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Title: A neural "tuning curve" for multisensory experience and cognitive-perceptual schizotypy

Authors: Francesca Ferri[*,1,2,§], Yuliya S. Nikolova[3,§], Mauro Gianni Perrucci[4], Marcello Costantini[1,4], Antonio Ferretti[4], Valentina Gatta[5], Zirui Huang[2], Richard A. E. Edden[6,7], Qiang Yue[8], Marco D'Aurora[5], Etienne Sibille[3,9], Liborio Stuppia[5], Gian Luca Romani[4], Georg Northoff[2]

[§] These authors contributed equally to the article.

*To whom correspondence should be addressed; Department of Psychology, University of Essex, Wivenhoe Park, Colchester CO4 3SQ, UK; email: fferri@essex.ac.uk; tel: +44 (0)1206 873710

Affiliations: [1] Department of Psychology, University of Essex, Colchester, CO4 3SQ, UK; [2] Institute of Mental Health Research, Brain and Mind Research Centre, University of Ottawa, Ottawa, ON, K1Z 7K4, Canada; [3] Campbell Family Mental Health Research Institute on CAMH, University of Toronto, Toronto, ON, M5T 1R8 Canada; [4]Department of Neuroscience, Imaging and Clinical Science, ''G.d'Annunzio'' University of Chieti, and ITAB - Institute for Advanced Biomedical Technologies, Chieti, 60100, Italy; [5] Department of Psychological, Humanities and Territorial Sciences, ''G.d'Annunzio'' University of Chieti, Chieti, 60100, Italy; [6] Russel H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University, Baltimore, Maryland, MD 21287, USA; [7] F. M. Kirby Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, Maryland, USA. [8] Department of Radiology, West China Hospital of Sichuan University, Chengdu, 610041, China; [9] Departments of Psychiatry and of Pharmacology and Toxicology, University of Toronto, Toronto, ON, M5T 1R8 Canada.

ABSTRACT

Our coherent perception of external events is enabled by the integration of inputs from different senses occurring within a range of temporal offsets known as the temporal binding window (TBW), which varies from person to person. A relatively wide TBW may increase the likelihood that stimuli originating from different environmental events are erroneously integrated and abnormally large TBW has been found in **psychiatric** disorders characterized by unusual perceptual experiences. Despite strong evidence of inter-individual differences in TBW, both within clinical and non-clinical populations, the neurobiological underpinnings of this variability remain unclear. We adopted an integrated strategy linking TBW to temporal dynamics in fMRI-resting-state activity and cortical excitation/inhibition balance, indexed by glutamate/GABA concentrations and common variation in glutamate and GABA genes in a healthy sample. Stronger resting-state long-range temporal correlations, indicated by larger power-law exponent (PLE), in the auditory cortex, robustly predicted narrower audio-tactile TBW, which was in turn associated with lower cognitive-perceptual schizotypy. Furthermore, PLE was highest and TBW narrowest for individuals with intermediate levels of excitation/inhibition balance, with shifts towards either extreme resulting in reduced multisensory temporal precision and increased schizotypy, effectively forming a neural "tuning curve" for multisensory experience and schizophrenia risk. Our findings shed light on the neurobiological underpinnings of multisensory integration and its potentially clinically relevant inter-individual variability.

INTRODUCTION

Our coherent and unified perception of external events in everyday life depends upon the ability to correctly bind information across senses.[1] Stimuli from different sensory modalities occurring in close temporal proximity have the highest likelihood of being bound together and attributed to the same environmental event. However, we are able to tolerate a certain range of temporal asynchrony between stimuli in order to maintain a unitary perception of multisensory events.[2] This range defines the individual's temporal binding window (TBW[3]). Within his or her TBW, the individual will perceive multisensory stimuli as synchronous, despite their physical temporal distance. Critically, the width of the TBW shows large inter-individual differences among healthy individuals[4] and even greater variability across the continuum from healthy to clinical conditions. For instance, enlarged TBWs have been reported in schizophrenia[5-8] and autism,[9, 10] where they may contribute to abnormal perceptual experiences. **Interestingly, multisensory perceptual experiences predicted by the individual TBW[11] seem to be abnormal also in sub-clinical populations with high levels of schizotypy.[12, 13] This suggests that lower temporal resolution in multisensory perception might be a behavioral marker of psychosis proneness. However, no study has investigated the TBW in schizotypy so far. Moreover,** notwithstanding the amount of research on the TBW, the neurochemical and genetic origins of its vast inter-individual variability remain unclear.

Spontaneous, or resting-state brain activity, may provide insight into an individual's propensity to integrate multisensory information over a wide or narrow temporal window. Indeed, spontaneous neural activity exhibits a rich temporal

structure[14, 15] that affects the timescale over which brain regions process information from external stimuli.[16, 17] More specifically, the temporal structure of spontaneous neural activity can be characterized by long-range temporal correlations (LRTCs) - i.e., scale-free dynamics, with a power spectrum following $P \propto 1/f^{\beta}$, where P is power, f is frequency, and β is the power law exponent (PLE[18, 19]). PLE is an index of the degree of LRTCs[20, 21]: stronger LRTCs, with larger PLE, suggest that the past pattern of a system has a stronger influence on its future dynamics.[22] In the human brain this relationship occurs across a range of timescales and frequencies including infra-slow brain amplitude fluctuations (<0.5 Hz) recorded using functional magnetic resonance imaging (fMRI) during resting wakefulness.[23, 24] **Recently, we demonstrated that resting-state LRTCs also affect response amplitude to stimuli delivered at a specific phase of spontaneous brain activity (e.g., higher LRTC, with larger PLE, amplify response to stimuli delivered at high-excitability phase[24]). Interestingly, response to multisensory stimuli and multisensory binding are primarily affected by the phase of spontaneous brain activity when stimuli arrive.[25] Based on this evidence, we hypothesized a possible relation between resting-state LRTCs and temporal binding of multisensory events.**

Although the molecular and cellular basis of these processes has yet to be elucidated, neuroimaging, neurophysiology and molecular neurobiology studies strongly suggest that the temporal structure of spontaneous neural activity,[26, 27] as well as multisensory integration,[28, 29] may be fine-tuned by the balance between excitatory (i.e. glutamatergic) and inhibitory (i.e., GABAergic) neurotransmission. Specifically, prior work using cell-based approaches in animal models has shown that pharmacological alterations of the excitation/inhibition (E/I) balance, induced by blockage of either the excitatory NMDA or the inhibitory $GABA_A$ receptors, impact

on LRTCs and their scale-free dynamics.[30] Similarly, animal studies clearly suggest that a strictly held E/I balance, with key contributions from these same receptors, governs multisensory processing.[31, 32] The role of E/I balance in multisensory integration is further supported by human studies demonstrating that multisensory behavioral performance depends on individual levels of GABA and glutamate in the brain, measured in vivo by magnetic resonance spectroscopy (MRS[33]).

Importantly, levels of glutamate, its metabolite glutamine (collectively denoted as Glx), and GABA in the living human brain show considerable inter-individual differences among healthy subjects.[34-36] This variability is even greater along the whole spectrum from healthy to clinical conditions, such as schizophrenia and autism,[37, 38] which are associated with abnormally increased E/I ratio.[39-41] Importantly, genetic association studies of schizophrenia and autism[42, 43] suggest that some of the variability in the E/I balance may be genetically driven. Specifically, both early candidate gene studies[44-47] and the most recent genome-wide associated study (GWAS) of schizophrenia[48] have associated the disorder with single nucleotide polymorphisms (SNPs) within or near genes known to regulate GABA or glutamatergic signaling.

Based on these findings, we hypothesized that functional genetic variation modulating glutamate and GABAergic signaling may affect E/I balance, and consequently resting state neural dynamics and multisensory integration, in the healthy brain, which may in turn create a propensity to unusual perceptual experiences. To test this hypothesis we adopted an integrative strategy (Figure 1), wherein first we assessed the relationship between resting state PLE values and individual audio-tactile TBW in the auditory cortex, where audio-tactile integration is known to occur.[49] We hypothesized that higher PLE would be associated with a

narrower TBW, indicative of higher temporal resolution (i.e. more precision) in multisensory perception (H1). We then hypothesized that Glx, and possibly GABA, would modulate both PLE (H2) and TBW (H3), conditional on each individual's genetically defined E/I balance. We focused our genetic analysis on four extensively characterized GABA- and glutamatergic SNPs (**Table 2**), which may stably bias the baseline E/I background against which the more dynamic excitatory and inhibitory neurotransmitter signaling unfolds. Further, we hypothesized a role of PLE as a mediator between the genetically-biased effect of excitatory and inhibitory neurotransmitters and multisensory perception (H4). Finally, we extended this model to schizotypal traits capturing propensity to unusual cognitive/perceptual experiences.

Insert Figure 1 around here

METHODS AND MATERIALS

Participants

Thirty-seven Caucasian, healthy, right-handed volunteers (12 females, mean age 21.8, age range 20-31 years) participated in the study after providing written informed consent. Participants were undergraduate and postgraduate students recruited via mailing lists at the University "G. D'Annunzio" of Chieti-Pescara. No participant had a history of neurologic, general medical or psychiatric conditions. All subjects received monetary compensation for their participation. The experimental protocol was approved by the University "G. D'Annunzio" of Chieti institutional ethics committee.

Behavioural session

Temporal Binding Window (TBW)

Participants' TBWs were obtained from four different tasks: (i) a multisensory audio-tactile Simultaneity Judgment task (SJ; Supplementary Figure 1), (ii) a unimodal auditory SJ, (iii) a multisensory audio-tactile Temporal Order Judgement task (TOJ), and (iv) a unimodal auditory TOJ. We adopted well-established procedures [50, 51] for both data collection and analysis (See Supplementary Methods and Supplementary Table 1).

The average TBWs from the SJ tasks were: for the multimodal audio-tactile, 359 ±135 ms (±s.d. indicated; range 172 - 646 ms); for the unimodal auditory, 80 ±48 ms (range 19 - 210 ms). The average TBWs from the TOJ tasks were: for the multimodal audio-tactile, 251 ±181 ms (range 55 - 700 ms); for the unimodal auditory, 99 ±55 ms (range 23 - 294 ms).

MR session

Spectroscopy (MRS) and functional (fMRI) data were acquired with a 3 Tesla Philips Achieva magnetic resonance scanner. The left primary auditory cortex was selected as the target region for MRS and fMRI investigations, due to its critical role in processing and integration of auditory and tactile stimuli,[49, 52] and because it has been associated with abnormal concentrations of neurotransmitters and gene expression in schizophrenia.[53, 54] The medial prefrontal cortex (MPFC), a higher order area characterized by different temporal dynamics,[17] was chosen as the control region. In both regions, we quantified Glx and GABA neurotransmitters, as well as the cerebral spinal fluid (CSF), gray matter (GM) and white matter (WM) content. Also, we computed the regional PLE and the Standard Deviation (SD), indices of the

resting-state temporal structural and variance respectively, as previously described[24, 55] (see Supplementary Methods, Supplementary Figure 2 **and Table 1**).

Insert Table 1 around here

Genetic Profile Scores

We compiled individual genetic profile scores[56] related to the balance between excitation and inhibition signalling (E/I). **The loci of interest were pre-selected based on the most recent published systematic review of cross-disorder (schizophrenia and bipolar disorder) association studies of common genetic variation in the GABA/Glutamate signaling system[43]. Out of dozens of loci reviewed therein, we selected the eight loci showing a positive association with schizophrenia in at least two independent studies (namely, *GRIN1*, *GRIN2A*, *GRIN2B*, *GRIK3*, *GRM3*, *GRM7*, *GAD1*, *GABRB2*[43]) and followed them up with a targeted literature search in PubMed to identify SNPs consistently driving their association with schizophrenia, along with the SNPs' functionality, and links to potential biological mechanisms. Thus, we focused on SNPs that are: 1) located within or near genes involved in the maintenance of E/I balance (i.e., major GABA and glutamate signaling regulatory proteins); 2) of known or hypothesized molecular functionality; 3) associated with schizophrenia in at least two independent studies; 4) associated with at least one additional disorder characterized by impairments in E/I balance and/or multisensory integration; and 5) associated with at least one behavioral or neural endophenotype of cross-disorder relevance. Only four SNPs fulfilled these stringent criteria (see Table 2 and Supplementary Table 2). No additional SNPs were probed in this sample.**

We incorporated these pre-selected SNPs into a multilocus genetic score.[56]

The score represented the total number of variants across the four functional polymorphic loci. Across all loci, relatively 'High' E/I genotypes were assigned a score of 1, 'Low' E/I genotypes a score of 0, and 'Intermediate' E/I genotypes a score of 0.5[56] (**Table 2**). Alleles associated with 'High' E/I had either a positive impact on glutamate signalling, or a negative impact on GABA signalling (or both in the case of *GAD1* rs3749034). Complementarily, alleles associated with 'Low' E/I had either a negative impact on the expression of glutamate-related genes, or a positive impact on the expression of GABA-related genes. These scores at each locus (**see Table 2 for their distribution**) were then summed to create an individual profile score, such that higher total scores reflect a putative shift towards higher excitation coupled with less efficient inhibition. **For example, the genetic profile score for an individual with the following four genotypes – *GRIN1* G/G, *GRIK3* T/G, *GAD1* A/A, *GABRB2* C/C - was 2.5 (1+0.5+0+1). The average E/I score was 2.351±0.551. All observed genotype frequencies were consistent with those reported for Caucasian populations in the 1000 Genomes project[57].**

Insert Table 2 around here

Schizotypal Personality Questionnaire (SPQ)

Schizotypy is thought to reflect the subclinical expression of the symptoms of schizophrenia in the general population and to constitute a dynamic continuum ranging from personality variation to psychosis.[76, 77] Schizotypal traits were assessed using the Italian version of the Schizotypal Personality Questionnaire (SPQ[78]). It consists of three subscales capturing the "Interpersonal", "Cognitive-Perceptual" and "Disorganization" aspects of schizotypy. The Cognitive-Perceptual component

concerns the disposition to unusual perceptual experiences, such as hallucinations, which are associated with impaired multisensory integration **and TBW** in patients.[7, 79] Hence, we specifically focused on this subscale in our analysis. While its distribution was slightly positively skewed, its skewness and kurtosis were within the acceptable range (skewness<1, kurtosis<2.5). Thus, we used raw Cognitive-Perceptual SPQ scores (**range 0-17**).

Statistical analyses

All individual variable distributions had skewness<0.82 and kurtosis<4.3 (absolute value). Thus, no power transformations were applied. Correlations among the main variables are listed in Supplementary Table 3. Three principal analyses were conducted. i) Pearson's correlation coefficients were computed using either PLE or SD values as an independent variable predicting individual TBWs. ii) Moderation analyses (Model 1 in the SPSS PROCESS macro;[80] **performed to probe genetic moderation by individual E/I genetic profiles of the effects of the more dynamic[81-85] local concentrations of Glx, GABA or their ratio (Glx/GABA) on either PLE or TBW**, with and without CSF fraction and GM/WM ratios as covariates. Significant interactions were further probed using the Johnson-Neyman (J-N) method,[86] as implemented in the SPSS MODPROBE macro.[87] The J-N method calculates the critical moderator variable values at which the relationship between the focal predictor (Glx, GABA or Glx/GABA) and the dependent variable (PLE or TBW) changes significance. J-N regions of significance are reported using standardized Z scores. iii) A moderated mediation analysis (Model 8 in the SPSS PROCESS macro[80]) was performed to probe any effects of metabolite concentrations on individual TBW, mediated by its effects on PLE in the auditory cortex, conditional

on E/I genetic profile. i) and ii) were carried out with standardized values for all the variables. Consistent with published guidelines[88, 89] and in light of our relatively small sample size, we report 95% confidence intervals (CIs) based on 5000 bootstrap iterations (bias-corrected) for all major effects. **Cohen's f^2 was computed to quantify effect sizes in individual regression analyses.[90]**

RESULTS

Resting state temporal dynamics (PLE) and temporal binding window (TBW).

As hypothesized, we found a strong negative correlation between PLE in the auditory ROI and individual audio-tactile TBW for both the SJ (r=-.557, p <.001, 95%CI [-.779, -.261], **Cohen's f^2=.45**; Figure 2a-b) and the TOJ (r=-.428, p=.008, 95%CI [-.663, -.172], **Cohen's f^2=.22**; not shown) tasks: the higher the degree of LRTCs (i.e., larger PLE) in auditory cortex, the narrower the audio-tactile TBW. In contrast, the correlation between PLE in the control MPFC ROI and individual audio-tactile TBW did not survive bootstrap correction (SJ, 95%CI [-.664, .021], Figure 2a; TOJ, 95%CI [-.417, .240], not shown). This relative region-specificity suggests the observed relationship is confined to the primary cortical area where multisensory integration is known to occur, as compared to higher-order information processing regions. Critically and in contrast to PLE, the SD of the signal recorded from the same auditory ROI did not predict individual TBWs from either task (SJ, 95%CI [-.213, .349]; TOJ, 95%CI [-.121, .391]), suggesting individual audio-tactile TBWs is predicted by the temporal structure (PLE), rather than the mere variance (SD), of resting state temporal dynamics. Finally, demonstrating the specificity of our findings to multi- rather than uni-modal sensory phenomena, no significant correlation was found between PLE in the auditory ROI and individual unimodal auditory-auditory

TBW for either task (SJ, 95%CI [-.488, .029]; TOJ, 95%CI [-.490, .142]). Given the stronger correlation between PLE and individual audio-tactile TBW measured by SJ - than by TOJ- task, we used only the former in all subsequent analyses.

Insert Figure 2 around here

Excitation/inhibition (E/I) balance and resting state temporal dynamics (PLE).

A significant interaction emerged between individual E/I genetic profile scores and concentrations of Glx in the Auditory ROI predicting PLE (ΔR^2=.2065, b=-.6063, 95%CI [-.976, -.218], p=.0056, **R^2=.226, Cohen's f^2=.29**), wherein higher concentrations of Glx were associated with higher PLE values only for participants with relatively low E/I genetic profile scores (e.g., 1 s.d. below the mean; Figure 3c) - i.e. participants showing E/I balance shifted towards inhibition. Specifically, J-N region of significance analyses indicated that higher concentrations of Glx were associated with higher PLE in participants with E/I genetic profile scores below -0.09 (mean-centred around 0), but with lower PLE in participants with E/I genetic profile score above 1.47 (i.e. showing E/I balance shifted towards excitation).

Importantly, the interaction term explained significant PLE variance above and beyond the main effects of individual E/I genetic profile (b=.1285, p=.4302) and Glx concentration (b=.2929, p=.0842). Furthermore, the interaction effect remained significant after controlling for either grey matter to white matter (GM/WM) ratios or the fraction of CSF (p values<0.006). Consistent with prior work,[56] the additive effects of all the polymorphisms were crucial to explaining a significant proportion of inter-individual variance in PLE. Indeed, after removing each of the polymorphisms

from the E/I genetic profile, the moderation model was never significant (all p values>.12).

In contrast to auditory cortical Glx concentration, no significant interaction was found between the individual E/I genetic profile score and the concentration of GABA (Supplementary Figure 3) or the Glx/GABA ratio in the auditory ROI (p values>0.19). Likewise, no significant interactions were found between the individual E/I genetic profile score and the concentration of either Glx or GABA in the MPFC ROI (p values>0.25; Figure 3d).

Insert Figure 3 around here

Excitation/inhibition (E/I) balance and temporal binding window (TBW).

In addition to predicting PLE, the interaction between individual E/I genetic profile scores and concentrations of Glx in the Auditory ROI also significantly predicted individual audio-tactile TBW (ΔR^2=.2590, b=.6790, 95%CI [.283, 1.075], p=.0014, **R^2=.30, Cohen's f^2=.42**). The interaction effect was such that higher concentrations of Glx were associated with narrower TBW for participants with relatively low E/I score (1 s.d. below the mean; J-N: Z<-0.17), but wider TBW for those with high E/I score (1 s.d. above the mean; J-N: Z>0.94) (Figure 3e).

As with PLE, the interaction effect remained significant after controlling for either GM/WM or the fraction of CSF (p values<0.002), and was not present when we performed the same analyses using the unimodal auditory-auditory task (p=.3527). In contrast to auditory cortical Glx concentration, no significant interaction was found between the individual E/I genetic profile score and the concentration of GABA in the Auditory ROI (p=.4201; Supplementary Figure 3). Similarly, no significant interactions were found between the individual E/I genetic profile score and the concentration of either Glx or GABA in the MPFC ROI (p values>.1; Figure 3f and

Supplementary Figure 3). However, the Glx/GABA ratio interacted with E/I genetic profile score to predict TBW (ΔR^2=.2656, b=.6445, 95%CI [.276, 1.013], p=.0011, R^2=.31, **Cohen's f^2=.45**), such that higher Glx/GABA ratios were associated with narrower TBW for participants with relatively low E/I score (1 s.d. below the mean; J-N: Z<-0.12), but not for participants with relatively high E/I score (1 s.d. above the mean; J-N: Z>1.9).

Resting state temporal dynamics (PLE) mediate the effects of excitation/inhibition (E/I) balance on the temporal binding window (TBW).

To integrate these findings, we used a moderated mediation model to examine possible effects of Glx concentrations on TBW, mediated by PLE and conditional on individual E/I genetic profiles (Figure 3g). We found that PLE mediated the relationship between Glx concentrations and TBW, such that for those with low E/I scores (≤mean), higher Glx was associated with higher PLE and, subsequently, narrower TBW, whereas for those with high E/I scores (> +1.1s.d), higher Glx was associated with lower PLE and, subsequently, wider TBW. Notably, there was also a conditional direct effect of Glx concentration on TBW (b=.4287, p=.040) in the model including PLE as a covariate, suggesting PLE was only a partial mediator of the relationship among these variables (Figure 3h).

TBW and Schizotypal Personality Traits.

Despite relatively low power to detect a three-path mediated effect, we sought to extend this model to schizotypal personality, consistent with prior work suggesting a link between multisensory phenomena and psychosis proneness.[91] Thus, we found that PLE and TBW serially mediated a relationship

between Glx and Cognitive-Perceptual SPQ, conditional on individual E/I scores. Specifically, higher Glx was associated with higher PLE, narrower TBW and consequently lower SPQ in those with relatively low E/I genetic score, but with lower PLE, wider TBW and ultimately higher SPQ in those with relatively high E/I genetic score (Figure 4a). **Furthermore, this effect was amplified when limiting the analysis to participants reporting any (as opposed to no) degree of cognitive-perceptual schizotypy (i.e., SPQ>0, n=32), such that TBW accounted for 10% of all variance in SPQ Cog Perc (Cohen's f^2=0.11) and 26% variance (Cohen's f^2=0.35) in non-zero SPQ responses.**

Insert Figure 4 around here

DISCUSSION

In the current study, we adopted an integrative strategy (Figure 1) to identify the neurobiological and molecular underpinnings of inter-individual differences in multisensory perception and propensity to unusual perceptual experiences. We found that a larger power-law scaling exponent (PLE) in the resting-state temporal dynamics of the auditory cortex was associated with narrower audio-tactile TBW; that is, the higher the degree of long-range temporal correlations (LRTCs) in the resting state auditory cortex activity, the higher the temporal resolution or precision in audio-tactile perception. Furthermore, this effect accounted for more than one third of the variance in TBW and emerged specifically for the temporal structure, rather than the variance (SD), of spontaneous activity in the auditory cortex. Notably and as predicted, this association was not observed in the MPFC, a control brain area that is not directly involved in multisensory integration.

These results are in line with prior fMRI studies showing a functional link between the multiple timescales of neural dynamics in different brain regions and the multiple timescales within which the same regions reliably process unimodal sensory information.[17] They are also consistent with fMRI studies associating individual spontaneous brain temporal dynamics with behavioral accuracy during event-timing tasks.[19, 92] Here, for the first time we extend this prior work into the multisensory domain of human cognition and identify a novel task-free assessment and biomarker (i.e., PLE) of individual ability to integrate signals across sensory systems that may in turn predict propensity to unusual perceptual experiences.

A wider TBW indicates that stimuli originating from different environmental events are more likely to be bound together, which may give rise to unusual sensory phenomena, possibly continuous with the positive symptoms of schizophrenia. Consistent with this notion, we found that greater TBW width was associated with increased levels of schizotypy, specifically in the Cognitive-Perceptual domain. While prior work has shown abnormally wide TBW in individuals with schizophrenia,[5, 6, 8] here, for the first time, we extend these results to a dimensional measure of psychosis proneness. Indeed, even if most individuals with schizotypal traits are not expected to develop schizophrenia, increasing levels of schizotypy are robustly associated with heightened risk for the development of psychotic disorders.[93] Accordingly and consistent with the current results, substantial overlap has been found between schizotypy and schizophrenia in terms of etiological factors at the genetic, biological, and psychosocial levels,[94] but also concerning a wide range of perceptual, cognitive, and motor impairments.[95]

We further show that inter-individual variability in auditory resting state dynamics, audio-tactile TBW, and perceptual schizotypy were accounted for by local

concentrations of glutamatergic compounds (Glx) conditional on individual E/I genetic profiles. Specifically, for relatively lower values of the E/I score, indicating a putative genetic shift towards greater inhibition, higher concentrations of Glx were associated with higher values of PLE, narrower TBW and, ultimately, lower schizotypy; in contrast, for relatively greater values of the E/I score, indicating a putative shift towards greater excitation, higher concentrations of Glx were associated with lower PLE, wider TBW and higher schizotypy.

This interaction pattern is consistent with recent work, which describes the relationship between E/I balance and information processing efficiency as an inverted-U shaped curve that may differ per brain region and individual.[96] Importantly, the distribution of E/I balance in the healthy population is skewed with the majority showing a peak shifted towards inhibition. A transcranial direct current stimulation (tDCS) treatment which reduces inhibition (i.e., shifts the imbalance towards the optimum) thus typically improves an individual's performance.[96] According to this model, increased Glx in our participants is expected to be associated with improved neural and behavioral efficiency for everyone who is genetically predisposed to be on the non-optimal side of the balance closer to the inhibition end of the spectrum (i.e., low E/I genetic scores; Figure 4b). In contrast, higher levels of Glx might push those who are already genetically **predisposed** towards excitation (i.e., with high E/I genetic scores) over and/or further away from the peak of the curve toward the non-optimal side closer to excitation, in effect worsening neural and behavioral efficiency and increasing risk for schizotypal traits in the cognitive/perceptual domain, effectively forming a neural "tuning curve" for multisensory experience and perceptual risk for schizophrenia. **It is worth clarifying here that we do not believe individual genetic profiles are sufficient to determine**

the position of an individual on the E/I spectrum; rather, they represent a predisposing, or conditioning, factor. Through context-dependent interaction with excitatory and inhibitory neurotransmitters, individual genetic profiles would allow a range of possible dynamics of E/I balance and potentially clinically relevant gene-brain-behavior relationships.

Our results are further consistent with prior work, which has demonstrated the importance of glutamatergic neurotransmission for both resting state brain dynamics and audio-tactile integration. Specifically, previous studies in humans have suggested that Glx (or Glu) concentrations may exert a critical role in the synchronization of spontaneous neural activity.[97] However, a possible role of excitatory neurotransmission for LRTCs[30] and integration of auditory and somatosensory stimuli in the auditory system has only been previously demonstrated in animal models.[98] Thus, our study is the first to directly demonstrate the importance of glutamatergic neurotransmission, as constrained by common genetic variation, for LRTC and audio-tactile perception in humans. Most importantly, the degree of LRTC and the precision in audio-tactile perception were partial mediators of the link between Glx and schizophrenia proneness, in the presence of a direct negative link between Glx and SPQ in our sample. **Our results are thus also broadly consistent with prior evidence showing that altered glutamatergic neurotransmission, due to either increased (e.g., [99]) or reduced (e.g., [100]) glutamatergic metabolites, and altered activity of glutamate receptors (e.g., [101]) are associated with subclinical and clinical manifestations of psychosis. In addition, they suggest one possible mechanism that may specifically mediate this hypothesized link in the context of perceptual disturbance.** This may further explain the relative specificity of our findings to glutamate as opposed to GABA levels in the brain. **Moreover, another**

possible reason why we did not find significant effect of GABA levels on multisensory perception might be related to the fact that we did not quantify the levels of GABA while participants were performing the task, rather during resting state. Prior cellular studies, indeed, suggested that a crucial role played by inhibitory transmission in the healthy brain is to sharpen the response properties of excitatory neurons. By putting a brake on cortical excitability, inhibitory neurons provide temporal precision to cortical firing in response to sensory inputs and enhance their saliency.[102]

The current study is not without limitations. First, even though we selected biological predictors of TBW based on a strong a priori rationale, many additional factors not accounted for by our study are likely to contribute to this complex perceptual phenotype. Along the same lines, we do not assume the SNPs included in our E/I genetic profile exhaustively represent all genetically driven variability in E/I balance. Rather, they represent genotypes of convenience, which were chosen for this proof-of-principle study because of their known or hypothesized functionality on the molecular level, and their prior association with neuropsychiatric disorders characterized by perceptual disturbances. Future work incorporating additional genetic variability in a more exhaustive way is warranted. **Our study is also limited by its relatively small sample size of 37 participants. However, published power analyses suggest a sample size of 34 is sufficient to detect a large two-path mediated effect when using bootstrapped bias-corrected confidence interval statistics.[103] The large effect sizes, directions of effect and conceptual links at each step of our investigation are in turn broadly consistent with prior work,[79, 91, 104-107] which gives us confidence we did not overestimate effect sizes due to sampling error. While three-path mediation models generally require slightly**

larger sample sizes to test (n=~50 for medium to large three-path mediated effects[108]) this consistency of effect sizes and directionality in our current model supports its conceptual validity. Future studies in larger samples of healthy individuals and psychiatric patients will help to further generalize our findings, confirm effect size, and extend our proposed model. Finally, our results are correlational. Thus, while we propose PLE as a mediator between E/I balance and TBW, it is possible that the effects of GABA/Glx and E/I genetic score on TBW may also contribute to shaping LRTC phenomena. This is a particularly intriguing possibility, given that all our mediation effects were partial, suggesting the presence of additional factors. Future work in preclinical models of multisensory integration would be required to determine true causality in the proposed pathway.

These limitations notwithstanding, the current study is the first empirical demonstration that neural, neurochemical and genetic factors related to excitation-inhibition mechanisms contribute to inter-individual differences in multisensory perception and propensity to unusual sensory experiences in healthy humans. Further, our **postulated tuning curve model might improve our understanding of clinical conditions associated with impaired multisensory perception and open the door to innovative neuromodulation interventions (e.g., TMS, tDCS) informed by individual genetic and neurochemical profiles. In individuals with profiles shifted towards inhibition, excitatory neuromodulation treatment would bring cortical neurotransmission closer to an optimal excitation/inhibition balance. The same would hold true for inhibitory neuromodulation treatment in individuals with profiles shifted towards excitation.** In sum, using a multimodal approach within an integrative framework, we delineate a promising novel

mechanism of perceptual variability, and identify directions for future research with potential clinical implications.

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FIGURE LEGENDS

Figure 1 *Overview of the study.* TBW=Temporal Binding Window; PLE=Power Law Exponent; SNP=Single Nucleotide Polymorphism; GABA= Gamma-AminoButyric Acid; H=Hypothesis.

Figure 2 *Predictive power of PLE for individual TBWs in Auditory and MPFC ROIs.* a) PLE was strongly negatively correlated with TBW (r=-0.557) in the auditory ROI (left panel), but not the MPFC (r=-0.312, right panel). b) TBW predicted by PLE in the Auditory ROI for two single representative subjects showing either a wide (s36, left) or a narrow (s15, right) TBW. ***$p \leq 0.001$.

Figure 3 *Genetic moderation of Glx effects on PLE and TBW.* a) Conceptual and b) statistical depiction of the effects tested, i.e. the main effect of each of the two factors and their interaction. (c-d) Glx was positively correlated with PLE in individuals with relatively low E/I genetic score (1 SD below mean; light purple line), but not in those with relatively high E/I genetic score (1 SD above mean; dark purple line) in the auditory cortex (c). Notably, Glx became a significant positive predictor of PLE at E/I score values >1.47 SD above the mean (not visualized). This interaction did not emerge for the MPFC (d). Analogously, auditory cortex Glx was negatively correlated with TBW width in those with low E/I scores (light purple line), but negatively correlated with TBW in those with high E/I scores (dark purple line, e). E/I score did not moderate a relationship between Glx and TBW in the MPFC (f). Statistical analyses were carried out with standardized values for all the variables. Notably, for visualization purposes, slope estimates are presented at discrete values of the moderator (mean levels and +/- 1SD away from the mean). However, these estimates are based on the linear trends present in the entire sample (i.e. no arbitrary splitting of the sample was performed). (g) Conceptual depiction of the moderated mediation model tested. (h) Results from a path analysis testing the moderated mediation

model presented in (g). PLE mediated a significant relationship between Glx concentrations and TBW at Low (Mean-1s.d.), Intermediate (Mean) and High (Mean-1.1s.d.),) values of E/I scores. There was also a conditional direct interaction effect on TBW. Numbers represent standardized parameter estimates (bootstrapped standard errors in parentheses). Indirect (i.e. mediated) effects are represented as parameter estimates along with 95% bias-corrected bootstrapped confidence intervals computed at representative values of the moderator (E/I genetic scores). As the model was saturated, only individual paths were tested for significance and no overall model fit statistics were produced.

*$p \leq 0.05$; **$p \leq 0.01$.

Figure 4 *Proposed integrated model of the results.* (a - top) A conceptual depiction of the moderated mediation model tested. PLE and TBW were tested as serial mediators of a genetically moderated indirect link between Glx and Cognitive-Perceptual SPQ. (a - bottom) Path analysis showed that, via its genetically moderated effects on PLE and TBW, higher Glx was associated with *lower* SPQ in those with relatively low E/I scores (mean or lower), but with *higher* SPQ in those with relatively high E/I score (>1.3SD above the mean). Notably, the mediation effect was partial, as it emerged in the context of a significant negative direct path from Glx to SPQ. Numbers represent standardized parameter estimates (bootstrapped standard errors in parentheses). Indirect (i.e. serially mediated) effects are represented as parameter estimates along with 95% bias-corrected bootstrapped confidence intervals computed at representative values of the moderator (E/I genetic scores). As the model was saturated, only individual paths were tested for significance and no overall model fit statistics were produced.

(b) Our results support an inverted-U shape relationship between excitation/inhibition (E/I) balance and both the temporal structure of resting state activity (*Green curve*) as well as the temporal resolution of multisensory perception (*Red curve*). Individual TBW and power

spectra are depicted for subjects representative of the four main combinations of E/I genetic score (*Purple arrows*) and Glx levels (*Orange arrows*). Subjects for whom both are low or both are high fall on the non-optimal left and right side of the curve, respectively, whereas those with low-high or high-low combinations are near the putative optimal level of excitation/inhibition on top of the curve.

Figure 1

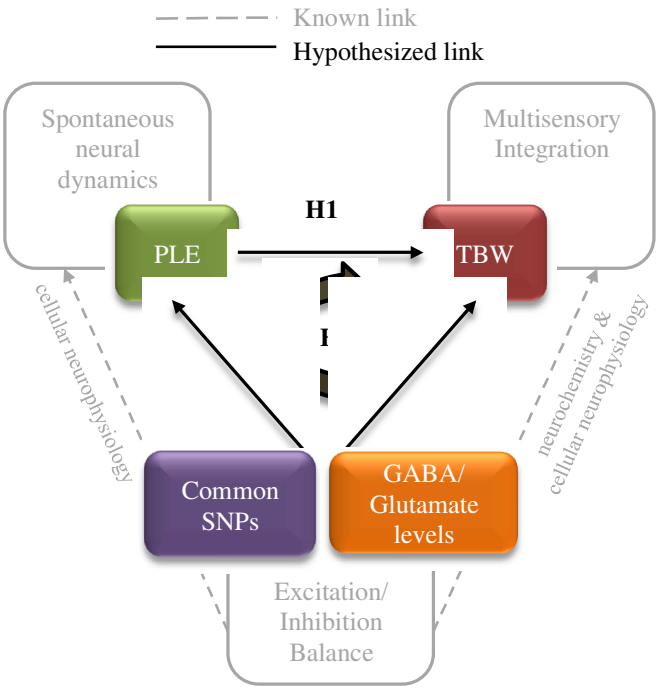

Known link
Hypothesized link
Spontaneous neural dynamics
Multisensory Integration
PLE
TBW
H1
H
cellular neurophysiology
neurochemistry & cellular neurophysiology
Common SNPs
GABA/ Glutamate levels
Excitation/ Inhibition Balance

Figure 2

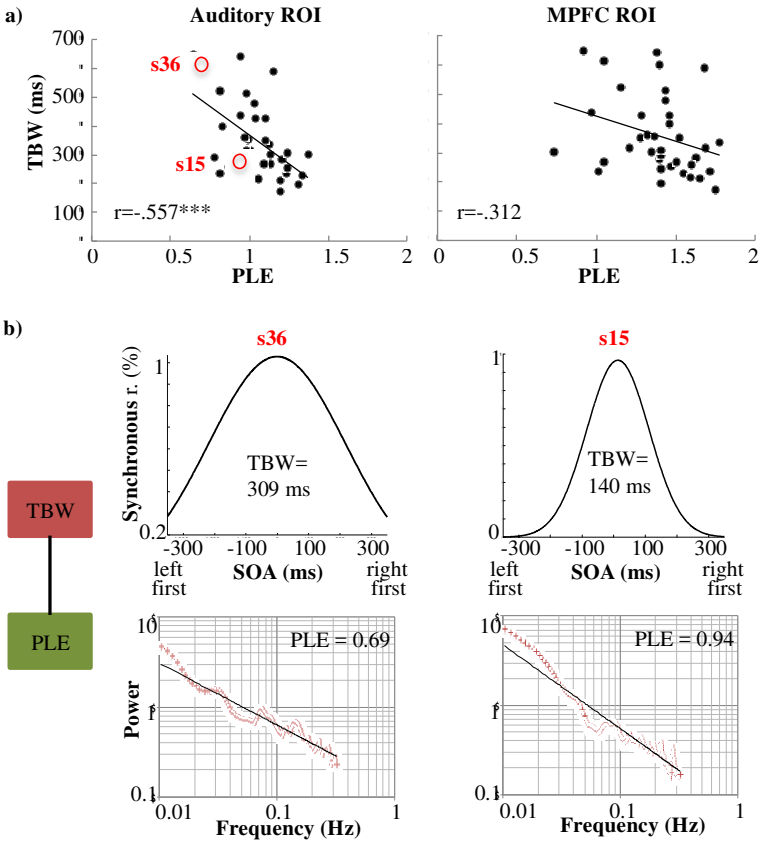

a)
Auditory ROI
MPFC ROI
TBW (ms)
700
500
300
100
s36
s15
r=-.557***
r=-.312
0
0.5
1
1.5
2
PLE
b)
TBW
PLE
s36
s15
Synchronous r. (%)
1
0.2
TBW=
309 ms
TBW=
140 ms
-300
-100
100
300
left
first
SOA (ms)
right
first
Power
10
1
0.1
PLE = 0.69
PLE = 0.94
0.01
0.1
1
Frequency (Hz)

Figure 3

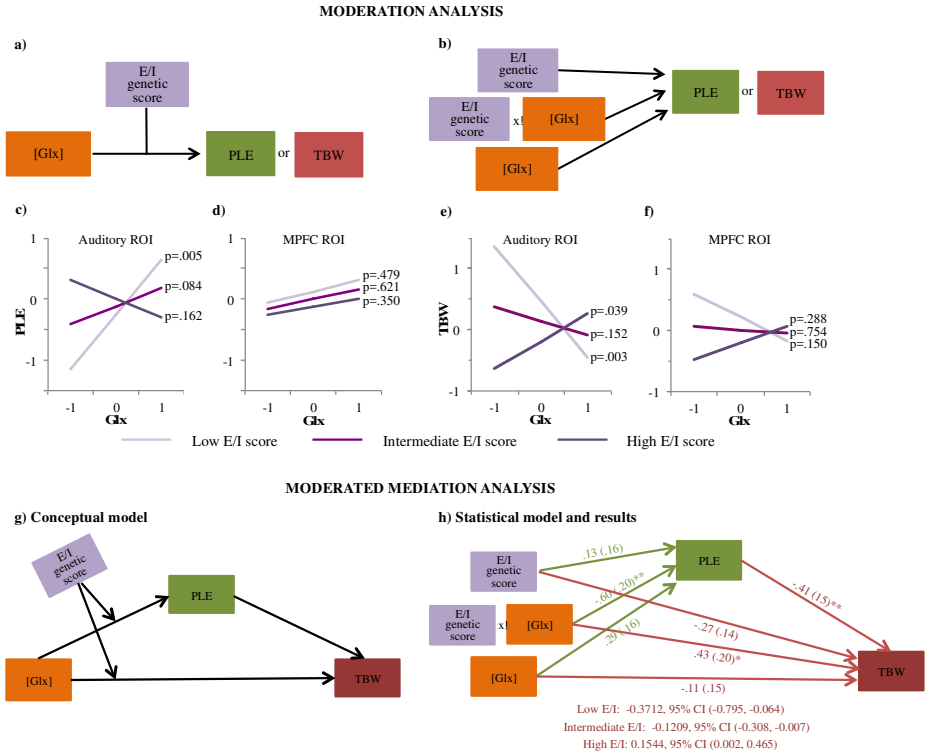
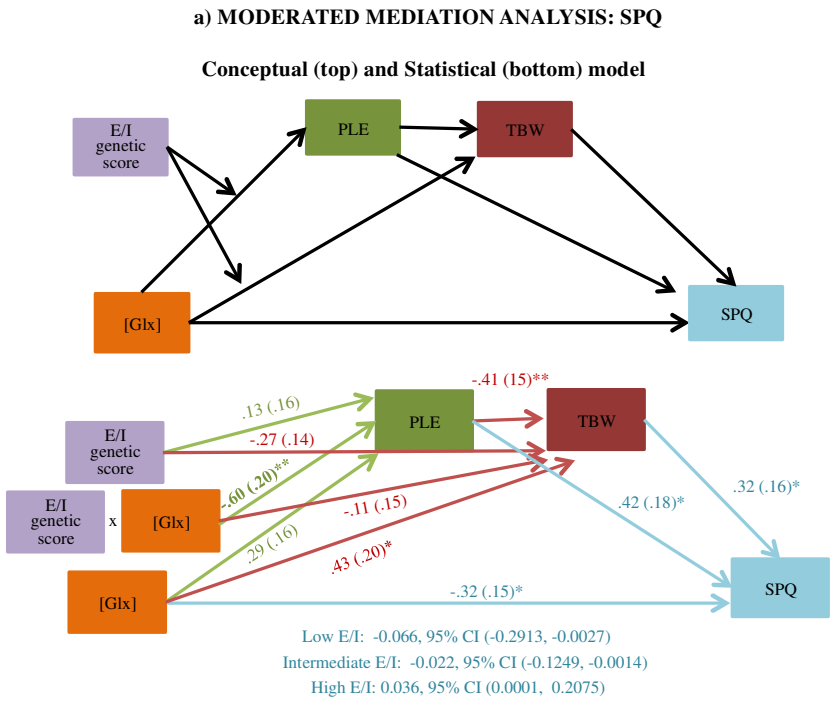
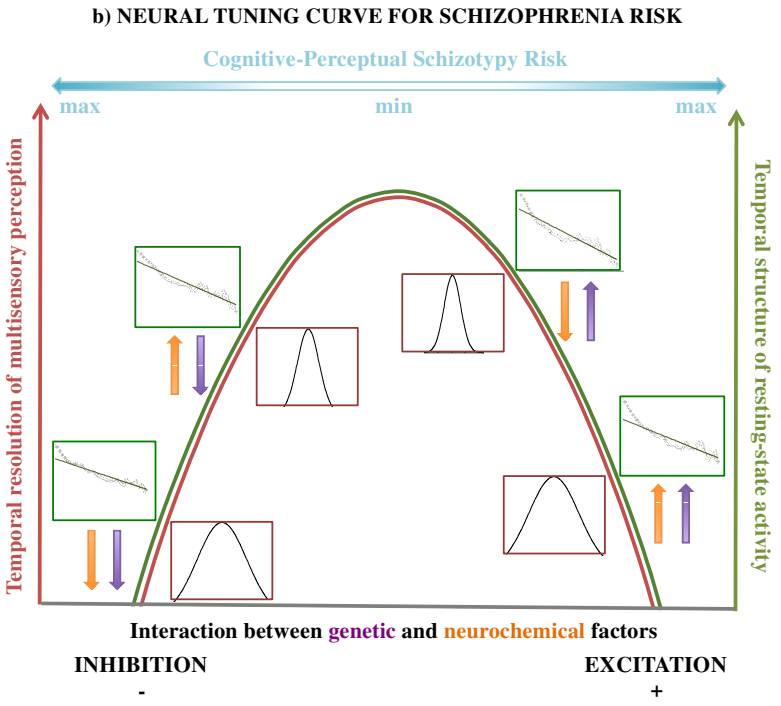

MODERATION ANALYSIS
a)
E/I genetic score
[Glx]
PLE
or
TBW
b)
E/I genetic score
E/I genetic score
x
[Glx]
[Glx]
PLE
or
TBW
c)
Auditory ROI
p=.005
p=.084
p=.162
PLE
Glx
d)
MPFC ROI
p=.479
p=.621
p=.350
Glx
e)
Auditory ROI
p=.039
p=.152
p=.003
TBW
Glx
f)
MPFC ROI
p=.288
p=.754
p=.150
Glx
Low E/I score
Intermediate E/I score
High E/I score
MODERATED MEDIATION ANALYSIS
g) Conceptual model
E/I genetic score
PLE
[Glx]
TBW
h) Statistical model and results
E/I genetic score
E/I genetic score
x
[Glx]
[Glx]
PLE
TBW
.13 (.16)
-.60 (.20)**
.29 (.16)
-.41 (.15)**
-.27 (.14)
.43 (.20)*
-.11 (.15)
Low E/I: -0.3712, 95% CI (-0.795, -0.064)
Intermediate E/I: -0.1209, 95% CI (-0.308, -0.007)
High E/I: 0.1544, 95% CI (0.002, 0.465)

Figure 4


a) MODERATED MEDIATION ANALYSIS: SPQ
Conceptual (top) and Statistical (bottom) model
E/I genetic score
PLE
TBW
[Glx]
SPQ
-.41 (15)**
.13 (.16)
-.27 (.14)
E/I genetic score
PLE
TBW
E/I genetic score
x
[Glx]
-.60 (.20)**
-.11 (.15)
.42 (.18)*
.32 (.16)*
.29 (.16)
.43 (.20)*
[Glx]
-.32 (.15)*
SPQ
Low E/I: -0.066, 95% CI (-0.2913, -0.0027)
Intermediate E/I: -0.022, 95% CI (-0.1249, -0.0014)
High E/I: 0.036, 95% CI (0.0001, 0.2075)


b) NEURAL TUNING CURVE FOR SCHIZOPHRENIA RISK
Cognitive-Perceptual Schizotypy Risk
max
min
max
Temporal resolution of multisensory perception
Temporal structure of resting-state activity
Interaction between genetic and neurochemical factors
INHIBITION
-
EXCITATION
+

	AUDITORY	MPFC
Glx/NAA_{tot}	0.587±0.096	0.684±0.088
$GABA/NAA_{tot}$	0.269±0.036	0.339±0.040
CSF	0.115±0.037	0.106±0.035
GM/WM	1.1632±0.352	1.744±0.229
PLE (β)	1.027±0.188	1.431±0.233
SD (σ)	0.390±0.078	0.503±0.009

Table 1: mean values ± SD of neurochemical variables.

			Molecular Characteristics			Phenotype Association Studies		Genotype Distribution		
Gene	**Protein/ Function**	**SNP**	**SNP location**	**Effect on expression**	**Hypothesized mechanism**	**Disorders**	**Endophenotype**	**Genotypes**	**N**	**E/I profile**
GRIN1	Excitatory NMDA receptor (subunit NR1)	rs11146020	5'UTR	N/A	C allele may alter consensus binding sequence of p50 subunit of NF-kB transcription factor[44]	schizophrenia[44, 58] bipolar disorder[59]	depressive symptoms[60]	G/C G/G	8 29	Intermediate High
GRIK3	Excitatory glutamate kainate receptor (subunit 3)	rs6691840	coding	T allele associated with lower expression in brain tissue[61]	T allele may decrease expression by facilitating allele-specific imprinting[61]	schizophrenia[45, 62, 63], recurrent depression[64]	depressive symptoms[65]	T/T T/G G/G	19 16 2	Low Intermediate High
GAD1	glutamate decaroboxylase 1 enzyme – converts Glu to GABA	rs3749034	5'UTR	G allele associated with lower expression in brain tissue of schizophrenic patients[46]	G allele may alter binding sites of transcription factors AREB6 and MYOD1[46]; may further modulate E/I balance by altering expression of nearby potassium-chloride transporter gene *SLC12A5* (KCCN2)[66, 67]	schizophrenia [46, 68, 69], panic disorder (females only)[70]	working memory and PFC function [46, 69]; cortical thickness in parahippocampal gyrus[71]	A/A G/A G/G	2 11 24	Low Intermediate High
GABRB2	Inhibitory GABA A receptor (beta 2 subunit)	rs187269	intronic	C allele associated with lower expression in brain tissue of sz patients[67, 72]	C allele may alter an intronic splice site and reduce expression of select splice variants[72]	schizophrenia[47, 73], bipolar disorder[74]	psychotic symptom severity; altruism/social cognition[75]	T/T C/T C/C	12 21 4	Low Intermediate High

Table 2 Characteristics of the SNPs and distribution of the genetic profile score.

SUPPLEMENTARY METHODS

Behavioral Session

Apparatus and Experimental Procedure

The order of the Simultaneity Judgment (SJ) and Temporal Order Judgment (TOJ) tasks was counterbalanced across participants. During each experiment, participants were blindfolded and comfortably seated beside a table (Supplementary Figure 1a). The audio-tactile apparatus, which was mounted on the table, consisted of (i) two identical loudspeakers, positioned 25 cm to the left and right of the participants' midline, and 30 cm from the participants' body; and (ii) a constant-current electrical stimulator controlling two pairs of neurological electrodes attached on the participant's right and left index fingers. Auditory stimuli consisted of a 3.500-Hz pure tone of 30 ms. Tactile stimuli were single, constant voltage, rectangular monophasic pulse of 100 μs. Participants kept both middle fingers on two separate keys placed on a response box (Cedrus RB-834). Using a staircase procedure, stimulus intensity was titrated at a threshold of 100% of detection for the both auditory and tactile stimulus.

In each SJ and TOJ task, participants received pairs of either auditory-tactile or auditory-auditory stimuli at each trial. The two stimuli in a pair were delivered in opposite hemispaces. The association between side and modality was balanced across trials in the audio-tactile tasks. Stimulus pairs were presented in a randomly interleaved fashion at the following stimulus onset asynchronies (SOAs): ±5. ±10. ±15. ±25. ±40. ±70. ±120. ±200 and ±350 ms (Supplementary Figure 1b). During the audio-tactile tasks the leading stimulus could be either auditory or tactile. The mean intertrial interval was 2000 ms (range: 1500-2500 ms). For each experiment, all the participants completed two blocks of 16 experimental trials per condition (32 in total), each preceded by a block of 16 practice trials.

During the SJ tasks participants had to indicate whether the two stimuli appeared to have been presented simultaneously or asynchronously, while during the TOJ tasks they had to indicate which stimulus in a pair, either the left or the right stimulus, appeared first. Participants responded by button press. We used both tasks, i.e. SJ and TOJ, as they imply different perceptual and/or cognitive operations [1]. Indeed, while SJ task requires a low-level analysis of stimuli in terms of temporal relationships, TOJ task implies additional processing steps following the lower-level analysis of temporal relationships. Despite such dissimilarity, the two tasks share a common underlying process responsible for the ascription of temporal identity at a stimulus level [2]. Such common characteristic allowed us to genuinely measure temporal constraints of multisensory integration in our participants.

Measure of TBWs

A measure of TBW was derived from each Simultaneity Judgment (SJ) and Temporal Order Judgment (TOJ) task.

To calculate the individual TBW in both the multimodal audio-tactile and the unimodal auditory-auditory SJ tasks we first computed the percentage of simultaneous responses across all SOAs for each participant. The observed distribution of responses was fitted to a Gaussian function [3, 4] using the *fit* function implemented in MATLAB (fit type: gauss1). The peak of this curve is referred to as the point of subjective simultaneity (PSS), in that it is assumed that, at this particular SOA, the information from the different modalities is perceived as being maximally simultaneous. Another measure that can be derived from this curve is its standard deviation. The standard deviation is reflected in the width of the curve and is taken as the window of temporal

integration (i.e. Temporal Binding Window, TBW), because it represents the range of SOAs at which the brain treats the two sensory information as belonging to the same event.

The TBW in the both the multimodal audio-tactile and the unimodal auditory-auditory TOJ tasks were calculated for each participant as follows: first we calculated a rate of "right stimulus first" responses with each SOA. Then, a single psychometric function in form of a cumulative Gaussian was fitted to the response rates across all SOAs [2]. This best-fit function was calculated using the *glmfit* (fit type: binomial, probit) function in MATLAB. Each participant's PSS was then extracted. PSS is defined in TOJ tasks as the temporal interval between the stimuli at which "left stimulus first" and "right stimulus first" responses are equally likely (50%). Individual left and right TBWs with respect to the PSS were then estimated. The TBW was measured as the difference in ms between the SOA at which the best-fit sigmoids y value equaled a 25% and the individual's PSS for the left window, and between the 75% and the individual's PSS for the right window [2]. Each participant's left and right TBWs were then summed to produce a third, whole individual TBW.

All participants had good Gaussian fittings for the distributions of their reports of synchrony as a function of SOA during both the unimodal and multimodal Simultaneity Judgement (SJ) tasks (all $R^2 > 0.7$, see Supplementary Table 1). Thus, all participants were considered in the subsequent analyses on the bimodal audio-tactile SJ and the unimodal auditory SJ. In the Temporal Order Judgement (TOJ) tasks, all participants had good cumulative Gaussian fittings for the distributions of their reports of which stimulus came first as a function of SOA during the bimodal audio-tactile task (all $R^2 > 0.7$). Notably, however, one participant did not show a good fitting in the unimodal auditory TOJ task ($R^2 < 0.7$, see Supplementary Table 1). Thus, all participants were considered in the subsequent analyses on the bimodal audio-tactile

TOJ task, while one participant was excluded from the following analysis on the unimodal TOJ task (for similar criteria see [5-8]).

Supplementary Table 1: Goodness-of-fit index (R^2) for the distribution of responses during Simultaneity Judgment (SJ) and Temporal Order Judgment (TOJ) tasks. AT=Audio-Tactile: A=Auditory

	SJ (R^2)		TOJ (R^2)	
Participant	AT	A	AT	A
1	0.71	0.91	0.81	0.92
2	0.94	0.97	0.88	0.91
3	0.95	0.97	0.79	0.93
4	0.81	0.97	0.85	0.86
5	0.96	0.97	0.92	0.94
6	0.96	0.99	0.93	0.44*
7	0.92	0.93	0.90	0.92
8	0.94	0.94	0.79	0.80
9	0.85	0.73	0.82	0.77
10	0.95	0.97	0.75	0.88
11	0.98	0.94	0.85	0.87
12	0.99	0.89	0.77	0.86
13	0.97	0.97	0.82	0.79
14	0.97	0.96	0.88	0.93
15	0.96	0.96	0.67	0.97
16	0.93	0.97	0.86	0.82
17	0.92	0.97	0.78	0.95
18	0.92	0.91	0.86	0.87
19	0.98	0.95	0.89	0.95
20	0.97	0.99	0.87	0.83
21	0.96	0.96	0.88	0.77
22	0.96	0.97	0.82	0.89
23	0.88	0.96	0.77	0.86
24	0.98	0.95	0.80	0.98
25	0.89	0.96	0.88	0.81
26	0.90	0.96	0.82	0.71
27	0.94	0.98	0.90	0.93
28	0.81	0.98	0.79	0.87
29	0.90	0.80	0.81	0.81
30	0.75	0.96	0.76	0.82
31	0.94	0.92	0.71	0.81
32	0.98	0.91	0.85	0.88
33	0.84	0.96	0.82	0.80
34	0.98	0.96	0.85	0.97
35	0.95	0.97	0.89	0.91
36	0.95	0.98	0.90	0.95
37	0.94	0.92	0.87	0.93

MR session

MRS Data Acquisition and Analysis

During MRS acquisition, the scanner was equipped with a Transmit/Receive head coil. First, a 3D T1-weighted anatomical image was acquired (Turbo Field-Echo sequence TFE, TR/TE = 11/5 ms, voxel size 1x1x1 mm^3) for MRS voxel placement and segmentation. Then, 1H-MRS spectra were acquired from two voxels placed in i) the left Auditory cortex (30x30x20 mm^3), parallel to Heschl's gyrus on axial slice, and ii) the MPFC (30x20x30 mm^3), anterior to the genu of the corpus callosum, parallel to the AC-PC plane (Supplementary Figure 2a). The same investigator performed the placement for all subjects. The acquisition order was the same across subjects. For each voxel, GABA+ - edited MEGA-PRESS [9, 10] data were acquired using 14-ms sinc-Gaussian editing pulses applied at 1.9 ppm (ON scans) and 7.46 ppm (OFF scans) and the following parameters: TR/TE=2000/68 ms, spectral width 2000 Hz, data points 1024 for each dynamic scan, dynamic scans 40 (each consisting of a 8-scan phase cycle), total signals averaged 320.

Spectral data analysis (Supplementary Figure 2c) and absolute metabolite quantifications were performed with the well-established and validated LCModel software (http://s-provencher.com/ pub/LCModel/manual/manual.pdf 2005) using a simulated basis set optimized for the scanner (provided by the software producer) which included NAA and NAAG for the fitting. Only quantification results with Cramer–Rao lower bounds (CRLB) below 20% were considered for statistical analysis. Measurements of the GABA and Glx (Glu+Gln) normalized by the complex [NAA–NAAG] were analysed. Thus, hereafter, GABA and Glx will always refer to GABA/[NAA–NAAG] and Glx/[NAA–NAAG], respectively. Results from glutamate and glutamine were quantified together because their spectral peaks overlap considerably, and

therefore the collectively denoted Glx signal is considered as a more robust proxy of the excitatory neurotransmission [11]. The cerebral spinal fluid (CSF), gray matter and white matter content of the MRS voxel were obtained from the T1 weighted image segmentation using SPM8 (Statistical Parametric Mapping release 8, London, UK) CSF fraction and GM/WM ratios were then used as covariates in the statistical analysis.

Resting State fMRI Data Acquisition and Analysis.

During MRI data acquisition, the scanner was equipped with an 8-channel phased array head coil. A 3D T1-weighted anatomical image was acquired (fast field echo T1-weighted sequence. TR/TE = 8.1/3.7 ms. flip angle = 8°, voxel size 1x1x1 mm^3). BOLD contrast images were acquired with a gradient-echo echo-planar sequence (TR 1550 ms; TE 30 ms; 29 axial slices, 0.5 mm gap; voxel size 3x3x3 mm^3). Eyes-closed resting-state data were acquired during two 6-min runs.

Preprocessing steps were implemented in AFNI [12]; http://afni.nimh.nih.gov/afni) including: (1) slice timing correction; (2) rigid body correction/realignment within and across runs; (3) co-registration with high-resolution anatomical images; (4) spatial normalization into Talaraich stereotactic space [13]; (5) resampling to 3×3×3 mm3 voxels; (6) regressing out linear and non-linear drift, head motion and its temporal derivative, and mean time series from the white matter (WM) and cerebrospinal fluid (CSF) to control for non-neural noise [14]. The WM and CSF masks were eroded by one voxel [15] to minimize partial voluming with gray matter. (7) Spatial smoothing with a 6 mm full-width at half-maximum isotropic Gaussian kernel; (8) data filtering between 0.01~0.32 Hz. The lower-frequency limit was chosen to avoid signal

contributions from scanner drift [16], whereas the higher limit on the frequency range was constrained by the sampling rate (Nyquist frequency). (9) For the Power Law Exponent calculation, the time course per voxel of each run was normalized to zero mean and unit variance (z-value) to account for differences in variance of non-neural origin (e.g. distance from head coil) [17].

ROIs were 10-mm radius spheres, drawn around the coordinates corresponding to where MRS voxels, either in the auditory cortex or in MPFC, showed the highest overlap across participants. Based on the highest inter-subject overlap of the corresponding MRS voxels. ROIs were drawn around the following peaks (Tailarach coordinates): -49 -17 7, for the Auditory ROI, and 0 47 10, for the MPFC ROI. Following standard preprocessing steps, for each ROI, we computed i) the Power Law Exponent (PLE), as a measure of the temporal structure [18] and self-organized criticality of spontaneous brain activity, and ii) the Standard Deviation (SD) of BOLD signal, as a measure of the temporal variance of the spontaneous activity [19]. We used SD to control for the specificity of the predictive power of PLE for TBW, as SD and PLE are known to be related [20].

i) PLE. First, for each participant and run, we computed the normalized power spectrum for each voxel using the AFNI program: 3dPeriodogram, with additional smoothing in the frequency direction by three point linear filter (0.15a+0.70b+0.15c). Second, the power spectra of the two runs were averaged. Similar to Welch's method, this approach could reduce noise, caused by imperfect and finite data, in exchange for reducing the frequency resolution. Third, the power spectra were averaged across the voxels and across subjects for each ROI. In a next step, the mean power spectrum of each ROI was fitted with a power-law function $P \propto 1/f^{\beta}$ using least-square estimation (in a log frequency by log power plot) in the frequency range of 0.01~0.32 Hz.

Lastly, the Power-Law Exponent of each ROI was defined as the slope of the linear regression of log-power on log-frequency corresponding to the straight-line regime.

ii) SD. First, for each participant and each voxel we calculated the SD of the BOLD signal across the concatenated time series, in the frequency range of 0.01~0.32 Hz. This yielded an SD map for each subject. Second, subject-level voxel-wise SD maps were standardized into subject-level Z-score maps, i.e. by subtracting the mean voxel-wise SD obtained for the entire brain, and then dividing by the SD [21]. Third, the standardized SD values were averaged across the voxels and across participants for each ROI.

The average PLE across participants in the Auditory ROI was 1.03 ±.19, ranging from .64 to 1.37, while in the MPFC ROI it was 1.43 ±.23, ranging from .86 to 1.80 (Supplementary Figure 2b). The average SD across participants in the Auditory ROI .54 ±.08 (± s.d. indicated) ranging from .41 to .77, while in the MPFC ROI it was .64 ±.10 ranging from .43 to .87.

Genotyping

Genomic DNA was extracted from blood samples by using the nucleoSpin Tissue kit (Macherey-Nagel). Samples were sequenced following PCR amplification using the primers listed in Supplementary Table 2. The amplification conditions were denaturation at 94°C for 10 min followed by 30 cycles at 94°C for 30 sec, 30 sec at the annealing temperature optimum for each pair of primers, 72°C for 30 sec, with a final elongation step at 72°C for 10 min. PCR products were separated on 2% agarose gel electrophoresis to confirm the specificity of the products amplificated. PCR products were purified and sequenced using an ABI PRISM 3100 genetic analyzer (Applied Biosystems, Carlsbad, CA, USA).

Supplementary Table 2

Polymorphism	Primer Forward	Primer Reverse	Annealing Temperature
GAD1 rs3749034	GGTCGCTAGCTTACCCACCT	CGCCTCTCCGAATCTCTCT	61
GABRB2 rs187269	TTCCTGTTATAGCACTTGCTGC	CTAGACCCTTACGGTTTTTTGG	61
GRIN1 rs11146020	GTCCAGTTTCCAGGCTCTC	CTCCCCACAAGGTTCAGAAA	60
GRIK3 rs6691840	GAAGCCCCTGGAATTCACCT	CCGGATTCTCAATGTGGACAA	60

Supplementary Table 3: correlation among the variables included in the moderated mediation model.

		TBW	PLE	Gscore	Glx	GABA	SPQ
TBW	Corr	1	-.557**	-.185	-.020	-.024	.324
	Sig. (2-tails)		.000	.272	.905	.889	.050
	N	37	37	37	37	37	37
PLE	Corr	-.557**	1	-.012	.139	.142	.067
	Sig. (2-tails)	.000		.943	.413	.400	.693
	N	37	37	37	37	37	37
Gscore	Corr	-.185	-.012	1	-.204	.266	-.084
	Sig. (2-tails)	.272	.943		.225	.111	.622
	N	37	37	37	37	37	37
Glx	Corr	-.020	.139	-.204	1	.061	-.277
	Sig. (2-tails)	.905	.413	.225		.719	.097
	N	37	37	37	37	37	37
GABA	Corr	-.024	.142	.266	.061	1	-.029
	Sig. (2-tails)	.889	.400	.111	.719		.866
	N	37	37	37	37	37	37
SPQ	Corr	.324	.067	-.084	-.277	-.029	1
	Sig. (2-tails)	.050	.693	.622	.097	.866	
	N	37	37	37	37	37	37

** p<0.01 (2-tails).

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FIGURE LEGENDS

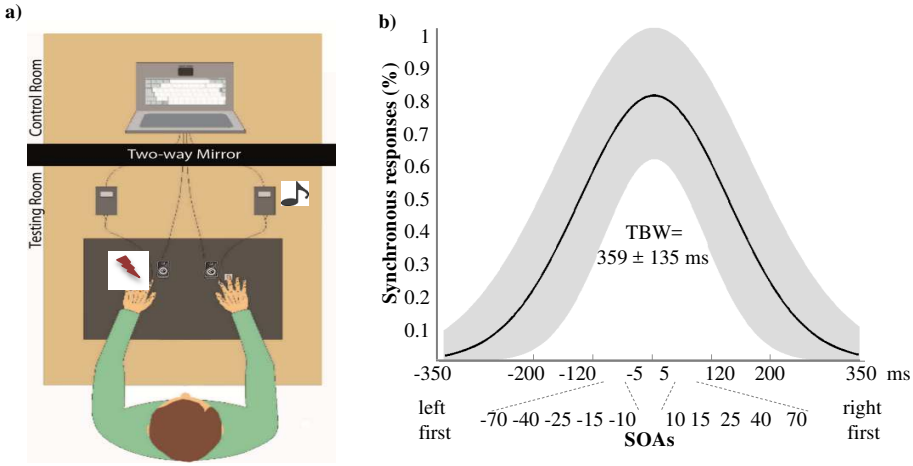
Supplementary Figure 1 *Audio-Tactile Simultaneity Judgment task.* a) Experimental set-up, b) Group mean curve (black), and standard deviations (gray), used to derive the mean Temporal Binding Window (TBW). SOAs=Stimulus Onset Asynchronies between the stimuli.

Supplementary Figure 2 a) VOIs for single voxel proton MR spectroscopy (one participant), b) Individual (gray) and group mean (black) resting-state power spectra from the Auditory and MPFC ROIs used to compute individual values of the Power Law Exponent (PLE), c) Representative MEGA-PRESS spectrum for each VOI (one participant). GABA=gamma-aminobutyric acid; Glx=glutamate+Glutamine; NAA= N-Acetylaspartate.

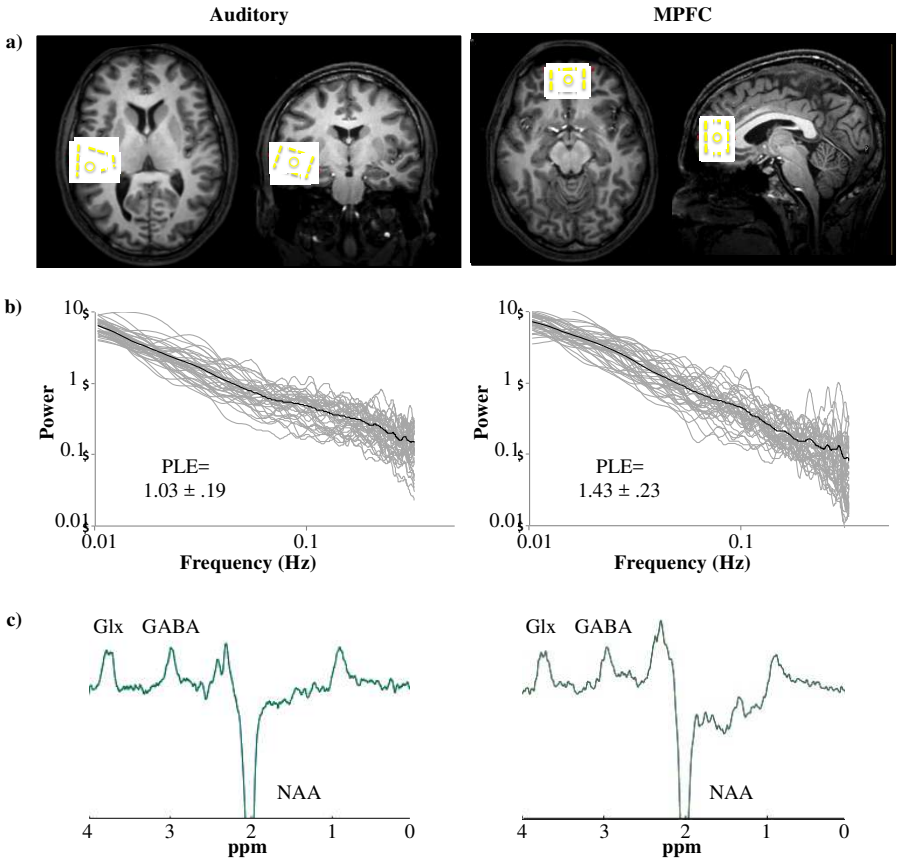
Supplementary Figure 3

a) *Moderation models testing the impact of GABA concentrations on PLE and TBW, at different values of individual E/I genetic scores (=the moderator).* a) Conceptual and statistical depiction of the effects tested, i.e. the main effect of each of the two factors and their interaction, b) Statistical relevance of the effects of Low, Intermediate and High E/I score values for the impact of GABA concentrations on PLE and TBW. No significant effects emerged. Statistical analyses were carried out with standardized values for all the variables. Notably, for visualization purposes, slope estimates are presented at discrete values of the moderator (genetic E/I scores). However, these estimates are based on the linear trends present in the entire sample (i.e. no arbitrary splitting of the sample was performed).

Supplementary Figure 1



Supplementary Figure 2



Supplementary Figure 3