

Pharmacological Enhancement of Dopamine Neurotransmission Does Not Affect Illusory Pattern Perception

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Abstract

Psychotic symptoms and delusional beliefs have been linked to dopamine transmission in both healthy and clinical samples and are assumed to result at least in part from perceiving illusory patterns in noise. However, the existing literature on the role of dopamine in detecting patterns in noise is inconclusive. To address this issue, we assessed the effect of manipulating dopaminergic neurotransmission on illusory pattern perception in healthy individuals ($n = 48$, $n = 19$ female) in a double-blind placebo-controlled within-subjects design (see preregistration at <https://osf.io/a4k9j/>). We predicted individuals on versus off L-DOPA to be more likely to perceive illusory patterns, specifically objects in images containing only noise. Using a signal detection model, however, we found no credible evidence that L-DOPA compared with placebo increased false alarm rates. Further, L-DOPA did not reliably modulate measures of accuracy, discrimination sensitivity, and response bias. In all cases, Bayesian statistics revealed strong evidence in favor of the null hypothesis. The task design followed previous work on illusory pattern perception and comprised a limited number of items per condition. The results therefore need to be interpreted with caution, as power was limited. Future studies should address illusory pattern perception using more items and take into account potential dose-dependent effects and differential effects in healthy versus clinical samples.

Key words: discrimination sensitivity; dopamine; L-DOPA; pattern perception

Significance Statement

Psychosis and delusional belief have been linked to dopamine transmission in healthy and clinical samples and are assumed to partly result from perceiving illusory patterns in noise. However, the findings on the role of dopamine in detecting illusory patterns are inconclusive. To address this, we assessed the effect of enhancing dopamine transmission on illusory pattern perception in healthy individuals. Our hypothesis that enhancing dopamine transmission would increase participants' tendency to perceive illusory patterns in noise was not confirmed. This null effect suggests that earlier findings may be less robust than previously thought and that the relationship between dopamine and illusory pattern perception may be subject to dose-dependent effects and that there may be differential effects in healthy versus clinical samples.

Introduction

Detecting relationships between stimuli or events enables individuals to make predictions for the future. Recent theories conceive the brain as a probabilistic inference system,

Received Oct. 30, 2023; revised May 21, 2024; accepted June 12, 2024.

The authors declare no competing financial interests.

Author contributions: E.S. and J.P. designed research; E.S., K.K., D.T., H.T., and T.E. performed research; E.S. and S.M. analyzed data; E.S. and S.M. wrote the paper.

We thank Lea Kemalides, Hannah Hacker, and Emily Burlon. This work was supported by the Deutsche Forschungsgemeinschaft (DFG, project no. PE1627/5-1). H.T. was supported by the Cologne Clinician Scientist Program (CCSP) of the Faculty of Medicine of the University of Cologne, funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation, project no. 413543196).

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predicting events and causes of sensory input to enable successful interaction with the environment (Friston and Stephan, 2007). Perceiving relationships between unrelated stimuli and patterns in noise may be maladaptive, however, since this prevents the formation of accurate representations. Delusional belief and psychotic symptoms are assumed to result from aberrant changes in dopaminergic signaling. Several studies point toward a link between dopamine transmission and delusional belief in healthy and clinical samples. For instance, manipulating dopamine transmission with haloperidol and L-DOPA in controls changed social attributions of harmful intent (Barnby et al., 2020). Further, the link between dopamine and delusions is supported by the effects of antipsychotics, which alleviate psychotic symptoms by antagonizing D₂ dopamine receptors (Kaar et al., 2020) and by PET imaging studies showing dysregulated dopamine synthesis in individuals suffering from delusions and schizophrenia (Cheng et al., 2020; for a review, see Rigney et al., 2021).

According to prevailing theories, this link is imparted by dopamine's role in the encoding of reward prediction errors (RPEs) and the assignment of aberrant salience. Within the framework of the prediction error minimization theory, the brain seeks to minimize the discrepancy between predicted and actual input (Clark, 2013). The theory has been widely adopted for describing decision-making in various domains, including reward-based learning (Schultz, 2016), perceptual (Bell et al., 2016), and social inference (de Bruin and Michael, 2021). A large body of research suggests that dopamine modulates striatal coding of prediction errors to enable learning (Pessiglione et al., 2006; Glimcher, 2011; Schlagenhaut et al., 2013; Schultz, 2016; Basanisi et al., 2023). Imaging studies in human schizophrenic participants have reported striatal dysfunction during learning (Schlagenhaut et al., 2014; Katthagen et al., 2020) and aberrant learning from feedback accompanied by altered EEG correlates (Kirschner et al., 2024). In monkeys, midbrain dopamine neurons have been found to code reward size but also uncertainty or confidence during perceptual decision-making (de Lafuente and Romo, 2011; Lak et al., 2017).

The aberrant salience framework of psychosis describes delusions as a dysfunctional computational mechanism at the neural level within a Bayesian predictive coding framework (Kapur, 2003). Representations are formed by weighting prior beliefs against sensory inputs based on their probabilities (Sterzer et al., 2018). Psychosis is assumed to result from low precision of prior beliefs and dysfunctional belief updating, conditioned by changes in dopamine signaling (Heinz et al., 2019). In mice, increasing striatal dopamine levels related to poor precision, i.e., high-confidence false alarms, in an auditory stimulus detection task, regarded as hallucination-like perceptions, (Schmack et al., 2021). A hyperdopaminergic state is thought to further cause aberrant assignment of salience to formed representations. Delusional beliefs reflect an individual's cognitive effort to explain experiences of aberrant salience, while hallucinations reflect the experience of aberrantly salient internal representations (Kapur, 2003).

Conceptually, paranormal belief, conspiratorial thinking, and schizotypy represent nonpathological states on a continuum converging toward delusional belief and psychosis (Kreweras, 1983; Denovan et al., 2018). For instance, conspiratorial beliefs, i.e., beliefs that certain events result from secret plots by powerful actors, correlated positively with paranormal beliefs, paranoid ideation, and schizotypy (Darwin et al., 2011). Interestingly, for both the social and perceptual domain, dopamine has been linked to delusional belief and psychotic symptoms in healthy and clinical samples (Sekine et al., 2001; Howes and Kapur, 2009; Krummenacher et al., 2010; Barnby et al., 2020). For the perceptual domain, studies assessing the ability to discriminate signals and noise in controls and individuals with hallucinations and schizophrenia yielded mixed results (Bentall and Slade, 1985; Ishigaki and Tanno, 1999; Krummenacher et al., 2010). Early studies report a more liberal criterion, i.e., a tendency to identify signals, but no difference in discrimination sensitivity, for individuals with high compared with low predisposition to hallucination in auditory signal detection (Bentall and Slade, 1985), and decreased discrimination sensitivity in patients with schizophrenia and auditory hallucinations compared with controls in a visual continuous performance test (Ishigaki and Tanno, 1999). In contrast, a more recent study reports individuals with paranormal beliefs to favor false alarms over misses and individuals skeptical about paranormal phenomena to show the reverse strategy. Enhancing dopaminergic neurotransmission lowered discrimination sensitivity compared with placebo in skeptics, but not believers (Krummenacher et al., 2010).

Dopamine has been assumed to reduce noise distortion in neuronal signal transmission (Walter and Spitzer, 2003; Vander Weele et al., 2018). However, considering the above findings and psychosis as hyperdopaminergic state characterized by a poor ability to discriminate relevant and irrelevant, and internal and external stimuli (Morris et al., 2013; Chu et al., 2021), this assumption falls short. The inconsistencies might be related to sample characteristics, for instance, to differences in predisposition to delusional thinking or symptomatology, or to the domain under study, such as auditory or visual. Further, most of the studies rely on rather small subgroup samples (Ishigaki and Tanno, 1999; Krummenacher et al., 2010; Barnby et al., 2020).

In view of these inconclusive findings, we aimed at investigating whether enhancing dopamine transmission elicits delusional beliefs already in healthy controls at an "early" perceptual (in contrast to, for instance, the cognitive process of establishing connections between events by means of complex explanations) stage, i.e., in visual perception. To this end, we used a pharmacological approach in healthy controls, increasing dopamine transmission with the dopamine precursor L-DOPA, and studied the effects on illusory visual pattern perception. Modeling discrimination performance with signal detection theory, we predicted participants on versus off L-DOPA to exhibit increases in false alarms, i.e., to perceive more illusory patterns, specifically objects in images containing only noise (see preregistration at <https://osf.io/a4k9j/>). With regard to response bias, discrimination sensitivity and accuracy, our hypotheses were nondirectional.

Materials and Methods

Ethics statement. The study was approved by the local ethics committee of the Faculty of Medicine of the University of Cologne, Germany.

Sample. A subset of $n = 49$ out of $N = 76$ participants from a larger pharmacological study performed a visual perception task, specifically the snowy pictures task (SPT; Ekstrom and Harman, 1976; Whitson and Galinsky, 2008). One participant was excluded due to side effects (nausea and vomiting) and did not complete the task. The final sample analyzed here included 48 participants, including 19 women, all right-handed, aged 25–40 ($M = 28.27$). The participants were recruited in Cologne, Germany. They were recruited through university bulletins, through mailing lists, and by word-of-mouth recommendation. For practical reasons, only a subset of participants completed the SPT. Therefore, no task-specific a priori power calculation was carried out. A post hoc power analysis (paired samples test with G*Power, version 3.1.9.7; Faul et al., 2009) yielded a power of 0.39 to detect a small effect ($d = 0.2$), power of 0.96 to detect a medium effect ($d = 0.5$), and a power of >0.99 to detect a large effect ($d = 0.8$). All participants had normal or corrected-to-normal vision, German as first language (or profound German language skills), and all women were taking hormonal contraceptives. General exclusion criteria for study participation were strongly impaired vision or strabismus, participation in other studies involving medications, intake of nonprescription and prescription drugs, pregnancy, acute infections, alcohol or drug intoxication or abuse, psychiatric disorders (past or current), neurological disorders, metabolic disorders, internal diseases, chronic pain syndrome, complications of anesthesia, and strong emotional burden or physical stress during the study period. Exclusion criteria considering contraindications regarding the intake of L-DOPA were hypersensitivity to L-DOPA or benserazide, intake of nonselective monoamine oxidase inhibitors, metoclopramide or antihypertensive medication (e.g., reserpine), disorders of the central dopaminergic system, e.g., Lewy body dementia or Parkinson's disease, increased intraocular pressure (glaucoma), and breastfeeding.

Procedure. The current study was part of a larger pharmacological project assessing dopamine effects on decision-making and learning. Since the research questions, tasks and methods used are fundamentally different, reporting on all projects would go beyond the scope of the current article. Therefore, we focus on the analysis of the visual perception task and will report on the other projects elsewhere. After passing a medical examination by a physician to check for contraindications, the participants were invited to three testing sessions. During the first session, the participants underwent a baseline screening for putative dopamine proxies, specifically working memory capacity, spontaneous eyeblink rate, and impulsivity (Gibbs and D'Esposito, 2005; Dalley et al., 2007; Jongkees and Colzato, 2016). Since the investigation of the influence of putative proxies of dopamine function was only conducted for the effects of L-DOPA on intertemporal choice and reinforcement learning, the data from the baseline screening will be reported elsewhere. After the baseline screening, the participants completed two identical experimental sessions on separate days with an interval of approximately a week between the sessions. Thirty minutes prior to testing, the participants received a nondistinguishable tablet containing either 150 mg L-DOPA, a dopamine precursor, and benserazide, a peripheral decarboxylase inhibitor, or placebo and then completed an intertemporal choice task and a reinforcement learning task (see preregistration at <https://osf.io/a4k9j/>). Seventy-six participants completed the intertemporal choice and reinforcement task. Approximately 75 min after intake of the tablet, a subset of participants ($n = 49$ out of $N = 76$; see below, Snowy pictures task) additionally completed a visual perception task. The study was realized as double-blind placebo-controlled within-subjects design. Polling the participants showed that they could not guess the correct order of the experimental sessions $\chi^2(1, N = 48) = 0, p = 1.0$.

Snowy pictures task. We used a modified pen-and-paper version of the SPT (Ekstrom and Harman, 1976; Whitson and Galinsky, 2008). The task contains 24 grainy images. Some of the images contain hard-to-detect embedded objects (for instance, a chair and a knife), and some contain only noise (12 images with objects, 12 images with noise). The participants were asked to denote whether or not an object is present in the image, and if so, what object it is. They were instructed to complete the task as fast as possible without sacrificing accuracy. The participants completed two different versions of the task under placebo and L-DOPA, respectively, in counterbalanced order (12 images per session).

Data analysis. To assess the influence of enhancing dopaminergic transmission on the detection of objects in images, we calculated accuracies, false alarm rates, and the signal detection theory measures d' -prime and response bias per condition (placebo and L-DOPA). D' -prime is an index for the ability to disentangle signal from noise, with higher values reflecting greater discriminability, while the response bias reflects the tendency toward responding "yes" or "no." Negative values indicate a liberal response criterion (response bias toward responding "yes"), while positive values indicate a conservative response criterion (response bias toward responding "no"). D' -prime and response bias were computed participant- and condition-wise in MATLAB (version R2023a) based on Stanislaw and Todorov (1999). Following the $1/2N$ rule, we corrected perfect hit and false alarm rates by $-1/(2n_{\text{target}})$ and $+1/(2n_{\text{distractor}})$, respectively (Stanislaw and Todorov, 1999). Significant Shapiro–Wilk tests for accuracy $W = 0.928, p = 0.006$; false alarm rate $W = 0.909, p = 0.001$; and response bias differences $W = 0.934, p < 0.009$ indicated that differences between the matched pairs were not normally distributed. Therefore, we used nonparametric Bayesian Wilcoxon signed-rank tests as implemented in JASP (version

0.17.2.1) to compare the group means of accuracy, false alarm rate, and response bias between conditions. Since D -prime was normally distributed ($W = 0.971$; $p = 0.270$), we used a Bayesian paired samples t test to compare d -prime between conditions. The posterior distributions were obtained using Markov chain Monte Carlo (MCMC) sampling with five chains and 1,000 samples, using a Cauchy distribution with scale = 2 as prior. We report Bayes factors to evaluate evidence in favor of the null hypothesis (nondirectional, BF_{01} ; directional, BF_{0-}).

We further modeled the decisions with a hierarchical signal detection model (SDT) using Bayesian inference. The model was implemented using the *bhsdtr* package (version 2; Paulewicz and Blaut, 2020) for R (version 4.1.2; R Core Team, 2021). The model implements a hierarchical regression structure on the SDT parameters and accounts for parameter variability due to factors such as participants and items. The hierarchical general linear regression structure for the SDT parameters requires the parameters to be unconstrained. More specifically, to account for the assumption of normally distributed random effects, the model is reparameterized such that the parameters are unconstrained (since the normal distribution is unbounded). D -prime (d') is derived from $\delta = \ln(d')$, allowing random effects to be modeled by assuming that δ is normally distributed. For a full description of the model, the reader is referred to Paulewicz and Blaut (2020). For d -prime, we modeled the drug effect as fixed effect and participants and items as random effects. For the threshold (response bias), we modeled the drug effect as fixed effect and participants as random effects:

$$\delta = \sim\text{drug} + (1|\text{id}) + (1|\text{trial}),$$

and

$$\gamma = \sim\text{drug} + (1|\text{id}).$$

For the priors on the random effects correlations, the *bhsdtr* package implements Cholesky decomposition of the correlation matrices, with uniform priors by default. For both d -prime and the threshold, we used normal priors for fixed effects (with $\mu = 0.5$, $\sigma = 1$ and $\mu = 0.5$, $\sigma = 1$, respectively) and uniform priors for random effects. To assess a possible drug effect on d -prime and the threshold, we calculated the Savage–Dickey density ratio for the posterior difference distributions for placebo versus L -DOPA by dividing the value of the posteriors over the parameters evaluated at $\theta = 0$ by the priors. Sampling was performed with Hamiltonian Monte Carlo sampling, using the *Stan* modeling language (Stan Development Team, 2023) via the *rstan* interface (version 2.32.2; Stan Development Team, 2024), with four chains, 1,000 warmup samples, and 2,000 iterations. We determined chain convergence by inspecting the traceplots and accepting values of $\hat{R} \leq 1.01$ (Gelman and Rubin, 1992).

Code and data accessibility. The data and the code used to analyze the data are freely available online at <https://osf.io/m5u6v/> and <https://osf.io/m7g3p/>, respectively.

Results

On average, and across both conditions (placebo and L -DOPA), participants correctly detected objects or correctly rejected noise in 81.77% of all images. The average response bias across both conditions of 0.65 indicates an overall tendency toward responding “no” (i.e., no object identified in an image). Under L -DOPA, participants made false alarms in 11.28% of all images, i.e., identified objects in images containing only noise, compared with 12.15% in the placebo condition (see Table 1 and Fig. 1 for accuracy, hits, false alarms, d -prime, and response bias per drug condition). Testing for group differences in accuracy, false alarm rate, response bias, and d -prime between the conditions revealed that the null effect of no difference in accuracy under L -DOPA and placebo was 14 times more likely than a difference between the conditions ($BF_{01} = 14.48$). Likewise, a null effect for the false alarm rate between L -DOPA and placebo was 20 times more likely than an increased false alarm rate under L -DOPA versus placebo ($BF_{0-} = 20.25$). Furthermore, Bayesian analyses revealed evidence in favor of the null hypothesis for the response bias ($BF_{01} = 6.37$) and d -prime ($BF_{01} = 11.46$). These results were confirmed when analyzing the data using a hierarchical Bayesian implementation of the SDT (Paulewicz and

Table 1. Means and standard deviations for task performance per drug condition

	Drug condition			
	Placebo		L -DOPA	
	M	SD	M	SD
Accuracy	0.81	0.13	0.83	0.12
Hit rate	0.43	0.13	0.44	0.14
False alarm rate	0.12	0.14	0.11	0.12
D -prime	0.89	0.54	0.98	0.48
Response bias	0.63	0.27	0.68	0.33

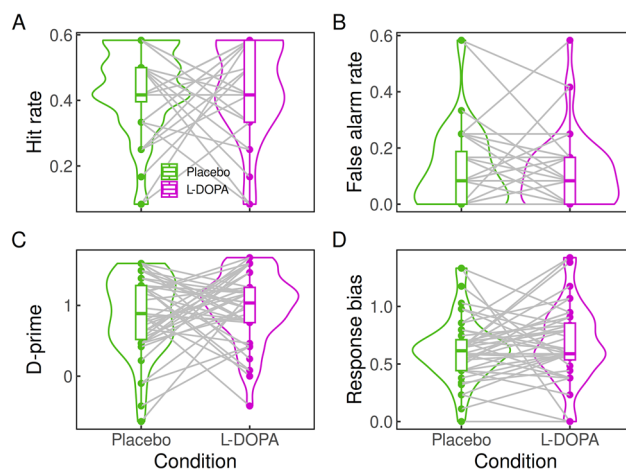


Figure 1. Distribution of accuracy (**A**), false alarm rate (**B**), d -prime (**C**), and response bias (**D**) per condition. Horizontal line, median; box, first and third quartiles; lower whisker, lowest value not $\sim 1.5 \times \text{IQR}$ (interquartile range) from the first quartile; upper whisker, highest value no further than $1.5 \times \text{IQR}$ from the third quartile; dots, outliers (data points outside the lower and upper whisker). For the hit rate and false alarm rate (panels **A** and **B**, respectively), there are overlapping data points.

Blaut, 2020) that may be more robust, given the low trial numbers in individual participants. The group-level posterior distributions for d -prime and threshold are depicted in Figure 2. Given the priors and the data, null effects for the drug effect on d -prime and threshold (response bias) were more likely than the alternative ($\text{BF}_{01} = 7.29$ and $\text{BF}_{01} = 47.76$, respectively).

Discussion

We studied the effects of enhancing dopamine neurotransmission using the dopamine precursor L-DOPA on illusory pattern perception using a visual perception task. Participants completed two versions of the modified SPT (Ekstrom and Harman, 1976; Whitson and Galinsky, 2008) under placebo and L-DOPA, respectively. Applying signal detection theory, our hypothesis that participants on L-DOPA would be more likely to perceive illusory patterns, specifically objects in images containing only noise was not confirmed. In contrast, Bayesian analyses revealed strong evidence in favor of the null hypothesis for false alarm rates. Likewise, for accuracy, discrimination sensitivity, and response bias, Bayesian analyses revealed evidence in favor of the null hypothesis.

Changes in discrimination sensitivity and social attributions relevant to paranoia following dopaminergic modulation have previously been reported in perceptual and social decision-making in healthy samples (Krummenacher et al., 2010; Barnby et al., 2020). The involvement of dopamine in delusional ideation is further substantiated by the efficacy of antipsychotic treatment (Kaar et al., 2020), and a study assessing perceptual discrimination in controls and individuals with hallucinations and schizophrenia reported lower discrimination sensitivity in patients with auditory hallucinations (Ishigaki and Tanno, 1999). The present null effect of L-DOPA on illusory pattern perception in the current study may be for several reasons. First, earlier studies reporting a relationship between dopamine and discrimination sensitivity or paranoid inferences rely on rather low sample sizes [30 participants in within-subjects design in Barnby et al. (2020), 20 participants per belief group in between-subject design in Krummenacher et al. (2010), 11 participants per patient group in Ishigaki and Tanno (1999)]. Low sample sizes increase the variance in effect sizes even under the null, such that previously reported findings may have been false positives. Alternatively, the present null effect may be related to dose-dependent effects or a single dose may have not been sufficient to elicit detectable changes in pattern perception. The effect of pharmacological DA manipulation might also depend on interindividual differences, such as a predisposition to delusional thinking, belief in the paranormal (Krummenacher et al., 2010), magical ideation (Mohr et al., 2006), and predisposition to hallucinations (Bentall and Slade, 1985). For instance, L-DOPA increased semantic priming only in participants with high magical ideation (due to longer response times for unrelated prime-target pairs), and participants with high magical ideation under placebo performed comparable with participants with low magical ideation under L-DOPA (Mohr et al., 2006). It is further conceivable that dopamine is related to delusional beliefs, while manifesting itself only in the pathological state or in individuals scoring high on schizotypy (Mohr and Ettinger, 2014). Lastly, the nature of the task may not be suitable to detect dopamine-related changes in illusory pattern perception, since it covers the visual domain only, and requires no inferences about events or social intentions.

Limitations

The current study has some limitations. Plasma levels peak 30–60 min after intake of L-DOPA, while plasma half-life is ~ 90 min (Hauser, 2009; Keller et al., 2011). Being part of a larger project, the present task was performed following two other behavioural tasks. The task was completed ~ 75 min after intake and was typically completed in 5–10 min.

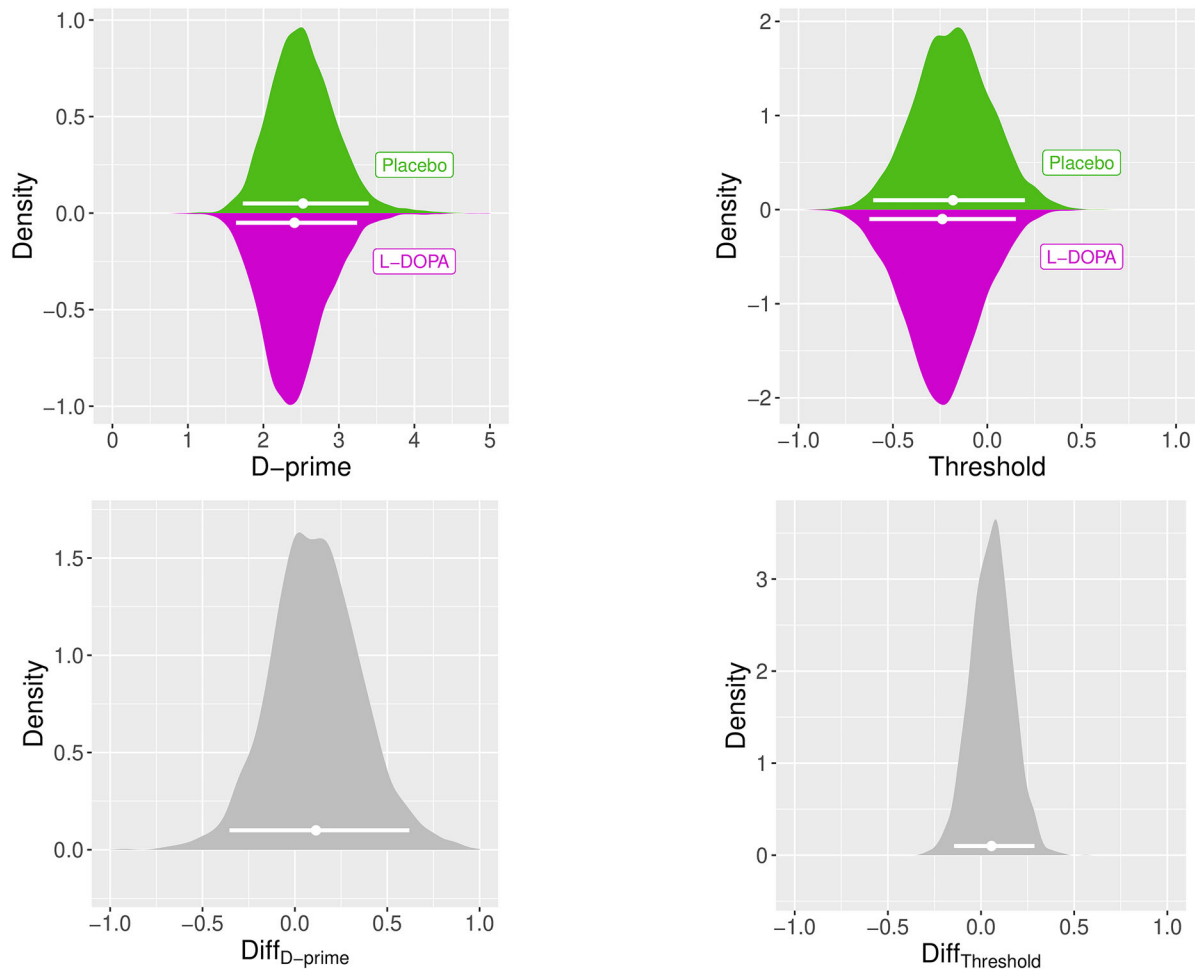


Figure 2. Top row, Group-level posterior distributions for d-prime and threshold (response bias), for the placebo (green, top) and L-DOPA (magenta, bottom) condition. Bottom row, Difference distributions. The horizontal solid lines indicate the 95% highest posterior density intervals.

Accordingly, the task was completed after plasma levels had peaked, but likely before the plasma half-life was reached. Still, the timing, and therefore the dose during task performance, may have contributed to the null effects of L-DOPA on pattern perception. Dose-dependent effects on perceptual decision-making have been reported in another study, which modulated dopamine transmission via methylphenidate (Beste et al., 2018). Further, we did not assess the participants' baseline dopamine synthesis capacity and their predisposition to delusional thinking or paranormal belief. The participants in our sample may not have had such a predisposition, and a single dose of L-DOPA may therefore not have been sufficient to induce such effects. Also, since overall accuracy was rather high, and false alarm rates rather low, the task may be susceptible to ceiling effects.

The SPT has been frequently used to study illusory pattern perception. However, the task comprises a comparatively small number of items. In the original publication, using a between-subjects design, Whitson and Galinsky (2008) report differences between experimental conditions (lack of control vs baseline) using the same number of items per condition as in the present study. Using the same task, group differences in task performance between controls and patients with schizophrenia have been reported (Moritz et al., 2014), within-subject differences in terms of higher confidence in errors under L-DOPA compared with placebo (Andreou et al., 2015), and associations between illusory pattern perception in the SPT and conspiracy belief (Hartmann and Müller, 2023). Of note, however, a more recent study (van Elk and Lodder, 2018) found no evidence that loss of control affects illusory pattern perception in the SPT. A strength of the current study is the within-subjects design, yielding higher power compared with between-subjects designs. Still, the low number of items may have limited power so as to detect small to medium effects. Furthermore, we additionally implemented a hierarchical Bayesian SDT model that might be more robust given the low number of trials per participant. This model confirmed the original result, such that null effects were substantially more likely given the data. Hierarchical Bayesian models also come with some limitations. Such models are sensitive to the choice of the prior distribution. Using hierarchical Bayesian

modeling, we assume a specific type of distribution for the variability across the group, which may fall short in some cases (McGlothlin and Viele, 2018).

Conclusion and perspectives

We assessed the effect of enhancing dopaminergic neurotransmission on illusory pattern perception. There was no evidence that L-DOPA, compared with placebo, increases the detection of patterns in noise. Rather, Bayesian analyses provided strong evidence in favor of the null hypothesis. Future studies should control for predisposition to delusional thinking and belief in the paranormal or magical ideation and may assess changes in pattern perception across different domains (e.g., auditory and visual).

Data Availability

The data that support the findings of this study are openly available at <https://osf.io/m5u6v/>. The study protocol was preregistered (see <https://osf.io/a4k9j/>).

References

- Andreou C, Bozikas VP, Luedtke T, Moritz S (2015) Associations between visual perception accuracy and confidence in a dopaminergic manipulation study. *Front Psychol* 6:414.
- Barnby J, Bell V, Deeley Q, Mehta M (2020) Dopamine manipulations modulate paranoid social inferences in healthy people. *Transl Psychiatry* 10:214.
- Basanisi R, Marche K, Combrisson E, Apicella P, Brovelli A (2023) Beta oscillations in monkey striatum encode reward prediction error signals. *J Neurosci* 43:3339–3352.
- Bell AH, Summerfield C, Morin EL, Malecek NJ, Ungerleider LG (2016) Encoding of stimulus probability in macaque inferior temporal cortex. *Curr Biol* 26:2280–2290.
- Bentall R, Slade PD (1985) Reality testing and auditory hallucinations: a signal detection analysis. *Br J Clin Psychol* 24:159–169.
- Beste C, Adelhöfer N, Gohil K, Passow S, Roessner V, Li SC (2018) Dopamine modulates the efficiency of sensory evidence accumulation during perceptual decision making. *Int J Neuropsychopharmacol* 21:649–655.
- Cheng PWC, et al. (2020) The role of dopamine dysregulation and evidence for the transdiagnostic nature of elevated dopamine synthesis in psychosis: a positron emission tomography (PET) study comparing schizophrenia, delusional disorder, and other psychotic disorders. *Neuropsychopharmacology* 45:1870–1876.
- Chu RS-T, Ng C-M, Chan K-N, Chan K-W, Lee H-M, Hui L-M, Chen E, Chang W-C (2021) Aberrant learned irrelevance in patients with first-episode schizophrenia-spectrum disorder. *Brain Sci* 11:1370.
- Clark A (2013) Whatever next? Predictive brains, situated agents, and the future of cognitive science. *Behav Brain Sci* 36:181–204.
- Dalley JW, et al. (2007) Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science* 315:1267–1270.
- Darwin H, Neave N, Holmes J (2011) Belief in conspiracy theories. The role of paranormal belief, paranoid ideation and schizotypy. *Pers Indiv Dif* 50:1289–1293.
- de Bruin L, Michael J (2021) Prediction error minimization as a framework for social cognition research. *Erkenntnis* 86:1–20.
- de Lafuente V, Romo R (2011) Dopamine neurons code subjective sensory experience and uncertainty of perceptual decisions. *Proc Natl Acad Sci U S A* 108:19767–19771.
- Denovan A, Dagnall N, Drinkwater K, Parker A (2018) Latent profile analysis of schizotypy and paranormal belief: associations with probabilistic reasoning performance. *Front Psychol* 9:35.
- Ekstrom RB, Harman HH (1976) *Manual for kit of factor-referenced cognitive tests, 1976*. Princeton: Educational Testing Service.
- Faul F, Erdfelder E, Buchner A, Lang A-G (2009) Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods* 41:1149–1160.
- Friston KJ, Stephan KE (2007) Free-energy and the brain. *Synthese* 159:417–458.
- Gelman A, Rubin DB (1992) Inference from iterative simulation using multiple sequences. *Stat Sci* 7:457–472.
- Gibbs SE, D'Esposito M (2005) Individual capacity differences predict working memory performance and prefrontal activity following dopamine receptor stimulation. *Cogn Affect Behav Neurosci* 5:212–221.
- Glimcher PW (2011) Understanding dopamine and reinforcement learning: the dopamine reward prediction error hypothesis. *Proc Natl Acad Sci U S A* 108:15647–15654.
- Hartmann M, Müller P (2023) Illusory perception of visual patterns in pure noise is associated with COVID-19 conspiracy beliefs. *Iperception* 14:1.
- Hauser RA (2009) Levodopa: past, present, and future. *Eur Neurol* 62:1–8.
- Heinz A, Murray GK, Schlagenhauf F, Sterzer P, Grace AA, Walter JA (2019) Towards a unifying cognitive, neurophysiological, and computational neuroscience account of schizophrenia. *Schizophr Bull* 45:1092–1100.
- Howes OD, Kapur S (2009) The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophr Bull* 35:549–562.
- Ishigaki T, Tanno Y (1999) The signal detection ability of patients with auditory hallucination: analysis using the continuous performance test. *Psychiatry Clin Neurosci* 53:471–476.
- Jongkees BJ, Colzato LS (2016) Spontaneous eye blink rate as predictor of dopamine-related cognitive function—a review. *Neurosci Biobehav Rev* 71:58–82.
- Kaar SJ, Natesan S, Mccutcheon R, Howes OD (2020) Antipsychotics: mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology. *Neuropharmacology* 172:107704.
- Kapur S (2003) Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry* 160:13–23.
- Katthagen T, Kaminski J, Heinz A, Buchert R, Schlagenhauf F (2020) Striatal dopamine and reward prediction error signaling in unmedicated schizophrenia patients. *Schizophr Bull* 46:1535–1546.
- Keller GA, Czerniuk P, Bertuola R, Spatz JG, Assefi AR, Di Girolamo G (2011) Comparative bioavailability of 2 tablet formulations of levodopa/benserazide in healthy, fasting volunteers: a single-dose, randomized-sequence, open-label crossover study. *Clin Ther* 33:500–510.
- Kirschner H, et al. (2024) Transdiagnostic inflexible learning dynamics explain deficits in depression and schizophrenia. *Brain* 147:201–214.
- Kreweras G (1983) Approche bayésienne des phénomènes 'paranormaux'. *Math Sci Hum* 81:59–66.
- Krummenacher P, Mohr C, Haker H, Brugger P (2010) Dopamine, paranormal belief, and the detection of meaningful stimuli. *J Cogn Neurosci* 22:1670–1681.

- Lak A, Nomoto K, Keramati M, Sakagami M, Kepecs A (2017) Midbrain dopamine neurons signal belief in choice accuracy during a perceptual decision. *Curr Biol* 27:821–832.
- McGlothlin AE, Viele K (2018) Bayesian hierarchical models. *J Am Med Assoc* 320:2365–2366.
- Mohr C, Ettinger U (2014) An overview of the association between schizotypy and dopamine. *Front Psychiatry* 5:184.
- Mohr C, Landis T, Brugger P (2006) Lateralized semantic priming: modulation by levodopa, semantic distance, and participants' magical beliefs. *Neuropsychiatr Dis Treat* 2:71–84.
- Moritz S, et al. (2014) Overconfidence in incorrect perceptual judgments in patients with schizophrenia. *Schizophr Res Cogn* 1:165–170.
- Morris R, Griffiths O, Le Pelley ME, Weickert TW (2013) Attention to irrelevant cues is related to positive symptoms in schizophrenia. *Schizophr Bull* 39:575–582.
- Paulewicz B, Blaut A (2020) The bhsdtr package: a general-purpose method of Bayesian inference for signal detection theory models. *Behav Res Methods* 52:2122–2141.
- Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD (2006) Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature* 442:1042–1045.
- R Core Team (2021). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available at: <https://www.R-project.org/>
- Rigney G, Ayubcha C, Werner TJ, Alavi A, Revheim M-E (2021) The utility of PET imaging in the diagnosis and management of psychosis: a brief review. *Clin Transl Imaging* 10:1–10.
- Stan Development Team (2024). 'RStan: the R interface to Stan.' R package version 2.32.2. Available at: <https://mc-stan.org/>
- Schlagenhauf F, et al. (2013) Ventral striatal prediction error signaling is associated with dopamine synthesis capacity and fluid intelligence. *Hum Brain Mapp* 34:1490–1499.
- Schlagenhauf F, Huys QJ, Deserno L, Rapp MA, Beck A, Heinze HJ, Dolan R, Heinz A (2014) Striatal dysfunction during reversal learning in unmedicated schizophrenia patients. *Neuroimage* 89:171–180.
- Schmack K, Bosc M, Ott T, Sturgill JF, Kepecs A (2021) Striatal dopamine mediates hallucination-like perception in mice. *Science* 372:eabf4740.
- Schultz W (2016) Dopamine reward prediction-error signalling: a two-component response. *Nat Rev Neurosci* 17:183–195.
- Sekine Y, Iyo M, Ouchi Y, Matsunaga T, Tsukada H, Okada H, Yoshikawa E, Futatsubashi M, Takei N, Mori N (2001) Methamphetamine-related psychiatric symptoms and reduced brain dopamine transporters studied with PET. *Am J Psychiatry* 158:1206–1214.
- Stanislaw H, Todorov N (1999) Calculation of signal detection theory measures. *Behav Res Methods Instrum Comput* 31:137–149.
- Stan Development Team (2023). Stan modeling language users guide and reference manual, 2.32. Available at: <https://mc-stan.org>
- Sterzer P, Adams RA, Fletcher P, Frith C, Lawrie SM, Muckli L, Petrovic P, Uhlhaas P, Voss M, Corlett PR (2018) The predictive coding account of psychosis. *Biol Psychiatry* 84:634–643.
- Vander Weele CM, et al. (2018) Dopamine enhances signal-to-noise ratio in cortical-brainstem encoding of aversive stimuli. *Nature* 563:397–401.
- Van Elk M, Lodder P (2018) Experimental manipulations of personal control do not increase illusory pattern perception. *Collabra Psychol* 4:19.
- Walter H, Spitzer M (2003) The cognitive neuroscience of agency in schizophrenia. In: *The self in neuroscience and psychiatry* (Kircher T, David A, eds), pp 436–444. Cambridge: Cambridge University Press.
- Whitson JA, Galinsky AD (2008) Lacking control increases illusory pattern perception. *Science* 322:115–117.