Perceptual phenotypes: Perceptual gains and losses in synesthesia and schizophrenia

Tessa M. van Leeuwen[1,2,3,*], Andreas Sauer[1,2], Anna-Maria Jurjut[1], Michael Wibral[4], Peter J. Uhlhaas[1,5], Wolf Singer[1,2,6], Lucia Melloni[1,7,8*]

[1]Department of Neurophysiology, Max Planck Institute for Brain Research, Frankfurt am Main, Germany

[2]Ernst Strüngmann Institute (ESI) for Neuroscience in Cooperation with Max Planck Society, Frankfurt am Main, Germany

[3]Radboud University, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, the Netherlands

[4]Magnetoencephalography Unit, Brain Imaging Center, Johann Wolfgang Goethe University, Frankfurt am Main, Germany

[5]Institute of Neuroscience and Psychology, University of Glasgow, Scotland

[6]Frankfurt Institute for Advanced Studies, Johann Wolfgang Goethe University, Frankfurt am Main, Germany

[7] Department of Neurology, New York University School of Medicine, New York, USA

[8]Department of Neuroscience, Max Planck Institute for Empirical Aesthetics, Frankfurt am Main, Germany

* Corresponding authors: T.M.v.L. (tesvlee@gmail.com) and L.M. (lucia.melloni@ae.mpg.de)

Running title: Perception in synesthesia and schizophrenia

Manuscript length: 2626 words

Abstract

No two individuals experience the world the same way. On a spectrum of inter-individual variability, synesthetes, for instance, experience additional sensations, while schizophrenia patients suffer perceptual deficits. Is there a unifying principle explaining inter-individual variability in perception? Perceptual experience results from inferential processes whereby sensory evidence is weighted by prior knowledge about the world. Different perceptual phenotypes may then stem from different weighting of sensory evidence and prior knowledge. We tested this hypothesis by comparing visibility thresholds in a perceptual closure task across medicated schizophrenia patients (N=20), synesthetes (N=20), and controls (N=26). Participants rated the subjective visibility of illusory contours of stimuli embedded in noise while the availability of sensory evidence was manipulated parametrically. Additionally, implicit priors in synesthetes were manipulated by presenting either synesthesia-inducing or neutral stimuli. Schizophrenia patients showed increased visibility thresholds, consistent with overreliance on sensory evidence and reduced influence of prior knowledge. In contrast, synesthetes exhibited lowered thresholds exclusively for synesthesia-inducing stimuli suggesting synesthetic experiences arise through excess implicit priors. Additionally, both in synesthetes and schizophrenics explicit top-down priors lowered thresholds but did not normalize perception in either group. Our results indicate that perceptual phenotypes might be traced to automatic differences in perceptual inference which are not overcome by conscious, explicit priors.

Keywords: perceptual closure, predictive coding, circular inference, inter-individual variability, synaesthesia, schizophrenia

Introduction

Schizophrenia is a neuropsychiatric disorder that is not only characterized by positive symptoms like hallucinations and delusions, but also by perceptual *deficits* such as impaired perceptual grouping and object recognition deficits (Doniger *et al.*, 2001; Uhlhaas and Silverstein, 2005; Berkovitch *et al.*, 2017; van de Ven *et al.*, 2017). On the other end of the spectrum lies synesthesia, a form of altered perception in which specific stimuli (e.g., letters) automatically trigger vivid *additional* conscious experiences (e.g., color), described as being percept-like (Ward, 2013). These synesthetic experiences are associated with activation of cortical areas (e.g., color-sensitive) known to process stimulus qualities of the synesthetic concurrent experience (e.g. van Leeuwen *et al.*, 2010; for a review see Rouw *et al.*, 2011).

Is there a unifying principle that can explain such disparate perceptual phenotypes? Perceptual experience results from inferential processes whereby sensory evidence is weighted by top-down prior knowledge about the world (Friston, 2005). Inter-individual differences in how top-down priors are balanced against sensory evidence during perceptual inference may explain differences in perceptual experience (Powers *et al.*, 2017; Karvelis *et al.*, 2018). A recent study has demonstrated such an imbalance in inferential processes for confidence judgments in schizophrenia, resulting in erroneous metacognition (Jardri *et al.*, 2017). Confidence, however, does not directly capture the subjective, qualitative aspect of perception (Rosenthal, 2018). Thus, whether alterations in inferential processing can explain *perceptual* differences across individuals and patient populations remains unknown.

Here, we focus on schizophrenia and synesthesia and investigate whether alterations in *perceptual* inference may explain their diverse perceptual phenotypes. In schizophrenia, forward propagation of sensory evidence without appropriate top-down corrective priors may cause overreliance on sensory information (Jardri and Denève, 2013a; Jardri and Denève, 2013b; Sterzer *et al.*, in press) thereby explaining for instance the paradoxical immunity to perceptual illusions observed in schizophrenics (Uhlhaas *et al.*, 2004). In synesthesia, excess (top-down) priors may explain the experience of concurrent sensations (e.g., color) without actual sensory input (e.g., black letters) (Seth, 2014; van Leeuwen, 2014). Priors may dominate in synesthesia due to hyperexcitability of (visual) cortex in synesthetes (Terhune *et al.*, 2011; Terhune *et al.*, 2015); the resulting noisy sensory processing may cause a stronger reliance on priors than on sensory information. Alternatively, excessive neural communication due to increased white

matter connectivity might lead to enhanced top-down propagation of priors (Rouw and Scholte, 2007). Excess forward propagation (schizophrenia) or excess priors (synesthesia) may then erroneously be re-interpreted along the cortical hierarchy, leading to 'circular inference' (Jardri and Denève, 2013b; Jardri *et al.*, 2017) and help explain insensitivity to perceptual illusions and the emergence of additional percepts, respectively.

We evaluated the weighting of sensory signals and priors in perceptual inference in schizophrenia patients, synesthetes, and controls. We used a well-established visual closure paradigm (Fig. 1A) which relies on perception of contours of letters or symbols in noise (Kleinschmidt *et al.*, 2002; Melloni *et al.*, 2011; Mayer *et al.*, 2016). Illusory contour perception is vivid, strongly influenced by previous experience (implicit priors) (Wokke *et al.*, 2013), and believed to rely on cortical NMDA(N-methyl-D-aspartate)-dependent feedback projections (van Loon *et al.*, 2016). The effect of top-down priors is strongest when sensory input is weak, noisy and ambiguous (de Lange *et al.*, 2018). We capitalized on this effect to investigate the relative weighting of sensory evidence and priors in perception across the three populations. We hypothesized that if sensory evidence is weighted heavily compared to implicit priors, perception of illusory boundaries is less likely and visibility is low. This may occur in schizophrenics. In contrast, if priors are dominant, perception of illusory boundaries is more likely and concomitantly visibility should be higher. This may occur in synesthetes when confronted with stimuli inducing strong priors, e.g., graphemes.

To test these predictions, we parametrically manipulated sensory evidence (Fig. 1A) while subjects rated stimulus visibility. To manipulate implicit priors in synesthetes we presented either synesthesia-inducing stimuli (letters/numbers) or neutral stimuli (symbols) (Fig. 1B). Thus, we expected priors to selectively affect visibility for synesthesia-inducing stimuli in synesthetes, while the neutral condition served as an internal control. For schizophrenia patients, we hypothesized fewer perceived stimuli regardless of stimulus condition due to pervasive overreliance on sensory evidence.

We also evaluated whether additional, explicit top-down priors can normalize perception, i.e., bring schizophrenics' and synesthetes' perception closer to that of controls. For this purpose, we first increased sensory evidence until all stimuli were clearly recognized (Level 4 in Fig 1A); from this point on, an explicit prior was available. We then continuously decreased sensory evidence again to test this prior's effect (Kleinschmidt *et al.*, 2002; Melloni *et al.*, 2011; Mayer *et*

al., 2016). This manipulation allowed us to separately investigate the contribution of implicit, automatic, and explicit priors to perception. While both affect perception their underlying mechanism are thought to differ; and might be independently affected.

Materials and Methods

Participants

Twenty synesthetes (mean age 29.2±8.2 years, 19 females), twenty schizophrenia patients (mean age 39.7±12.4 years, 9 females), and twenty-six control participants (mean age 30.7±7.8 years, 17 females) participated in the study. A subset of 20 controls were specifically matched to the synesthete group in age and gender and an overlapping subset of controls was matched to the schizophrenia patients (all $p>.10$, see Table 1). Age and gender differed significantly between the synesthete and the schizophrenia group ($t(38)=-3.08$, $p<.01$ and $t(38)=-4.01$, $p<.001$, respectively) and were included as covariates of no interest in all analyses. All participants gave written informed consent prior to the study, in accordance with the declaration of Helsinki. The study was approved by the ethics committee of the Medical Faculty at Goethe University Frankfurt, Germany.

All participants completed a short screening questionnaire about their medical history and a test for synesthesia prior to participation (the "Synesthesia Battery", Eagleman *et al.*, 2007; for procedure see Supplementary Material, for scores see Table 1). Synesthetes additionally completed two questionnaires about the spatial location of their synesthesia: the Projector-Associator questionnaire (Rouw and Scholte, 2007; van Leeuwen *et al.*, 2010), and the Illustrated Synesthetic Experience Questionnaire (Skelton *et al.*, 2009). Controls and synesthetes reported no history of neurological or psychiatric disease, no medication use at the time of the study, and normal or corrected-to-normal vision. Chronic schizophrenia patients were recruited from the psychiatric out-patient unit of the Clinic Frankfurt-Höchst. All patients fulfilled DSM-IV criteria for schizophrenia as verified by a trained psychologist by means of a Structural Clinical Interview for DSM-IV-R (SCID) prior to inclusion. Average disease duration was 14.1±12.9 years; all patients were medicated with atypical neuroleptics. Current psychopathological symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) for schizophrenia (Kay *et al.*, 1987). Scores were obtained for Negative, Positive, Excitement, Cognitive, Depression, and Disorganization subscales (see Table 1). Cognitive function was

assessed with the German version of the Brief Assessment of Cognition in Schizophrenia (BACS) in all subjects (Keefe *et al.*, 2004), for scores see Table 1.

Stimuli and Design

We used a perceptual closure task (Kleinschmidt *et al.*, 2002; Melloni *et al.*, 2011; Mayer *et al.*, 2016) in which participants viewed letters, numbers and symbols embedded in a colored noise background. Sensory evidence was parametrically manipulated by varying the noise level of the stimulus (Fig. 1A) with respect to its background in four steps, effectively providing contours for figure-ground segregation thereby controlling for stimulus' visibility. Sensory evidence was first increased during the first 4 trials, thereby increasing visibility, and subsequently decreased, decreasing visibility. The same token (letter, number or symbol) was used across a sequence of 7 trials. Perception is dominated by bottom-up input and implicit priors during the initial, *sensory evidence increasing phase* of the sequence. In the final, *sensory evidence decreasing phase* of the sequence, when subjects have recognized the stimuli, explicit top-down priors can aid recognition (Kleinschmidt *et al.*, 2002; Melloni *et al.*, 2011; Mayer *et al.*, 2016).

Stimuli used in the sequences were such that in synesthetes they could either elicit synesthesia (letters and/or digits), or be neutral, not eliciting synesthesia (symbols). In the synesthesia inducing condition, the background color was congruent with the synesthetic color of the stimuli. For controls and schizophrenia patients none of the stimuli elicited synesthesia. Thus, this manipulation was only relevant for synesthetes and used to elicit their implicit priors. Example stimuli for both conditions are shown in Fig. 1B. The background color was also randomly assigned to tokens of the neutral, non-synesthetic condition, as symbols did not elicit synesthesia. This prevented precuing a condition (i.e., synesthetic or non-synesthetic condition). Further details about stimulus selection and presentation are provided in the Supplementary Material and Methods.

A total of 1260 trials were presented in four experimental blocks. On each trial (Fig. 1A and Supplementary Fig. 1A), participants rated the subjective visibility of the stimuli on a 4-point Perceptual Awareness Scale (PAS) (Overgaard *et al.*, 2006) defined as 1. No experience; 2. Brief glimpse; 3. Almost clear impression; 4. Clear impression. The use of the PAS was rehearsed with the participants in a practice session of 5-10 sequences to ensure that participants grasped the difference between level 2 (not visible) and 3 (visible) responses. To evaluate the use of the PAS

by the participants and false alarm rate, clearly visible (Level 4) and clearly invisible (Level 1) stimuli where added to the sequence.

Fitting of psychometric functions

For analyses, responses were recoded into a visibility measure of recognition with categories: Not visible (responses 1 and 2) or Visible (responses 3 and 4). The resulting psychometric data from each participant and condition was fitted with logistic functions, each defined by three parameters: threshold, slope, and fixed lapse-rate (Wichmann and Hill, 2001), using the Palamedes Toolbox (Version 1.6.0) for Matlab (http://www.palamedestoolbox.org/). Guess rates were fixed at 0.5 (i.e., chance level) across all subjects and conditions. All three parameters were fitted separately per subject and stimulus condition. Quality of fit for each subject was determined by assessing the square sum of the errors.

Statistical analysis

Fitted threshold and slope values for each participant were submitted to a mixed-repeated measures ANOVA with Group as a between-subject factor (synesthetes, controls, schizophrenia patients) and as within-subject factors Stimulus Condition (synesthesia inducing/neutral) and Phase (sensory evidence increase/sensory evidence decrease). Age and gender were included as covariates of no interest. Data from 5 subjects were removed before statistical analysis because they performed 2 SD below their group mean (2 controls, and 2 schizophrenia patients), or because the curve fitting was of questionable quality (1 control).

Results

Visibility thresholds

Perceptual thresholds differed across groups ($F(2,56)=6.89$, $p<.01$), and were further modulated by whether stimuli induced synesthesia (Group x Stimulus condition $F(2,56)=6.76$, $p<.01$, Fig. 1C-D). Compared to controls, schizophrenia patients perceived fewer stimuli during the increasing sensory evidence phase (group effect $F(1,37)=11.90$, $p<.01$) both for synesthesia-inducing ($F(1,37)=6.63$, $p<.05$) and neutral stimuli ($F(1,37)=16.83$, $p<.001$), indicating more ‘veridical perception’ and suggesting an overreliance on sensory evidence. Synesthetes

selectively perceived more stimuli than controls in the synesthesia-inducing condition during sensory evidence increase; there was no group effect for the neutral condition (Group x Stimulus condition $F(1,39)=9.12$, $p<.01$; Group effect synesthesia-inducing $F(1,39)=10.62$, $p<.01$; Group effect neutral $F(1,39)=1.59$, $p=.215$). This suggests that synesthetes profited specifically from an additional implicit prior (synesthetic color). The specific form of synesthesia (projector/associator) did not affect perceptual thresholds (see Supplementary Results for analyses).

We also evaluated the contribution of *explicit* top-down priors to perception. We found that while they boosted perception ($F(1,56)=5.77$, $p<.05$) by lowering perceptual thresholds in the sensory evidence decreasing condition similarly across schizophrenics, synesthetes, and controls ($F(2,56)<1$, n.s., Fig. 2), they did not override the different perceptual phenotypes that were evident in the increasing sensory evidence phase (Supplementary Fig. 1B/C).

Learning of the stimulus set

To determine whether the lowered perceptual threshold in synaesthetes could be explained by the strategic use of their synesthetic colors to infer the hidden stimulus, as opposed to the contribution of an implicit prior, we focus on learning of the stimulus set during the experiment. We analyzed visibility scores and reaction times (RTs) for the first three instances of each stimulus for synesthetes (N=20) and their matched controls (N=20) (for methods details see Supplementary Methods). While learning commonly occurs during experiments, and thus a main effect of repetition could be anticipated, we focused on an interaction between group, condition, and repetition, which would indicate that learning occurs at a differential rate for synesthetes and specifically for the synesthesia inducing condition, i.e., letters/numbers.

For visibility scores, none of the interactions with Repetition were significant (all $p>.10$). As expected, we found a main effect of Repetition ($F(2,76)=15.9$, $p<.001$), indicating that stimuli were better recognized with repeated occurrences. A Group x Condition interaction was also present ($F(1,38)=7.32$, $p<.05$) confirming our main results of better performance for the synesthetes specifically in the synesthesia inducing condition. For RTs, we only observed a Repetition x Group interaction, $F(2,76)=4.00$, $p<.05$), whereby synesthetes exhibited a repetition effect ($F(2,38)=9.20$, $p<.01$) while controls did not ($F(2,38)=1.39$, $p=.26$). Critically, the effect of repetition in the RTs in synesthetes was not modulated by whether the stimuli elicited a

synesthetic experience (interaction of Repetition x Condition ($F(2,38)<1$)) and there was also no main effect of Group in the RTs ($F(1,38)=0.67$, $p=.42$). These results indicate that synesthetes do not appear to make strategic use of their synesthetic color which could explain their lowered psychophysical thresholds in the main experiment. Additional support for this conclusion comes from the analysis of RTs for synesthesia inducing stimuli upon the first encounter of the stimulus, which shows that synesthetes are not faster than controls to recognize synesthesia inducing stimuli at first presentation (see Supplementary Results).

Discussion

The results on perceptual thresholds support the hypothesis that imbalances in perceptual inference may underlie different perceptual phenotypes. While the performance of schizophrenia patients on our perceptual closure task can be explained by an overreliance on sensory evidence, synesthetes appeared to profit from additional implicit priors. Analysis on the learnability of the stimulus set rules out the possibility that the lowered visibility threshold in synaesthetes may be explained by strategic control reinforcing the proposal that enhanced use of implicit priors specific to that population may explain the differences in perceptual threshold.

In schizophrenia, dysfunction of NMDA-receptors has been implicated both in disease progression and symptoms (Snyder and Gao, 2013). Proper glutamatergic NMDA-receptor mediated signaling is implicated in top-down predictive signals that lead to inhibition of incoming sensory information (Sterzer *et al.*, in press). Hence, dysfunction of NMDA-receptors could explain perceptual deficits due to an overreliance on sensory evidence not properly counterbalanced by priors. These results are also compatible with the account of circular inference in which sensory evidence may be ‘counted’ several times (Jardri *et al.*, 2017). When considering the underlying mechanisms we note that our patients were medicated at the time of study.

Synesthesia is characterized by enhanced white matter connectivity indicative of excessive neural communication (Rouw and Scholte, 2007). Excess connectivity may be driving the stronger influence of prior information during perceptual inference and explain the lowered visibility thresholds specifically for synesthesia-inducing stimuli. Alternatively, reliance on sensory evidence may be reduced due to hyperexcitability of the cortex (Terhune *et al.*, 2011; Terhune *et al.*, 2015).

Remarkably, while clearly differing in the weighting of implicit priors, schizophrenics and synesthetes profit equally from additional, explicit top-down knowledge to improve perception. Yet, those explicit cues do not normalize perception neither in schizophrenics nor in synesthetes relative to controls. This suggests that additional priors derived from context are not strong enough to overcome the fundamental imbalance that is present in perceptual inference in both conditions.

In summary, we demonstrate that for a spectrum of perceptual phenotypes – from schizophrenia patients to synesthetes – perceptual variability can be explained by differential weighting of bottom-up sensory evidence and top-down priors. Additionally, the results are in line with the hypothesis of circular inference in schizophrenia, extending this framework from deficits in metacognition to inter-individual differences in phenomenological experience.

Acknowledgments

We thank Caspar M. Schwiedrzik for invaluable comments on the manuscript and Dr. Michael Grube for assistance in recruitment of schizophrenia patients.

Funding

This study was funded by LOEWE-Neuronale Koordination Forschungsschwerpunkt Frankfurt (NeFF).

Author Contributions

T.M.v.L. performed experiments; L.M. conceptualized the study; T.M.v.L. and L.M. designed the experiments, analyzed the data, and wrote the paper; A.S. assisted in patient recruitment and behavioral testing; A.-M.J. assisted in participant recruitment; M.W. provided data acquisition resources; P.J.U. assisted in patient recruitment and institutional review board approval; W.S. reviewed and edited the paper. W.S. and L.M. secured funding.

Declaration of Interests

The authors declare no competing interests.

References

Berkovitch L, Dehaene S, Gaillard R. Disruption of Conscious Access in Schizophrenia. Trends Cogn Sci 2017; 21(11): 878-92.

de Lange FP, Heilbron M, Kok P. How Do Expectations Shape Perception? Trends Cogn Sci 2018; 22(9): 764-79.

Doniger GM, Silipo G, Rabinowicz EF, Snodgrass JG, Javitt DC. Impaired sensory processing as a basis for object-recognition deficits in schizophrenia. Am J Psych 2001; 158(11): 1818-26.

Eagleman DM, Kagan AD, Nelson SS, Sagaram D, Sarma AK. A standardized test battery for the study of synesthesia. Journal of Neuroscience Methods 2007; 159(1): 139-45.

Friston K. A theory of cortical responses. Philos Trans R Soc B-Biol Sci 2005; 360(1456): 815-36.

Jardri R, Denève S. Circular inferences in schizophrenia. Brain 2013a; 136: 3227-41.

Jardri R, Denève S. Computational Models of Hallucinations. In: Jardri R, Cachia A, Thomas P, Delphine P, editors. The Neuroscience of Hallucinations. New York, USA: Springer Science+Business Media 2013b.

Jardri R, Duverne S, Litvinova AS, Denève S. Experimental evidence for circular inference in schizophrenia. Nat Comm 2017; 8: 14218.

Karvelis P, Seitz AR, Lawrie SM, Seriès P. Autistic traits, but not schizotypy, predict increased weighting of sensory information in Bayesian visual integration. eLife 2018; 7: e34115.

Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophr Bull 1987; 13(2): 261-76.

Keefe RSE, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res 2004; 68(2-3): 283-97.

Kleinschmidt A, Büchel C, Hutton C, Friston KJ, Frackowiak RSJ. The Neural Structures Expressing Perceptual Hysteresis in Visual Letter Recognition. Neuron 2002; 34(4): 659-66.

Mayer A, Schwiedrzik CM, Wibral M, Singer W, Melloni L. Expecting to See a Letter: Alpha Oscillations as Carriers of Top-Down Sensory Predictions. Cereb Cortex 2016; 26(7): 3146-60.

Melloni L, Schwiedrzik CM, Müller N, Rodriguez E, Singer W. Expectations Change the Signatures and Timing of Electrophysiological Correlates of Perceptual Awareness. J Neurosci 2011; 31(4): 1386-96.

Overgaard M, Rote J, Mouridsen K, Ramsoy TZ. Is conscious perception gradual or dichotomous? A comparison of report methodologies during a visual task. Conscious Cogn 2006; 15(4): 700-8.

Powers AR, Mathys C, Corlett PR. Pavlovian conditioning–induced hallucinations result from overweighting of perceptual priors. Science 2017; 357(6351): 596-600.

Rosenthal D. Consciousness and confidence. Neuropsychologia 2018.

Rouw R, Scholte HS. Increased structural connectivity in grapheme-color synesthesia. Nat Neurosci 2007; 10(6): 792-7.

Rouw R, Scholte HS, Colizoli O. Brain areas involved in synaesthesia: A review. Journal of Neuropsychology 2011; 5(2): 214-42.

Seth AK. A predictive processing theory of sensorimotor contingencies: Explaining the puzzle of perceptual presence and its absence in synesthesia. Cogn Neurosci 2014; 5(2): 97-118.

Skelton R, Ludwig C, Mohr C. A novel, illustrated questionnaire to distinguish projector and associator synaesthetes. Cortex 2009; 45(6): 721-9.

Snyder MA, Gao W-J. NMDA hypofunction as a convergence point for progression and symptoms of schizophrenia. Frontiers in Cellular Neuroscience 2013; 7(31).

Sterzer P, Adams RA, Fletcher P, Frith C, Lawrie SM, Muckli L, *et al.* The Predictive Coding Account of Psychosis. Biological Psychiatry in press.

Terhune DB, Song SM, Cohen Kadosh R. Transcranial alternating current stimulation reveals atypical 40 Hz phosphene thresholds in synaesthesia. Cortex 2015; 63: 267-70.

Terhune Devin B, Tai S, Cowey A, Popescu T, Cohen Kadosh R. Enhanced Cortical Excitability in Grapheme-Color Synesthesia and Its Modulation. Curr Biol 2011; 21(23): 2006-9.

Uhlhaas PJ, Silverstein SM. Perceptual organization in schizophrenia spectrum disorders: Empirical research and theoretical implications. Psychol Bull 2005; 131(4): 618-32.

Uhlhaas PJ, Silverstein SM, Phillips WA, Lovell PG. Evidence for impaired visual context processing in schizotypy with thought disorder. Schizophr Res 2004; 68(2): 249-60.

van de Ven V, Rotarska Jagiela A, Oertel-Knöchel V, Linden DEJ. Reduced intrinsic visual cortical connectivity is associated with impaired perceptual closure in schizophrenia. NeuroImage: Clinical 2017; 15(Supplement C): 45-52.

van Leeuwen TM. Constructing priors in synesthesia. Cogn Neurosci 2014: 1-2.

van Leeuwen TM, Petersson KM, Hagoort P. Synaesthetic Colour in the Brain: Beyond Colour Areas. A Functional Magnetic Resonance Imaging Study of Synaesthetes and Matched Controls. PLoS ONE 2010; 5(8): e12074.

van Loon AM, Fahrenfort JJ, van der Velde B, Lirk PB, Vulink NCC, Hollmann MW, *et al*. NMDA Receptor Antagonist Ketamine Distorts Object Recognition by Reducing Feedback to Early Visual Cortex. Cereb Cortex 2016; 26(5): 1986-96.

Ward J. Synesthesia. Annu Rev Psychol 2013; 64(1): 49-75.

Wichmann FA, Hill NJ. The psychometric function: I. Fitting, sampling, and goodness of fit. Percept Psychophys 2001; 63(8): 1293-313.

Wokke ME, Vandenbroucke ARE, Scholte HS, Lamme VAF. Confuse Your Illusion: Feedback to Early Visual Cortex Contributes to Perceptual Completion. Psychol Sci 2013; 24(1): 63-71.

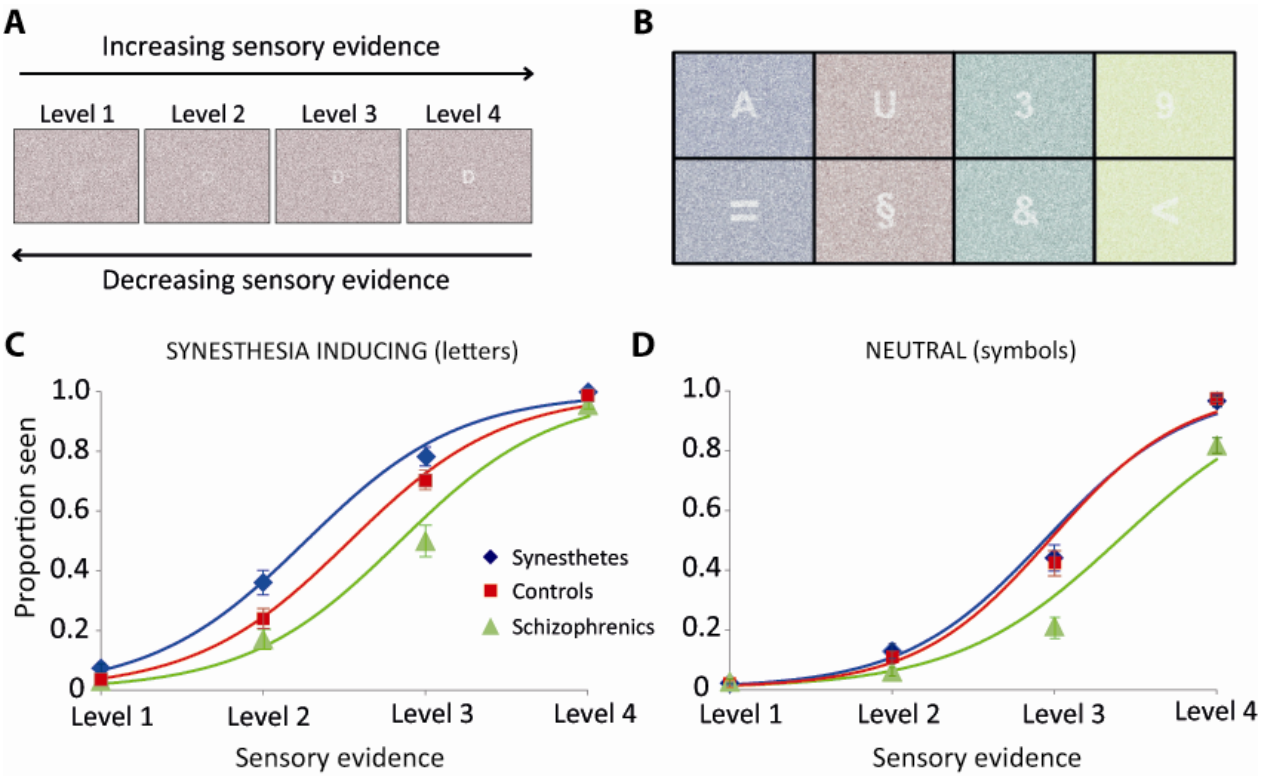

Figure 1. Paradigm and main results.

(A) Example sequence from the synesthesia inducing stimulus condition: Across a sequence of 7 trials, sensory evidence was first parametrically increased across 4 levels (trial 1 to 4) and then decreased (trial 5-7). The same token (letter, number or symbol) was used in a sequence. During the phase in which sensory evidence is increased, perception is strongly influenced by sensory evidence and implicit top-down priors. In turn, when sensory evidence is decreased, after subjects have recognized the stimuli (around level 3-4), explicit top-down perceptual expectations further contribute to perception. (B) Example stimuli from the synesthesia (top) and neutral (bottom) condition. Stimulus background was colored either congruently with synesthetic stimuli (e.g., letters for the synesthetes), or was neutral (e.g., symbols). (C and D) Psychometric curve fits for each group in the synesthesia-inducing and the neutral condition, respectively, for trials in which sensory evidence was increased. Error bars depict the standard error of the mean. For results see main text.

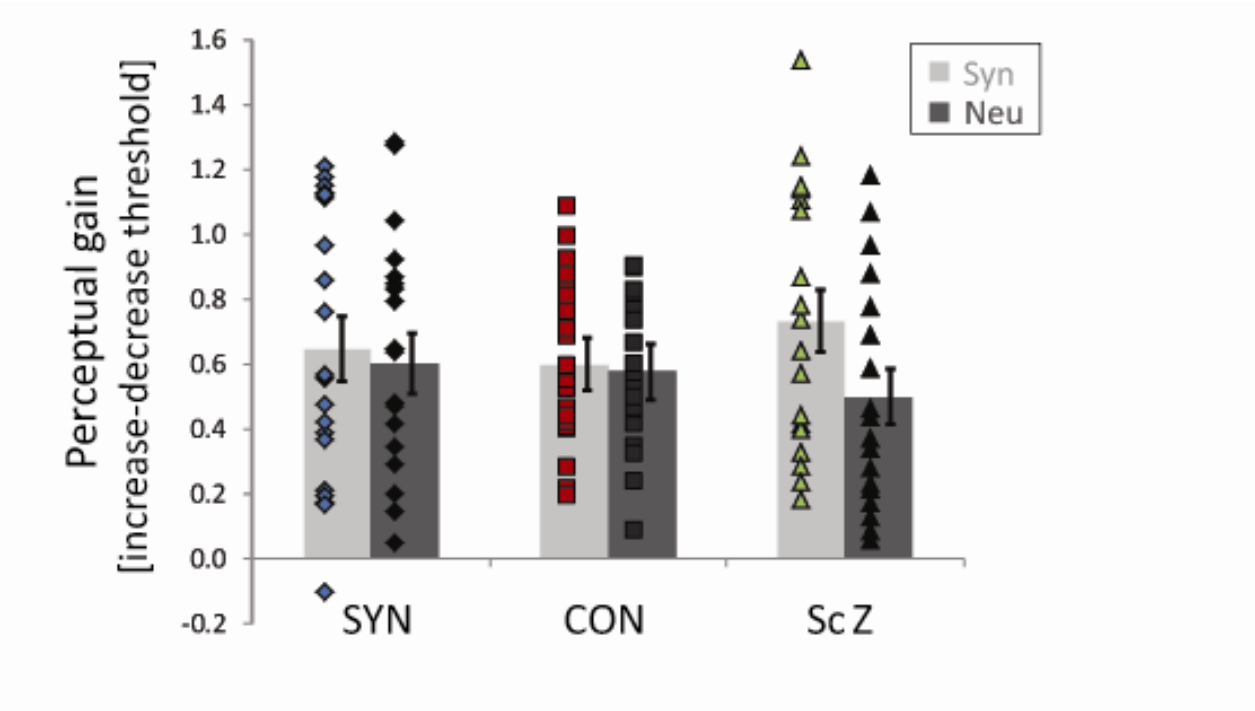

Figure 2. Explicit priors boost perception

Recognizing the stimuli creates an explicit prior which lowers the threshold of perception when sensory evidence is decreased (trials 5-7). This results in higher number of perceived trials than in the increasing sensory evidence condition (1-3, Fig 1C) even though sensory evidence is the same in both conditions. Plotted here is the perceptual gain, i.e. perceptual threshold for increasing minus decreasing sensory evidence trials. Perceptual gain is similar across groups. Diamonds, squares, and triangles represent single participants. SYN = synesthete group, CON = control group, ScZ = schizophrenia patients, Syn = synesthesia inducing condition, Neu = neutral stimulus condition.

Table 1. Demographics, PANSS and BACS scores of participants.

	Schizophrenia patients (N=20)	Healthy controls (N=26)	Synesthetes (N=20)	Statistics ScZ-HC	Statistics HC-SYN
Demographics					
Gender (M/F)	11/9	9/17	1/19		
Age (yrs)	39.65 ± *12.64**	30.73 ±*7.84**	29.25 ±*8.22*	$t_{(35)}$= 1.56 p=0.13*	$t_{(38)}$= 0.12, p=0.91*
Handedness (R/L)	19/1	23/3	17/3		
BACS**					
Verbal memory	39.76 ±*7.73*	60.46 ±*7.86*	60.84 ±*6.84*	$t_{(39)}$= 8.36 p<.001	$t_{(41)}$= 0.17 n.s.
Digit	16.00 ±*2.55*	24.88 ±*3.08*	24.74 ±*2.31*	$t_{(39)}$= 9.73 p<.001	$t_{(41)}$= -0.16 n.s.
Motor	78.53 ±*20.80*	92.26 ±*7.39*	94.32 ±*6.77*	$t_{(39)}$= 2.99 p<.01	$t_{(41)}$= 0.96 n.s.
Fluency	45.24 ±*13.34*	64.33 ±*11.46*	64.79 ±*10.35*	$t_{(37)}$= 4.86 p<.001	$t_{(39)}$= 0.13 n.s.
Symbol coding	45.41 ±*11.75*	66.50 ±*12.40*	71.16 ±*13.30*	$t_{(39)}$= 5.48 p<.001	$t_{(41)}$= 1.18 n.s.
Tower of London	14.76 ±*5.06*	19.30 ±*1.96*	19.05 ±*2.39*	$t_{(39)}$= 4.01 p<.001	$t_{(41)}$= -0.36 n.s.
Total score	239.71 ±*31.75*	328.15 ±*28.29*	334.84 ±*23.79*	$t_{(37)}$= 9.18 p<.001	$t_{(39)}$= 0.81 n.s.
PANSS***					
Negative	14.44 ±*4.98*	-	-		
Excitement	6.06 ±*1.73*	-	-		
Cognitive	9.00 ±*1.83*	-	-		
Positive	9.13 ±*3.59*	-	-		
Depression	11.75 ±*2.62*	-	-		
Disorganization	4.56 ±*1.46*	-	-		
Total score	55 ±*9.38*	-	-		
Synaesthesia battery	2.03 ±*0.62*	2.24 ±*0.69*	0.70 ±*0.28*	$t_{(35)}$ = 0.94 n.s.	$t_{(38)}$= 8.99, p<.001
Total score	55 ±*9.38*	-	-		

* A subset of 19 controls was optimally age-matched to the 18 ScZ patients that were included in the final analyses (control group age 32.90 ±*8.02* years (M/F 8/11), ScZ group age 38.22 ±*12*.44 years (M/F 11/7), $t_{(35)}$= 1.56 p=0.13). An overlapping subset of 20 controls was optimally matched to the synesthete group (control group age 28.95 ±*7.90* years (M/F 3/17), $t_{(38)}$= 0.118 p=0.91).

**BACS scores from 1 synesthete, 1 control and 1 ScZ patient were not available. BACS Fluency data from 2 healthy controls were lost because of technical failure in the auditory recording equipment.

***Data from 16 patients.