensory input s , was controlled by parameter ν (an index of prior weighting, akin to Kalman gain²⁵), and was specific to each subject. Based on the strong-prior theory of hallucinations, we expected higher ν values in the SCZH⁺ group.

Eight variants of the HGF model were fitted to the behavioral data ('Yes'/'No' responses), each with different sets of free / fixed parameters (**Table S3**). The models were inverted at the subject-level, using trial-by-trial tone intensities and participant responses. The best-fitting model was detected through a Bayesian model comparison procedure based on the protected exceedance probability²⁶.

Results

Sample characteristics

Participant demographics are presented in **Table 1**. The groups were matched for age and sex, but there was a significant difference in years of education ($F(2)=6.42$, $p=0.003$), mainly due to a difference between patients and controls (CTR vs SCZH⁻: $p=0.002$; CTR vs SCZH⁺: $p=0.03$; SCZH⁻ vs SCZH⁺: $p=0.36$). Hallucinators and non-hallucinators were also matched for duration of illness as well as severity of negative symptoms.

Behavior

Detection threshold estimates did not differ between groups (CTR: -17.77 ± 2.85 dBSNR; SCZH⁻: -19.29 ± 4.69 dBSNR; SCZH⁺: -17.91 ± 4.66 dBSNR; $p=0.90$). There was also no difference between groups in the number of missed trials ($p=0.11$).

In agreement with previous reports^{4,6}, we found a significant effect of group on CH ($\chi^2(2)=7.68$, $p=0.022$), with SCZH⁺ endorsing more CH than SCZH⁻ ($z=2.23$, $p=0.026$) and CTR ($z=2.53$, $p=0.011$) (**Figure 2A**). No difference was observed between CTR and SCZH⁻ ($p=0.86$), or between CTR and SCZ (collapsed SCZ⁺ and SCZ⁻ groups) ($p=0.11$), indicating that the effect is specific to SCZs who hallucinate. Importantly, we also found a significant positive correlation between the percentage of endorsed CH and hallucination-severity in the whole sample ($r_s=0.341$, $p_s=0.008$; remained significant after controlling for site ($r_{s,site}=0.326$, $p_{s,site}=0.013$) and diagnosis ($r_{s,diagnosis}=0.273$, $p_{s,diagnosis}=0.038$)) and in patients ($r_s=0.33$, $p_s=0.05$) (**Figure 2B**).

Beyond no-tone trials, no significant differences were observed in the number of hits ('Yes' responses) at the 75% ($p=0.65$) and 50% detection conditions ($p=0.42$), while at the 25%

detection condition a significant difference was evidenced only between SCZH⁺ and SCZH⁻, with SCZH⁺ achieving more hits ($z=2.05$, $p=0.041$) (**Figure S1**). Additionally, we found no differences in reported confidence between groups, but observed the predicted profile across conditions (increase in reported confidence in 'Yes' responses (decrease in 'No' responses), from no-tone to 75% detection condition) (**Figure S2**). Finally, we found a positive correlation between CH and confidence ratings related to CH ($r_s=0.310$, $p_s=0.018$; $r_{s,site}=0.285$, $p_{s,site}=0.032$; $r_{s,diagnosis}=0.295$, $p_{s,diagnosis}=0.026$): subjects who endorsed more CH also reported more confidence in their CH (**Figure S3**).

Figure 2: Conditioned hallucinations and clinical hallucinations. (A.) Conditioned hallucinations rate was significantly elevated in SCZH⁺, compared to SCZH⁻ or CTR. Error bars represent ± 1 SEM. **(B.)** The conditioned hallucinations rate correlated with clinical hallucination severity. Red: CTR; Blue: SCZ.

Computational modeling

Model 4 (free parameters: ω_2 , β and ν ; ω_3 was fixed; **Figure 3A**) emerged as a clear winner (PEP₄=0.999; groups did not differ in model fit) (**Figure S4**), consequently all the following results are with respect to this model, unless mentioned otherwise. Note that adding ν significantly increased log-model evidence, despite increasing the complexity of the model.

We found no significant differences in parameter estimates between groups (ω_2 : $p=0.996$; β : $p=0.20$; ν : $p=0.30$) (**Figure S5**), except for a trend for lower β in hallucinators (SCZH⁺) as compared to non-hallucinators (CTR and SCZH⁻ collapsed) ($p=0.07$). Nonetheless, we found significant correlations between CH and β ($r_s=-0.72$, $p_s<0.001$; $r_{s,site}=-0.71$, $p_{s,site}<0.001$; $r_{s,diagnosis}=-0.72$, $p_{s,diagnosis}<0.001$) (**Figure 3D**) as well as ν ($r_s=0.59$, $p_s<0.001$; $r_{s,site}=0.56$, $p_{s,site}<0.001$; $r_{s,diagnosis}=0.57$, $p_{s,diagnosis}<0.001$) (**Figure 3B**). In other words, endorsement of more CH was related with more stochastic decisions and stronger prior weighting (the 2 parameters were not correlated $r_s=-0.10$, $p_s=0.45$). Interestingly, although confidence ratings were not used to fit model parameters, we observed a correlation between confidence in reporting CH and ν ($r_s=0.46$, $p_s<0.001$; $r_{s,site}=0.44$, $p_{s,site}<0.001$; $r_{s,diagnosis}=0.44$, $p_{s,diagnosis}<0.001$) (**Figure 3C**). Finally, with regard to belief trajectories, we found, that SZH⁺ had a tendency to update their perceptual (X_1) and contingency beliefs (X_2) less (X_1 : a trend for elevated X_1 beliefs in SZH⁺ compared to CTR ($p=0.097$); X_2 : a trend for elevated X_2 beliefs in SZH⁺ compared to CTR ($p=0.069$) and a significant block effect ($t(409)=-2.15$, $p=0.032$); X_3 : a significant block effect ($t(409)=4.18$, $p<0.001$)).

Figure 3: Hierarchical Gaussian Filter. (A.) Illustration of the (best-performing) HGF model (perceptual and decision component) that was fitted to behavioral data (left). Gray nodes correspond to states (U : Sensory inputs; X_1 : Probability of a tone being present; X_2 : Audiovisual association; X_3 : Volatility of the audiovisual association), orange nodes to parameters (ω_2 ; v ; β) and the green node to response/percept. SCZH⁺ showed a tendency towards reduced updating of their perceptual (X_1) and contingency (X_2) beliefs (right – middle and lower panels). We found no group-effect on volatility estimates (X_3 ; right upper panel). Shaded areas represent ± 1 SEM. **(B,C,D.)** Prior weighting (v) correlated with CH rate **(B.)** and CH-related confidence **(C.)**. Inverse temperature (β) correlated only with CH rate **(D.)**. Red: CTR; Blue: SCZ

MR Spectroscopy

Glx levels were measured in four brain regions (LIN, ACC, LAC and rdIPFC) (**Figure 4A-D**). We hypothesized that prior weights (ν) might be encoded in (or associated with) LIN⁴. The following datasets were excluded from further analyses, due to poor spectral quality: 1 from the LAC (1 SCZH⁻), 2 from the ACC (2 SCZH⁺) and 2 from the rdIPFC (2 SCZH⁻). Regional concentrations of Glx and spectral quality are presented in **Table S2**. We found no differences in Glx in any of the four regions (or in total Glx), except for a trend for lower Glx concentration in SCZH⁺ in LIN (**Figure S6**). Furthermore, in agreement with our hypothesis, we observed a significant negative correlation between Glx concentration in LIN and the ν parameter ($r_s=-0.28$, $p_s=0.043$; $r_{s,age}=-0.30$, $p_{s,age}=0.027$; but $r_{s,site}=-0.20$, $p_{s,site}=0.14$), with stronger prior weighting (higher ν) being associated with lower Glx levels (**Figure 4E**) (trend-wise correlation when controlling for diagnosis: $r_{s,diagnosis}=-0.25$, $p_{s,diagnosis}=0.068$ or medication: $r_{s,medication}=-0.26$, $p_{s,medication}=0.056$; but significant when we also took into account age: $r_{s,diagnosis,age}=-0.28$, $p_{s,diagnosis,age}=0.046$; $r_{s,medication,age}=-0.29$, $p_{s,medication,age}=0.037$). Crucially, ν did not correlate with Glx in any other region (ACC: $r_s=-0.20$, $p_s=0.15$; LAC: $r_s=-0.16$, $p_s=0.24$; rdIPFC: $r_s=0.16$, $p_s=0.24$; correlations remained non-significant after controlling for diagnosis and age) (**Figure S7**) or with total Glx ($r_s=-0.12$, $p_s=0.39$) and Glx in LIN did not correlate with β ($r_s=0.12$, $p_s=0.37$), CH ($r_s=-0.21$, $p_s=0.12$; trend-wise negative correlation when controlling for age: $r_{s,age}=-0.24$, $p_{s,age}=0.081$), BPRS-12 ($r_s=-0.19$, $p_s=0.18$), age ($r_s=-0.17$, $p_s=0.22$) or medication ($r_s=-0.14$, $p_s=0.32$). Stepwise linear regressions with ν as dependent variable and the four Glx levels as potential predictors (with and without “site” as a predictor) or Glx in LIN as dependent variable and β , ν as potential predictors confirmed that the only significant predictor of ν is the Glx concentration in LIN ($F(53)=4.2$, $p=0.045$).

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282 **Figure 4: MR Spectroscopy – voxels and correlation with model parameters. (A-D.)** Illustration of MRS
 283 voxel placement: **(A.)** ACC, **(B.)** LIN, **(C.)** LAC and **(D.)** rdIPFC. **(E.)** Correlation between the prior weighting
 284 and Glx level in LIN. Red: CTR; Blue: SCZ.

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286 Discussion

287 Using a conditioned hallucinations task to probe prior-weighting^{4,6}, and MRS to measure
 288 glutamate levels we replicated and extended previous findings regarding the neurobiology of

hallucinations. In a previous functional neuroimaging study insula cortex responses were associated with conditioned hallucinations and prior-weighting⁴. We found that patients who hallucinate endorse more CH in comparison to non-hallucinators and healthy controls, and CH rate correlated with ratings of hallucinations outside the laboratory, in agreement with previous reports^{4,6}. Additionally, participants who endorsed more CH exhibited stronger prior weighting (higher ν) and more stochastic decisions (lower β), while hallucinators were more rigid with regard to their perceptual beliefs (flatter X_1 , X_2 beliefs, i.e. reduced belief updating). Finally, we observed a negative correlation between prior-weighting and anterior insula Glx levels, but no relationship with sensory or association cortices.

Our findings are consistent with the results of previous functional imaging studies suggesting the engagement of anterior insula in CH⁴ and in AVH^{27,28}. We speculate that the negative correlation between priors and insular Glx might be driven by a hypofunction of glutamatergic (NMDA) receptors situated on inhibitory interneurons, resulting in disinhibition of the anterior insula (also observed with ketamine infusion in healthy volunteers²⁹). Future studies are needed to further explore the exact nature of the underlying biophysical mechanisms.

Subtle alterations in glutamate transmission and excitation / inhibition balance play a critical role in the pathophysiology of SCZ^{30–32}. A mega-analysis suggested lower glutamate in SCZ, perhaps as a function of medication status, with elevations in those who were more severely ill¹⁷. Some MRS studies have compared hallucinators with non-hallucinators, with mixed results. In sensory areas, a recent study found higher glutamate and glutamine in SCZ compared to CTR³³ while another study found reduced Glu in the occipital cortex in SCZ and their healthy relatives,

suggesting an association with illness liability³⁴. Other studies found reduced Glx concentrations in the auditory cortex in patients compared to healthy controls, but elevated Glx in the same region in hallucinators compared to non-hallucinators^{18,19}. Our study went a step further, suggesting a functional interpretation to those neurochemical observations. We suggest that glutamate levels in left anterior insula are associated with (and might encode) the precision of prior distributions which, combined with sensory inputs, give rise to percepts. Low glutamate concentrations are related to overly-precise priors and hallucinations¹.

Prior weighting correlated with glutamate levels specifically in LIN, and not in any other voxel (LAC, ACC or rdIPFC). Several studies have implicated insula in the pathophysiology and computational anatomy of hallucinations: Powers et al found that CH were associated with a stronger insula response in people who hear voices and had strong beliefs in the visual-auditory association during the task. Other studies have demonstrated a link between anterior insula and hallucinations, directly (e.g.^{27,35–38}) or indirectly (e.g.³⁹). That being said, other brain regions, not explored in the present study, might also be implicated in perceptual precision weighting. A good candidate is STS, for which a tripartite relation with CH and hallucinations has also been observed⁴. Importantly, the lack of correlation between ν and global Glx can be interpreted as evidence against a global cortical glutamate theory of psychosis/hallucinations (in line with predominant glutamatergic theories positing a widespread cortical NMDA hypofunction) and more in favor of localized hypo-glutamatergia.

Some predictive processing theories of psychosis posit that strong high-level priors are paradoxically driven by weak lower-level priors (or strong prediction errors)². Such a conclusion

appears incompatible with the present results. If high-level strong priors were driven by low-level weak priors, we would expect significant but opposite associations between prior strength and low-level (LAC) / high-level (LIN) glutamate concentrations. Instead, we only observed a negative correlation between insular Glx and v , which is compatible with high-level prediction errors being driven either by within-insula aberrant prediction errors, likely tethered to neuromodulators (dopamine, acetylcholine or serotonin)² or by abnormalities in a parallel hierarchy, e.g. weak egocentric corollary discharge signals⁴⁰. For instance, low glutamate concentration might be the result of excessive striatal dopamine release, which has also been linked to overreliance on prior expectations⁴¹ and increased detection of missing tones in a conditioned hallucinations task⁵.

One limitation is that patients were classified as hallucinators based solely on their current experiences and not on their history. A more careful examination of the psychotic symptoms' trajectory in a small subset of the participants (not presented here) revealed important variability even within subgroups, which might have obscured the most nuanced differences. This might explain why we did not find group differences in model parameters or in Glx levels (only trends), although medication and the moderate level of hallucinations (40% of hallucinators scored below 5 in BPRS-12) might have played a role too. Furthermore, three participants exhibited very high CH rates (~80%), a common behavior in CH tasks^{4,6}. Despite thorough training and exhaustive debriefing, it is difficult to know for certain whether those outliers reflect extreme but meaningful cases of conditioned hallucinations or poor performance. Finally, it is important to highlight the tentative nature of our MRS results: our hypothesis that glutamate concentration in anterior insula (and not in any other region) might be related to prior

weighting was entirely based on functional (fMRI) data⁴ and our result, although significant, would not survive a correction for multiple comparisons. Consequently, our conclusions, as well as the precise mechanisms underwriting the suggested associations, warrant further empirical attention.

In summary, this study represents a preliminary effort to describe a multiscale explanation of hallucinations, spanning behavior (conditioned hallucinations), information processing (strong priors) and neurochemistry (glutamate in LIN). Although this work bears further replication and extension, it provides neurochemical evidence to the relevance of prior beliefs to psychotic symptoms.

Conflict of interest: The authors report no conflicts of interest

Acknowledgements: This work was supported by R01MH12887 (JG/PRC), the Yale University Department of Psychiatry, the Connecticut Mental Health Center (CMHC) and Connecticut State Department of Mental Health and Addiction Services (DMHAS). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. We are grateful to Sarah Murphy for assistance with data collection.

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Supplementary Methods

CH task

Prior to the experiment, participants completed a short practice session which was repeated until their responses were at 85% detection accuracy. The main experiment took place in an MRI scanner and consisted of two parts. First, we determined individual 75% detection thresholds, using the QUEST maximum likelihood-based procedure for threshold estimation⁴². This was implemented in two 40-trial initially-ascending interleaved staircases, with step-size determined by QUEST based upon participant responses. We also estimated 25% and 50% detection-likelihood tone intensities, by fitting a psychometric function to the QUEST-computed 75% likelihood of detection of noise-embedded tone (**Figure 1B, left**)⁴³.

Throughout the experiment, participants were instructed to keep their eyes on a fixation cross. Trials were structured as follows (**Figure 1A**): there was a 500- to 1000-ms fixation from trial start, followed by the simultaneous presentation of the checkerboard and the tone (if present), for 1 s. Participant responses were recorded for 1000 to 1500 ms after stimulus offset. During the twelve main blocks, there was an additional 2000-ms period to record confidence-rating response, during which participants could hold down the response button to indicate their confidence level.

CH stimuli

A white visual fixation cross was present on a black background throughout the experiment. The visual stimulus was a 4×7 gray-on black checkerboard pattern, with gray squares at 25% brightness to maximize visual stimulation and minimize after-effect. The auditory stimulus consisted of a 1-kHz pure tone with a 100-ms tapered envelope to prevent transient effects and was presented via magnetic-resonance-compatible supra-aural headphones (Resonance Technology Corporation, Model#650-060). Participants were provided with foam earplugs for additional protection from scanner noise, which was estimated to be at 130dB SPL. In order to provide a consistent acoustic background for our auditory detection experiment, broadband white noise was presented at 130dB SPL; given the 40-dB attenuation afforded by the headphones, this was estimated to correspond to a level that was 40dB SPL louder than the scanner noise.

1H-MR Spectroscopy

We used Siemens 3T PRISMA MRI systems equipped with a 32-channel phase array head coils. Spectra were acquired from voxels encompassing the anterior cingulate cortex ($2 \times 2 \times 1.5$ cm) (ACC), left anterior insula ($2 \times 1.5 \times 1.5$ cm) (LIN), right dorsolateral PFC ($2 \times 2 \times 2$ cm) (rdlPFC), and left auditory cortex ($2.5 \times 1.5 \times 2.0$ cm) (LAC) (see **Figure 4A-D**) using PRESS localization (TR/TE= 2000/30ms, NEX=128 for the anterior cingulate, and 256 for other voxels, 2500-Hz spectral width, 2048 complex points). Water unsuppressed spectra (NEX=16) were acquired for referencing, as well for phase and eddy current correction. Spectra were analyzed with LCModel^{44,45} using a basis set that included alanine, aspartate, creatine, γ -aminobutyric acid,

glucose, glutamate (Glu), glutamine (Gln), glutathione, glycine, glycerophosphocholine, lactate, myo-Inositol, N-acetylaspartate, N-acetylaspartylglutamate, phosphocholine, phosphocreatine, phosphoroylethanolamine, scyllo-Inositol, and taurine generated in GAVA⁴⁶. Spectra were visually inspected for quality and only spectra with SNR > 10 and water FWHM < 0.1ppm were included. Metabolites were referenced to water and only metabolites with good fits (i.e. percent standard deviation, Cramer–Rao lower bounds < 20%) were included. Metabolites were referenced to water and presented in institutional units (I.U.) with values corrected for the proportion of the gray matter, white matter, and cerebrospinal fluid (CSF) water content within each spectroscopic voxel, and metabolite and water relaxation times according to⁴⁷ using in-house Matlab code utilized in other studies^{33,48}

Statistical analysis - Behavior

We compared the behavior of the different groups using exclusively non-parametric statistics. Between-group differences (CTR vs SCZH⁻ vs SCZH⁺) were assessed using the Kruskal Wallis H test. When necessary, we performed post-hoc 2-by-2 comparisons using the Mann-Whitney U test. All the analyses were two-tailed. Spearman's correlation coefficients were used to assess the relationships between the main behavioral variables (CH and confidence) and with hallucination-severity (BPRS-12 score). Given that we adopt a dimensional approach to hallucinations (psychosis) and in agreement with previous studies^{4,6}, we pooled data across groups. Spearman's partial correlations were used to control for confounders (site (CMHC vs MPRC) and diagnosis (CTR vs SCZ)).

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570 **Statistical analysis – Computational modeling**

571 The Kruskal Wallis H test and the Mann-Whitney U test were used to compare model-
572 parameters across groups. Spearman's correlation coefficients were used to assess the
573 relationships between model parameters and behavioral data / hallucination severity (and partial
574 correlations to control for confounders). Finally, the mean trajectories of $X_1 - X_3$ beliefs were
575 compared using linear mixed-effects models comprising group and block (linear part of the
576 trajectories, i.e. blocks 6-12; see also **Figure 1B, right**) as fixed effects together with Gaussian
577 random effects for intercepts and slopes.

578

579 **Statistical analysis - MRS**

580 Kruskal Wallis H test and Mann-Whitney U test were used to compare Glx values across
581 groups. We hypothesized that strong priors might be underscored by altered levels of Glx in LIN.
582 To test this hypothesis, we computed Spearman's correlation coefficients between Glx in LIN and
583 the ν HGF parameter. As a control (exploratory analysis), we also computed the correlations
584 between Glx in other regions (ACC, LAC and rdlPFC; we also looked at total Glx) and ν , as well as
585 between Glx in LIN and β , CH, hallucination severity, age and medication (CPZ equivalents).
586 Partial correlations were also used to control for confounders. To further test the specificity of
587 the dependence of strong priors on LIN, we performed two stepwise regressions with
588 bidirectional elimination and computed the p-values for the F-statistics of the change in the

589 residual sum of squares that results from adding or removing a term: 1. With v as the dependent
590 variable and Glx in the four regions as potential predictors, starting from a constant (only
591 intercept) or a full (intercept + Glx in all four regions) model. To control for the effect of site, we
592 repeated the stepwise regression adding site as a predictor. 2. With Glx (LIN) as the dependent
593 variable and β, v as potential predictors.

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606 **Supplementary Figures and Tables**

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608 **Figure S1: Hits and false alarms.** Group differences were observed only in the No-tone (see **Figure 1**) and

609 25% detection-rate conditions (SCZH⁺ vs SCZH⁻). Error bars represent ± 1 SEM.

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Figure S2: Confidence across conditions. We observed no significant group-differences for either response (positive or negative). Confidence when responding positively increased from left (No-tone) to right (75%). The opposite was true for negative responses. Error bars represent ± 1 SEM.

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617 **Figure S3: Correlation between conditioned hallucinations and confidence in reporting conditioned**
618 **hallucinations. Red: CTR; Blue: SCZ.**

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Figure S4: Bayesian model selection based on protected exceedance probability. Model 4 (3 free parameters: ω_2, ν, β) clearly outperformed the other models (see **Table S3** for more details).

Glutamate, strong priors and hallucinations

Figure S5: Model parameters. Estimated parameters didn't differ across groups. Error bars represent ± 1 SEM.

Figure S6: Glx concentration in LIN. We observed a trend towards reduced Glx in SCZH⁺. Error bars represent ± 1 SEM.

Figure S7: Correlation between prior weighting (ν) and the Glx concentration in ACC, LAC and rdIPFC.

None of the correlations was significant. Red: CTR; Blue: SCZ.

652 **Table S1: MRS Participant Characteristics (mean (SD))**

<i>Variables</i>	CTR (n=21)	SCZH⁻ (n=17)	SCZH⁺ (n=16)	Statistic	p value
Age	35.9 (10.6)	31.3 (9.6)	34.8 (10.1)	$F=1.02$	0.37
Gender	9/12	11/6	11/5	$\chi^2=3.03$	0.22
Race (African American/Caucasian/other/missing)	3 15 2 1	8 9 0 0	3 11 1 1	$\chi^2=7.42$	0.28
Participant Education	15.7 (2.0)	14.1 (1.2)	14.5 (1.7)	$F=4.78$	0.01
Maternal Education	14.6 (4.2)	14.5 (2.4)	14.4 (4.5)	$F=0.01$	0.99
Paternal Education	14.5 (4.6)	14.0 (4.7)	14.0 (6.9)	$F=0.10$	0.90
Neurocognitive test results					
WTAR	108.9 (28.7)	101.2 (28.5)	112.7 (9.2)	$F=0.92$	0.41
MD Processing Speed	51.0 (17.9)	42.5 (14.4)	47.8 (11.9)	$F=1.43$	0.25
MD Working Memory	52.6 (13.9)	43.1 (15.2)	49.0 (12.3)	$F=2.17$	0.12
MD Verbal Learning	46.1 (12.1)	42.9 (14.5)	44.7 (12.0)	$F=0.27$	0.76
Clinical Ratings					
BPRS Hallucinatory Behavior	1.0 (0.0)	1.0 (0.0)	4.6 (1.2)	-	-
BPRS Delusions	2.0 (0.0)	3.6 (1.8)	5.8 (1.8)	$t=3.40^1$	0.002¹
BPRS Negative Symptoms	3.4 (1.2)	6.1 (2.4)	4.9 (1.7)	$t=-1.68^1$	0.09 ¹
Duration of Illness (yrs)		8.4 (8.3)	12.7 (11.2)	$t=1.23$	0.23
Medication					
Antipsychotic (Atypical Typical)		16 1	14 2	$\chi^2=0.44$	0.51
Antipsychotic medication: CPZ equivalents (mg)		278.4 (259.5)	249.9 (198.6)	$t=-0.35$	0.73
Other psychotropic medication					
Antidepressant + Benzodiazepine + Mood stabilizer		1	0		
Antidepressant+ Benzodiazepine		0	3		
Benzodiazepine		0	3		
Antidepressant		4	3		
Mood stabilizer		3	0		

653 WTAR=Wechsler Test of Adult Reading, measure of premorbid intelligence; MD Working Memory=

654 Working memory domain (MATRICS); MD Processing Speed= processing speed domain (MATRICS); MD

655 Verbal Learning=verbal learning domain (MATRICS); CPZ= chlorpromazine equivalent; BPRS

656 Delusions=Suspiciousness+Unusual Thought Content; BPRS Negative Symptoms=Emotional

657 Withdrawal+Motor Retardation+Blunted Affect;

658 ¹ SCZH⁻ vs. SCZH⁺

<i>Variables</i>	CTR (n=21)	SCZH⁻ (n=17)	SCZH⁺ (n=16)	p value¹
<i>LIN</i>				
Glx	12.27 (1.09)	12.31 (1.26)	11.82 (1.03)	0.27
Glx fits (%SD)	4.62 (0.67)	4.71 (1.05)	4.38 (0.62)	0.49
FWHM	0.0337 (0.0065)	0.0343 (0.0099)	0.0335 (0.0078)	0.96
SNR	35.76 (6.90)	36.71 (8.54)	37.69 (7.03)	0.68
<i>ACC</i>				
Glx	15.54 (1.10)	15.37 (1.04)	15.21 (0.77)	0.71
Glx fits (%SD)	3.76 (0.54)	3.94 (0.24)	3.93 (0.27)	0.26
FWHM	0.0257 (0.0035)	0.0282 (0.0083)	0.0277 (0.0048)	0.46
SNR	42.43 (6.85)	43.71 (7.09)	42.57 (4.13)	0.64
<i>LAC</i>				
Glx	11.16 (1.26)	11.34 (1.16)	10.79 (0.86)	0.25
Glx fits (%SD)	4.90 (1.09)	4.94 (0.85)	4.50 (0.89)	0.28
FWHM	0.0382 (0.0077)	0.0407 (0.0136)	0.0374 (0.0103)	0.63
SNR	47.95 (14.32)	43.88 (11.30)	47.88 (10.26)	0.35
<i>rdIPFC</i>				
Glx	11.66 (1.44)	11.08 (1.55)	11.16 (1.65)	0.74
Glx fits (%SD)	4.57 (1.69)	4.80 (0.94)	5.19 (2.10)	0.36
FWHM	0.0387 (0.0132)	0.0370 (0.0076)	0.0389 (0.0091)	0.85
SNR	57.76 (12.38)	54.67 (12.80)	56.93 (13.46)	0.68

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662 **Table S2: Regional concentration means and SDs of Glx and data quality parameters.** FWHM: Full-663 Width Half Maximum; SNR: Signal-to-Noise Ratio. ¹ Kruskal-Wallis H test

<i>Models (free par.)</i> <i>Parameters (mean (var.))</i>	M1 $(\omega_2, \omega_3, \beta)$	M2 $(\omega_2, \omega_3, \beta, \nu)$	M3 (ω_2, β)	M4 (ω_2, β, ν)	M5 (β)	M6 (β, ν)	M7 (ω_2)	M8 (ω_2, ν)
$\mu_{0,2}$	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
$\mu_{0,3}$	1(0)	1(0)	1(0)	1(0)	1(0)	1(0)	1(0)	1(0)
$\sigma_{0,2}$	0.1(0)	0.1(0)	0.1(0)	0.1(0)	0.1(0)	0.1(0)	0.1(0)	0.1(0)
$\sigma_{0,3}$	1(0)	1(0)	1(0)	1(0)	1(0)	1(0)	1(0)	1(0)
κ	1(0)	1(0)	1(0)	1(0)	1(0)	1(0)	1(0)	1(0)
ω_2	-5.6(16)	-5.6(16)	-5.6(16)	-5.6(16)	-5.6(0)	-5.6(0)	-5.6(16)	-5.6(16)
ω_3	-7.5(16)	-7.5(16)	-7.5(0)	-7.5(0)	-7.5(0)	-7.5(0)	-7.5(0)	-7.5(0)
β	48(2.7)	48(2.7)	48(2.7)	48(2.7)	48(2.7)	48(2.7)	48(0)	48(0)
ν	-	1(2.7)	-	1(2.7)	-	1(2.7)	-	1(2.7)

Table S3: HGF models and sufficient statistics of Gaussian parameter priors. $\mu_{0,2}$: initial value of X_2 ; $\mu_{0,3}$: initial value of X_3 ; $\sigma_{0,2}$: initial uncertainty about X_2 ; $\sigma_{0,3}$: initial uncertainty about X_3 ; κ : $X_2 - X_3$ coupling; ω_2 : stimulus contingency evolution rate; ω_3 : volatility evolution rate (metavolatility); β : inverse decision temperature; ν : prior weighting. In all cases the drift was fixed to 0.