NEUROSCIENCE

Pavlovian conditioning-induced hallucinations result from over-weighting of perceptual priors

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Some people hear voices that others do not, but only some of those people seek treatment. Using a Pavlovian learning task, we induced conditioned hallucinations in four groups of people who differed orthogonally in their voice-hearing and treatment-seeking statuses. People who hear voices were significantly more susceptible to the effect. Using functional neuroimaging and computational modeling of perception, we identified groups of people who differed orthogonally in their voice-hearing and treatment-seeking. People who hear voices (P+) were significantly more susceptible to the effect. Using a Pavlovian learning task, we induced conditioned hallucinations in four groups of people who differed orthogonally in their voice-hearing and treatment-seeking statuses. People who hear voices (P+) were significantly more susceptible to the effect. Using functional neuroimaging and computational modeling of perception, we identified groups of people who differed orthogonally in their voice-hearing and treatment-seeking statuses. People who hear voices (P+) were significantly more susceptible to the effect. Using a Pavlovian learning task, we induced conditioned hallucinations in four groups of people who differed orthogonally in their voice-hearing and treatment-seeking statuses. People who hear voices (P+) were significantly more susceptible to the effect.

Perception is not simply the passive reception of inputs (1). We actively infer the causes of our sensations (2). These inferences are influenced by our prior experiences (3). Priors and inputs might be combined according to Bayes’ rule (4). Prediction errors, the mismatch between priors and inputs, contribute to belief updating (5). Hallucinations (percepts without external stimulus) may arise when strong priors cause a percept in the absence of input (6). We tested this theory by engendering new priors about auditory stimuli in human observers using Pavlovian conditioning.

Even in healthy individuals, the repeated occurrence of visual and auditory stimuli can induce auditory hallucinations (7). We examined this effect with functional imaging. Some argue that in patients with psychosis, weak priors lead to aberrant prediction errors, resulting in auditory verbal hallucinations (AVH) (8). Others have observed strong priors in patients, but the effects were not specific to hallucinations (9, 10). Such inconsistencies may reflect the hierarchical organization of perception: Perturbations may affect some levels of the hierarchy and not others (9). We used computational modeling to infer the strength of participants’ hierarchical perceptual beliefs from their behavioral responses during conditioning (11). Our model captured how priors are combined with sensory evidence, allowing us to test the strong-prior hypothesis directly.

Participants worked to detect a 1-kHz tone occurring concurrently with presentation of a checkerboard visual stimulus. First, we determined individual thresholds for detection and psychometric curves (12). Then, at the start of conditioning, the tone was presented frequently at threshold (Fig. 1A, left), engendering a belief in audio-visual association. This belief was then tested (Fig. 1A, right) with increasingly frequent subthreshold and target-absent trials (Fig. 1B). Conditioned hallucinations occurred when subjects reported tones that were not presented, conditional upon the visual stimulus.

We recruited four groups of subjects (Fig. 1C): people with a diagnosed psychotic illness who hear voices (P+H+; n = 15); those with a similar illness who did not hear voices (P+H−; n = 14); an active control group who heard daily voices, but had no diagnosed illness (P−H+; n = 15); and last, controls without diagnosis or voices (P−H−; n = 15).

Groups were matched demographically (tables S1 to S4). Rates of detection of tones at threshold **Corresponding author. Email: philip.corlett@yale.edu

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were similar across groups. All groups demonstrated conditioned hallucinations. However, those with daily hallucinations endorsed more conditioned hallucinations than those without, regardless of diagnosis ($F_{1,55} = 19.59, P = 5.82 \times 10^{-5}$) (Fig. 1D). This effect remained after accounting for differences in detection thresholds (Fig. 1E, fig. S1, and table S5). Group differences in propensity to report tones were observed only in the “no-tone” and 25% “likelihood of detection” conditions (intensity-by-hallucination status $F_{3,165} = 13.59, P = 5.73 \times 10^{-4}$) (Fig. 1F).

Participants also rated their decision confidence by holding down the response button (Fig. 1G). Participant confidence varied with stimulus intensity ("yes": $R = 0.39, P = 7.46 \times 10^{-10}$; "no": $R = 0.22, P = 9.02 \times 10^{-4}$). However, hallucinators were more confident in their conditioned hallucinations than nonhallucinators ($F_{1,53} = 6.50, P = 0.045$). Both conditioned hallucinations and confidence correlated with hallucination severity outside of the laboratory (Fig. 1, H and I, and fig. S3).

In order to establish whether conditioned hallucinations involved true percepts, we first identified tone-responsive regions from thresholding runs [peaks at (–60, –20, 2) and (62, –28, 10)] (Fig. 2A). As observed with elementary hallucinations (15), activity in tone-responsive regions was greater during conditioned hallucinations compared with correct rejections ($t_{56} = 4.93, P = 7.59 \times 10^{-6}$) (Fig. 2B). Electrical stimulation of this region in human patients produces AVH (16). Taken together, these findings are consistent conditioned hallucinations involving actual perception.

Whole-brain analysis revealed that conditioned hallucinations also engaged anterior insula cortex (AIC), inferior frontal gyrus, head of caudate, anterior cingulate cortex (ACC), auditory cortex, and posterior superior temporal sulcus (STS) (Fig. 2C and table S6). A meta-analysis of symptom-capture-based studies examining neural activity of AVH highlighted similar regions (Fig. 2D) (17). AIC and

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**Fig. 2. Imaging results.** (A) Bilateral supplemental auditory cortex covaried with tone intensity during thresholding (family-wise error rate–corrected, $P < 0.05$). (B) Parameter estimates from this region showed increased activation during conditioned hallucinations. ***$P < 0.001$. (C) Whole-brain analysis during conditioned hallucinations (false discovery rate–corrected, $P < 0.05$). (D) Clusters derived from a meta-analysis (17) of AVH experiences during functional imaging. (E and F) Hallucinators were much less likely to engage ACC during correct rejections. Error bars represent ±1 SEM.
ACC responses frequently correlate with stimulus salience (18). However, their activation before near-threshold stimulus presentation predicts detection (19). Caudate is engaged during audiovisual associative learning (20). Likewise, AIC and ACC are engaged during multisensory integration (21).

There were no significant between-group differences in brain responses during conditioned hallucinations. However, hallucinators deactivated ACC more (peak at \(-16, 54, 14\)) than control participants, with significant block-by-psychosis interaction. \(*P < 0.05\). Caudate engagement was also enhanced in those with hallucinations when compared with their nonhallucinating counterparts. \(**P < 0.001\).

We regressed model parameters onto task-induced brain responses (Fig. 3A). The \(X_1\) trajectory consisting of low-level perceptual beliefs (\(X_1\)), visual-auditory associations (\(X_2\)), and the volatility of those associations (\(X_3\)), as well as evolution rates encoding the relationships between levels (\(\alpha, \theta\)).

Critically, our perceptual model allowed for variability in weighting between sensory evidence and perceptual beliefs (parameter \(\nu\)). For \(\nu = 1\), prior and observation have equal weight; for \(\nu > 1\), the prior has more weight than that of the observation (strong priors); and for \(\nu < 1\), the observation has more weight than that of the prior (weak priors). The resultant posterior probability of a tone is then fed to a separate response model.

Model parameters were fit to behavioral data, and the model was optimized by using log model evidence and simulations of observed behavior (figs. S3 and S4). Mean trajectories of perceptual beliefs were compared across groups (Fig. 3, B to D). Participants with hallucinations exhibited stronger beliefs at levels 1 (\(X_1\): \(F_{11,605} = 4.8, P = 3.89 \times 10^{-7}\)) and 2 (\(X_2\): \(F_{11,605} = 3.89, P = 1.84 \times 10^{-5}\)) (Fig. 3D). \(X_3\) beliefs evolved less in those with psychosis, who failed to recognize the increasing volatility in contingencies (\(F_{11,605} = 2.11, P = 0.018\)) (Fig. 3A).

Consistent with strong-prior theory, \(\nu\) was significantly higher in those with hallucinations when compared with their nonhallucinating counterparts (\(***P < 0.001\)). **No main effects of group or interaction effects were seen for the decision noise parameter within the response model. Error bars and line shadings represent ±1 SEM. Purple, \(P+H+\); blue, \(P–H+\); red, \(P+H–\); white, \(P–H–\).**
covaried with several conditioned hallucination-responsive regions, including STS (table S7). X3 trajectories, by contrast, covaried with hippocampus/parahippocampal gyrus and medial cerebellum (table S8). Parameter estimates from the X1-sensitive STS [(-46, -36, 0), $T_{57} = 2.09, P = 0.042$] (Fig. 4B) and AIC [(36, 8, -8), $T_{57} = 2.26, P = 0.027$] (Fig. 4C) were significantly greater in those with hallucinations versus those without. This is consistent with STS conferring auditory expectations that are responsive to incoming visual input (22). Parameter estimates from the X3-responsive cerebellar vermis [(-2, -52, -16)] (Fig. 4D) were lower in participants with psychosis as compared with those without ($T_{57} = 2.05, P = 0.045$). In the model,

Fig. 4. HGF imaging results. (A) HGF trajectories for X1 (blue) and X3 (red) regressed onto blood oxygen level–dependent time courses for the conditioned hallucinations task. Regions that identified significantly active during conditioned hallucinations (from Fig. 3C) are highlighted in yellow for reference. All images are cluster-extent thresholded at starting value 0.05; critical $k_e$ for X1 = 545 and X3 = 406. (B and C) Parameter estimates of X1 fit extracted from 5-mm sphere centered on (B) STS and (C) anterior insula activation differ based on hallucination status. (D) Parameter estimates of X3 fit extracted from 1-mm sphere centered on cerebellar vermis activation differ based on psychosis status. Error bars represent 1 SEM.
subjects with psychosis were significantly less sensitive to the changes in contingency as the task progressed. Psychotic symptoms are often associated with pathological rigidity. Belief-updating correlates with responses in the hippocampus and cerebellum. Hippocampal activity correlates with uncertainty in perceptual predictions (25). The cerebellum has likewise been associated with production and updating of predictive models (24).

Our $X_0$, $X_2$, and $v$ findings are consistent with a strong-prior theory of hallucinations. The $X_3$ findings in psychotic patients may reflect a strong prior that contingencies are fixed. On the other hand, they could reflect a weak prior on volatility. These beliefs were not associated with hallucinations but rather psychosis more broadly. Under chronic uncertainty, secondary to consistent belief violation, it may be adaptive to resist updating beliefs (25).

Consistent with previous work applying signal detection theory (SDT) to AVH (26), we found liberal criteria and low perceptual sensitivity in our H+ groups. A liberal criterion may reflect poor reality monitoring (26). However, meta-d' (a metric of participants’ meta-cognitive sensitivity) did not differ significantly between groups (fig. S6). SDT is a descriptive tool that does not distinguish aberrant perceptions from decisions. Our modeling work, however, localized group differences to the perceptual model alone. The prior weighting parameter ($v$) distinguished H+ from H− groups and also predicted confidence in conditioned hallucinations (fig. S7). Our observations support an explanation of hallucinations based on strong perceptual priors. They suggest precision treatments for hallucinations, such as targeting cholinergically mediated priors (27), and interventions to mollify psychosis more broadly, such as cerebellar transcranial magnetic stimulation (28).

REFERENCES AND NOTES

ACKNOWLEDGMENTS
The authors dedicate this work to the memory and legacy of Ralph E. Hoffman, M.D. Additional thanks go to M. Kelley, A. Bianchi, S. Bhutta, and E. Feeny for technical assistance as well as A. Nidiffer, L. Marks, S. Woods, and J. Krystal for their advice. This work was supported by the Connecticut Mental Health Center (CMHC) and Connecticut State Department of Mental Health and Addiction Services (DMHAS). P.R.C. was funded by an International Mental Health Research Organization/Janssen Rising Star Translational Research Award; National Institute of Mental Health (NIMH) grant S01MH067073-09; Clinical and Translational Science Award grant U11 TR00042 from the National Center for Research Resources (NCRR) and the National Center for Advancing Translational Science (NCATS), components of the National Institutes of Health (NIH); NIH roadmap for Medical Research; the Clinical Neurosciences Division of the U.S. Department of Veterans Affairs; and the National Center for Post-Traumatic Stress Disorders, VA Connecticut Healthcare System (VACHS), West Haven, CT, USA. The contents of this work are solely the responsibility of the authors and do not necessarily represent the official view of NIH or the CMHC/DMHAS. A.R.P. was supported by the Integrated Mentored Patient-Oriented Research Training (IMPRT) in Psychiatry grant (1R01MH071584-07) as well as the Clinical Neuroscience Research Training in Psychiatry grant (5T32MH05961-14) from NIMH and a VA Schizophrenia Research Special Fellowship from VACHS, West Haven, CT, USA. Additional support was provided by the Yale Centre Fellowship for Translational Neuroscience as well as the Brain and Behavior Research Foundation in the form of a National Alliance for Research on Schizophrenia and Depression Young Investigator Award for A.R.P. The authors declare no conflicts of interest. Model code and data are stored at ModelDB (http://modeldb.yale.edu/229278). Imaging data are stored at NeuroVault (http://neurovault.org/collections/OCFEJKOC/).

SUPPLEMENTARY MATERIALS
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31 March 2017; accepted 4 July 2017
10.1126/science.aan3458
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*Science* 357 (6351), 596-600.
DOI: 10.1126/science.aan3458

**Neural mechanisms for hallucinations**
Pairing a stimulus in one modality (vision) with a stimulus in another (sound) can lead to task-induced hallucinations in healthy individuals. After many trials, people eventually report perceiving a nonexistent stimulus contingent on the presence of the previously paired stimulus. Powers et al. investigated how different groups of volunteers and patients respond to this conditioning paradigm. They used behavior, neuroimaging, and computational modeling to dissect the effect of perceptual priors versus sensory evidence on such induced hallucinations. People who are more prone to hear voices were more susceptible to the induced auditory hallucinations. The network of brain regions that was active during the conditioned hallucinations resembled the network observed during clinical symptom capture in individuals who hallucinate while in a brain scanner.

*Science*, this issue p. 596