### N-Methyl-D-aspartate receptor hypofunction causes recurrent and transient failures of perceptual inference

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# 1 1 Abstract

2 Perception is known to alternate between an external mode, driven by sensory inputs, and an

3 internal mode, shaped by prior knowledge about the world. Using a double-blind, placebo-

4 controlled, cross-over experiment in healthy human participants, we investigated the effects

5 of the N-Methyl-D-aspartate receptor (NMDAR) antagonist S-ketamine on the alternation

6 between external and internal modes. We found that pharmacologically induced NMDAR

7 hypofunction causes a shift of perception toward the external mode. Similarly, a case-control

8 study revealed that individuals with paranoid schizophrenia, a disorder repeatedly associated

9 with NMDAR hypofunction, spend more time in the external mode. This NMDAR-dependent

10 increase in the external mode suggests that the symptoms of schizophrenia are caused by

11 recurring dissociations of perception from prior knowledge about the world.

12 **2 Main**

13 Imagine a dimly lit room at a crowded party, where unclear visual signals, indistinct sounds,

14 and complex social interactions allow for multiple - and sometimes false - interpretations. In

15 such ambiguity, failures of perceptual inference, the ability to contextualize sensory inputs

16 with prior knowledge about the world, can lead to profound departures from reality: Faces

17 obscured in shadow may appear distorted, random noise could be perceived as a whisper,

18 and friendly smiles might seem derogatory.

19 This example illustrates why a disruption of perceptual inference is likely to play a crucial

20 role in schizophrenia (Scz), a chronic and severe mental disorder characterized by psychotic

21 symptoms such as delusions and hallucinations1–3. Yet despite considerable progress in the

22 computational understanding of psychosis, two key questions have remained unanswered.

23 The first question concerns the neural mechanisms that cause perceptual inference to fail in

24 Scz. Several lines of evidence point to N-Methyl-D-aspartate receptor (NMDAR) hypofunction

25 as a key factor in the pathophysiology of psychosis4. NMDAR antibodies5 and antagonists

26 such as ketamine6 mimic the symptoms of Scz, which is itself associated with a reduction

27 of NMDAR density in prefrontal cortex7. NMDARs control the ratio of neural excitation

28 and inhibition8, block the release of midbrain dopamine9, enable cortical feedback10 and

29 support synaptic short term plasticity11. While these NMDAR-dependent mechanisms are

30 likely critical for perceptual inference, it is yet to be determined how NMDAR hypofunction

31 may cause the psychotic symptoms that characterize Scz.

32 The second unresolved question concerns the temporal dynamics of psychotic experiences,

33 which often unfold as short-lived events spanning from seconds to minutes, especially at

34 early stages of Scz12,13. The transient nature of psychotic experiences challenges models

35 that assume a constant disruption of perceptual inference1–3. A solution to this problem

36 is suggested by the recent observation that perceptual inference is subject to spontaneous

37 fluctuations over time that occur at a timescale compatible with the duration of individual

38 psychotic experiences14–16. Such fluctuations have been related to two opposing modes of

39 inference, during which perception is driven predominantly either by external inputs or by

40 internal predictions that stem from recent perceptual experiences17 (Figure 1A). Although

41 preliminary evidence indicates a tendency toward the external mode in people with Scz18, the

42 neural mechanisms of mode fluctuations and their potential implications in psychosis have

43 remained elusive.

44 The objective of the current study was therefore twofold: First, to test whether NMDAR

45 hypofunction causes changes in perceptual inference that characterize Scz; and second, to

46 explore the effect of NMDAR hypofunction on ongoing fluctuations in perceptual inference

47 that may explain the transient nature of psychotic experiences. We addressed these aims in

48 a double-blind placebo-controlled cross-over experiment in 28 healthy human participants.

49 The participants attended two experimental sessions during which they received a continuous

50 intravenous infusion of either the NMDAR antagonist S-ketamine at a dose of 0.1 mg/kg/h or

51 a saline placebo. In each session, the participants viewed ten 120 sec blocks of an ambiguous

52 structure-from-motion (SFM) stimulus that induced the experience of a sphere rotating

53 around a vertical axis, and reported changes in the perceived direction of rotation (leftward

54 vs. rightward movement of the front surface) as well as their confidence in the choice (Figure

55 1B and Supplemental Video S1).

56 The ambiguity of the display induced the phenomenon of bistable perception, where sponta-

57 neous changes in the perceived direction of rotation occurred in average intervals of 13*.*75

58 ± 3*.*09 sec. In line with previous results19,20, these changes in perception occurred with a

59 probability of 0*.*11 ± 8*.*67 × 10*−*3 at brief depth-symmetric configurations of the stimulus (see

60 Supplemental Video S1 and Supplemental Figure S1A). We therefore divided the continuous

61 behavioral reports into a sequence of discrete states *t*. Each state was associated with a

62 perceptual experience *yt*, confidence *ct* and the external input *st*.

63 Bistable perception can be conceptualized as an inferential process about the cause of *st*, in

64 which previous experiences (*yt−*1) reflect internal predictions that provide prior knowledge

65 about the interpretation *yt* of the ambiguous stimulus20 (Figure 1C). To test how NMDAR

66 antagonism altered the balance between external inputs and internal predictions, we attached

67 a 3D signal to a fraction of the stimulus dots. The signal-to-ambiguity ratio (SAR) ranged

68 from complete ambiguity to full disambiguation across five levels and remained constant

69 in each block of the experiment. By changing the direction of rotation enforced by the 3D

70 signal at random in average intervals of 10 sec, we created dynamic conflicts between the

71 SAR-weighted input *st* and the stabilizing internal prediction *yt−*1. As expected, we found

72 that *yt* was driven by both *st* (*βS* = 3*.*01 ± 0*.*06) and *yt−*1 (*βP* = 2*.*06 ± 0*.*03). Importantly,

73 S-ketamine caused perception to shift toward *st* (0*.*45±0*.*08, z = 5*.*6, p = 1*.*71 × 10*−*7; Figure

74 2A and Supplemental Figure S2), indicating a stronger weighting of external inputs over

75 internal predictions during pharmacologically induced NMDAR hypofunction.

76 Next, we performed the same analysis on data from a previous case-control study using an

77 analogous task in patients with Scz19. In Scz patients and controls, *yt* was influenced by

78 the SAR-weighted input *st* (*βS* = 2*.*77 ± 0*.*11) and the stabilizing prediction *yt−*1 (*βP* =

79 1*.*5 ± 0*.*03). Similar to S-ketamine, *st* had a larger impact on perception in Scz patients

80 than controls (0*.*75 ± 0*.*15, z = 4*.*96, p = 5*.*6 × 10*−*6; Figure 2E and Supplemental Figure

81 S3). Together, these results align with the canonical predictive processing theory of Scz1–3:

82 Pharmacologically-induced NMDAR hypofunction and Scz are associated with a shift of

83 perceptual inference toward external inputs, and away from stabilizing internal predictions.

84 NMDAR hypofunction may thus trigger psychotic experiences by causing erratic inferences

85 about ambiguous sensory information.

86 As a mechanism for symptoms that are transient and recurring, NMDAR-dependent changes

87 in perceptual inference should not be constant, but fluctuate dynamically at a timescale that

88 is compatible with the duration of individual psychotic experiences. We tested this prediction

89 in Hidden Markov Models (HMM) that inferred transitions between two latent states, each

90 linked to an independent general linear model (GLM) that predicted *yt* from *st* and *yt−*1.

91 The *β* weights quantified the sensitivity to ambiguous sensory information (*βS* × *st*) relative

92 to the stabilizing effect of internal predictions provided by preceding experiences (*βP* × *yt−*1),

93 and allowed us to evaluate dynamic changes in the balance ∆*S−P* = *βS* − *βP* between the two.

94 Consistent with recent findings in humans and mice16,17, Bayesian model comparison indicated

95 a clear superiority of the two-state GLM-HMM over the standard one-state GLM in the

96 S-ketamine experiment (*δBIC* = −3*.*65 × 103). According to the two-state GLM-HMM,

97 perception fluctuated between an internal mode, shaped by the stabilizing internal prediction

98 *yt−*1, and an external mode, dominated by the SAR-weighted input *st*. External mode

99 increased ∆*S−P* by 2*.*8±0*.*29 (T(81) = 9*.*5, p = 5*.*22 × 10*−*13; Figure 2B-C). Switches between

100 modes occurred in intervals of 179*.*97 ± 19*.*39 sec.

101 The presence of slow fluctuations between external and internal modes suggests that, instead

102 of causing a constant increase in the sensitivity to external inputs, NMDAR hypofunction 103 may affect perception by shifting the dynamic balance between the two modes. Indeed,

104 S-ketamine did not alter the weights of the two-state GLM-HMM (Figure 2C), but increased

105 the probability of external at the expense of internal mode (1*.*01 ± 0*.*03, z = 30*.*7, p =

106 4*.*26 × 10*−*206; Figure 2D). This effect was stable over time and present across the full range

107 of SAR (Figure 2D). Inter-individual differences in the effects of S-ketamine confirmed that

108 NMDAR hypofunction raised the sensitivity to sensory information (Figure 2A) by modulating

109 the time participants spent in external and internal modes, respectively (*ρ* = 0*.*41, T(26) =

110 2*.*3, p = 0*.*03).

111 Strikingly, the data from the Scz-control study mirrored the effect of S-ketamine on the

112 balance between external and internal mode: The two-state GLM-HMM outperformed the

113 standard one-state GLM (patients: *δBIC* = −981*.*65; controls: *δBIC* = −862*.*91) and revealed

114 two opposing modes (∆*S−P* = 1*.*44 ± 0*.*33, T(44) = 4*.*33, p = 3*.*39 × 10*−*4; Figure 2F) that

115 alternated in intervals of 265*.*38±57*.*76 sec for patients and 230*.*99 ± 65*.*04 sec for controls.

116 Patients and controls did not differ with respect to the weights of the two-state GLM-HMM

117 (Figure 2G). Instead, Scz patients spent more time in external mode (0*.*52±0*.*03, z =16*.*88, 118 p = 1*.*23 × 10*−*63; Figure 2H).

119 We could not attribute between-mode transitions to fatigue, task difficulty (Figure 2D and

120 H), executive function as reflected by response times (RT, Supplemental Figure S1C and S4),

121 psychotomimetic effects of S-ketamine, global psychosis proneness, the clinical severity of Scz,

122 stereodisparity thresholds, or subjective arousal, intoxication and nervousness (Supplemental

123 Figure S5).

124 To our knowledge, these results are the first to uncover a neural mechanisms for the slow,

125 task-related fluctuations in perceptual inference that have been observed across variety of

126 tasks in humans and mice14–17. We found that healthy individuals who receive the NMDAR

127 antagonist S-ketamine and patients diagnosed with Scz are prone to an external mode of

128 perception. The external mode partly decouples perceptual inference from internal predictions

129 that reflect prior knowledge about the world. In health, this may prevent circular inferences in

130 recurrent neural networks, where predictive feedback modulates activity even at early stages

131 of sensory processing21,22. A predominance of external mode, on the other hand, exposes

132 perception to the destabilizing effects of ambiguity. Such transient failures of perceptual

133 inference may cause individuals to be deluded by spurious connections between unrelated

134 events3, to attribute the sensory consequences of their actions to an outside force, and to

135 hallucinate signals in noise3.

136 During external mode, healthy participants were more confident in their choices (0*.*72 ±

137 0*.*07, z = 9*.*92, p = 7*.*85 × 10*−*22, Supplemental Figure S1E) and scored higher on the 138*Clinician-Administered-Dissociative-States-Scale*23 (CADSS, 1*.*05 ± 0*.*54, T(208*.*05) = 1*.*95, p

139 = 0*.*05, Supplemental Figure S5B). Given the known association of psychosis with elevated

140 confidence24 and dissociative symptoms25, intervals of external mode may thus reflect the

141 computational correlate of individual psychotic experiences. The dynamic nature of between-

142 mode transitions illustrates how constant and potentially heritable dysfunctions of the

143 NMDAR, such as GRIN2A mutations in Scz26, may produce symptoms of psychosis that are

144 recurrent and transient in nature.

145 **3 Methods**

## 146 3.1 Ressource availability

### 147 3.1.1 Lead contact

148 Further information and requests for resources should be directed to and will be fulfilled by

149 the lead contact, Veith Weilnhammer (v[eith.weilnhamer@gmail](mailto:veith.weilnhamer@gmail.de).de).

### 150 3.1.2 Materials availability

151 This study did not generate new unique reagents.

### 152 3.1.3 Data and code availability

153 All data and code associated with this study will be made available on the associated Github

154 repository <https://github.com/veithweilnhammer/modes_ketamine_scz> upon publication.

155 Key resources are listed in Supplemental Table S1.

## 156 3.2 S-ketamine vs. placebo

157 The S-ketamine experiment consisted in a total of three experimental sessions. During the first

158 session, we screened participants for S-ketamine contraindications (arterial hypertension, prior

159 psychiatric or neurological diagnoses including substance use disorder, use of psychoactive

160 medication), and assessed psychosis proneness using the 40-item *Peters Delusion Inventory*

161 (PDI27) and the 32-item *Cardiff Anomalous Perception Scale* (CAPS28). Moreover, we

162 conducted three experimental pre-test runs that tested the ability to process stereodisparity

163 (run 1, SAR = 1, cut-off: perceptual accuracy > 0.75), ensured the experience of spontaneous

164 switches during bistable perception (run 2, SAR = 0, cut-off: perceptual stability < 0.96,

165 corresponding to phase durations < 40 sec), and familiarized participants with the main

166 experiment (run 3, see below for details).

167 In the subsequent two sessions, participants received a continuous intravenous infusion of

168 either S-ketamine at 0.1 mg/kg/h or a saline placebo. Health screenings were repeated before

169 each session to ensure the participants remained eligible. At each day of testing, we checked

170 for alcohol intoxication using a breathalyzer and recent illicit substance use via a urine drug

171 screen.

172 Our experimental protocol was double-blinded: The order of S-ketamine and placebo admin-

173 istration was counter-balanced across participants, with at least a two week interval between

174 sessions. The participants, as well as the experimenters tasked with collecting the behavioral

175 and psychometric data, were unaware of whether S-ketamine or placebo was administered

176 by an independent group of clinicians who excluded undiagnosed psychotic illness using the

177 *Brief Psychiatric Rating Scale* (BPRS29), established the intravenous line, started the infusion

178 15 min prior to the experiment, monitored the participants for side effects (blood pressure,

179 drowsiness and vasovagal reactions, psychotomimetic effects), and removed the intravenous

180 line at the end of the experiment, after which participants were monitored for at least 30

181 min. Deblinding occurred after data collection was complete.

### 182 3.2.1 Sample characteristics

183 We screened a total of 87 right-handed individuals with (corrected-to-) normal vision, who

184 were naive to the purpose of the study and gave written informed consent before participating.

185 All experimental procedures were approved by the ethics committee at Charité Berlin.

186 From the group of screened participants, 31 did not meet our pretest criteria (6 due to

187 perceptual accuracy < 0.75, 15 due to perceptual stability > 0.96, 8 due to substance use,

188 1 due to do a diagnosis of ADHD, and 1 due to medication with sertraline). Out of the

189 remaining 56 participants who were eligible for the S-ketamine experiment, we aborted

190 the main experiment in 1 participant due to high blood pressure at baseline (RR > 140/80

191 mmHG), in 2 participants due to strong psychotomimetic effects (micropsia) or dizziness under

192 S-ketamine, and in 1 participant due to a vasovagal syncope during intravenous insertion.

193 24 participants were not available for the main experiment after successful pre-testing. We

194 therefore report the data from a total of 28 participants (mean age: 28.93 ± 1.35 years, 18

195 female) who met all inclusion criteria and completed all experimental sessions.

### 196 3.2.2 Experimental paradigm

197 We presented the experiment using Psychtoolbox 330 running in Matlab R2021b (session

198 1: CRT-monitor at 85 Hz, 1280 x 1024 pixels, 60 cm viewing distance and 39.12 pixels per

199 degree visual angle; session 2 and 32: CRT-monitor at 85Hz, 1280 x 1024 pixels, 40 cm

200 viewing distance and 26.95 pixels per degree visual angle).

201 **Procedure**: Throughout the experiment, participants reported their perception of a discon-

202 tinuous SMF stimulus (Supplemental Video S1). In this stimulus, random dots distributed on

203 two intersecting rings induce the perception of a spherical object (diameter: 15.86°, rotational

204 speed: 12 sec per rotation, rotations per block: 10, individual dot size: 0.12°) that rotates

205 around a vertical axis with the front surface to the left or right20. Stimuli were presented in

206 120 sec blocks, separated by 10 sec fixation intervals.

207 Participants viewed the stimuli through a custom mirror stereoscope. In the pretest experi-

208 ment, we presented stimuli at complete disambiguation (run 1, SAR = 1), full ambiguity (run

209 2, SAR = 0) and across five levels ranging from full ambiguity to complete disambiguation

210 across five levels (run 3-5, *SAR* ∈ {0*,* 0*.*1*,* 0*.*25*,* 0*.*5*,* 1}). The SAR, which was constant within

211 blocks, defines the fraction of stimulus dots that received a disambiguating 3D signal. Within

212 each block, the direction of rotation enforced by the disambiguating 3D signal changes in

213 average intervals of 10 sec (i.e., at a probability of 0.15 per stimulus overlap, see below).

214 We pseudo-randomized the order of SAR across blocks and the direction of disambiguation

215 within blocks.

216 Participants were naive to the potential ambiguity in the visual display, passively experienced

217 the stimulus and reported changes in their perception alongside their confidence via button-

218 presses on a standard USB keyboard (right middle-finger on d: rotation of the front-surface

219 to the right at high confidence; right index-finger on f: rotation of the front-surface to the

220 right at low confidence; left middle-finger on k: rotation of the front-surface to the left at high

221 confidence; left index-finger on j: rotation of the front-surface to the left at low confidence;

222 thumb on space bar: unclear direction of rotation). Unclear perceptual states occurred at a

223 rate of 0.03 ± 0.01 and were excluded from further analyses.

224 The direction of rotation enforced by *st* (i.e., whether the parametric 3D signal enforced

225 leftward or rightward rotation of the front surface) changed at a rate of 0.15 per overlap (i.e.,

226 on average every 10 sec). Changes in *st* and the order of blocks, each corresponding to one

227 level of SAR, were pseudo-random.

228 In session 1 (pre-test), each run (runs 1 to 3) consisted of six blocks. In session 2 and 3 (main

229 experiment), each run (run 4 and 5) consisted of 10 blocks. After every third block, the main

230 experiment was paused to allow for the monitoring of the participants’ vital signs (blood

231 pressure and pulse rate) and dynamic changes in psychotomimetic experiences. The latter

232 was assessed using the 6 item *Clinician-Administered-Dissociative-States-Scale* (CADSS23)

233 and three additional questions (Q1: *How awake do you feel?*, Q2: *How intoxicated do you*

234 *feel?*, Q3: *How nervous do you feel?*) to which participants responded by clicking on a

235 continuous line that encoded responses from *not at all* to *very much*. To measure global

236 psychotomimetic effects of S-ketamine vs. placebo, participants completed the Questionnaire

237 for the *Assessment of Altered States of Consciousness* (5D-ASC31) at the end of session 2

238 and 3. In addition, we collected responses on a debriefing questionnaire, in which we asked

239 participants to describe whether they were able to accurately perceive the two directions of

240 rotation induced by the SFM stimulus, whether they noticed any differences between blocks,

241 whether they would guess that they received S-ketamine or placebo, and whether they had

242 experienced any effects that they would attribute to a psychoactive substance.

243 **Stereodisparity thresholds:** At the beginning of the session 2 and 3, we conducted an

244 independent stereo-acuity test to detect a potential effect of S-ketamine on stereodisparity

245 thresholds19. We presented 5000 dots (each at 0.15° visual angle) within a square of 11° x

246 11° around a central fixation cross (0.10°). We added a stereodisparity signal to all dots on

247 a Landolt C, i.e., a circle (1.37° radius, 2.06° width) with a 90° gap located either at the

248 left, top, right or bottom. Stimuli were presented for 1 sec, after which participants reported

249 the location of the gap by pressing the up-, down-, left- or right-arrow key within a 2 sec

250 response interval, followed by 5 sec of fixation before the next trial.

251 We adjusted the stereodisparity of the Landolt C in a two-up-one-down staircase across 40 trials

252 (initial stereodisparity: 0.0045°, correct response: decrease in the available stereodisparity

253 by one step; incorrect response: increase by two steps, initial step-size: 0.001°, reduction

254 to 0.0005° after first reversal). Stereodisparity thresholds were defined by the average

255 stereodisparity present at the last 10 trials of the staircase.

256 **Scores and Questionnaires:** Supplementary Table S2 provides an overview of our psycho-

257 metric data.

## 258 3.3 Scz patients vs. healthy controls

259 To test whether Scz patients show similar changes in bimodal inference as healthy participants

260 who receive the NMDAR-antagonist S-ketamine, we re-analyzed data from a previously

261 published case-control study19 that compared Scz patients to healthy participants in paradigm

262 analogous to the S-ketamine experiment described above.

### 263 3.3.1 Sample characteristics

264 We report data from 23 patients diagnosed with paranoid Scz (ICD-10: F20.0, 18 male, age

265 = 37.13±2.42) and 23 controls (17 male, age = 33.57±1.74) that were matched for gender,

266 age and handedness19.

### 267 3.3.2 Experimental paradigm

268 Stimuli were presented using Psychtoolbox 330 running in Matlab R2007b (CRT-Monitor at

269 60 Hz, 1042x768 pixels, 59.50cm viewing distance, 30.28 pixels per degree visual angle).

270 **Main Experiment**: Throughout the experiment, participants reported their perception of a

271 discontinuous SFM stimulus (see Supplemental Video S2) via button-presses on a standard

272 USB keyboard. In contrast to the S-ketamine experiment, the 300 dots (0.05°) that composed

273 the stimulus (2.05°x 2.05°) were not placed on rings, but on a Lissajous band defined by

274 the perpendicular intersection of two sinusoids (*x*(*p*) = *sin*(*A* ∗ *p*) and *y*(*p*) = *cos*(*B* ∗ *p* + *δ*)

275 with *A* = 3, *B* = 6, with *δ* increasing from 0 to 2*π* at 0.15 Hz. Overlapping configurations

276 of the stimulus occurred in intervals of 3.33 sec. Participants viewed the stimuli through a

277 mirror stereoscope. Fusion was supported by rectangular fusion-frames and a background of

278 random dot noise (700 dots of 0.05° which moved at a speed of 1.98° per sec and changed

279 their direction at a rate of 1 Hz).

280 We presented participants with 3 sessions of the main experiment, each consisting of 14

281 40.08 sec blocks that were separated by 5 sec of fixation and differed with respect to

282 the SAR, ranging from full ambiguity to complete disambiguation in 8 levels (*SAR* ∈

283 {0*,* 0*.*01*,* 0*.*04*,* 0*.*9*,* 0*.*16*,* 0*.*26*,* 0*.*50*,* 1}). The frequency of changes in the direction of the dis-

284 ambiguating signal corresponded to the frequency of spontaneous changes that participants

285 perceived during full ambiguity19 (SAR = 0). In contrast to the S-ketamine experiment,

286 participants only reported the perceived direction of rotation *yt* (left vs. rightward movement

287 of the front surface).

288 **Stereodisparity thresholds:** We assessed stereodisparity thresholds in Scz patients and

289 controls using the procedure described above.

290 **Scores and Questionnaires:** We used the PDI27 and the CAPS28 to measure delusional

291 ideation and perceptual anomalies in Scz patients and controls. Clinical symptom severity

292 was assessed using the *Positive and Negative Syndrome Scale* (PANSS)32.

## 293 3.4 Quantification and statistical procedures

294 This manuscript was written in RMarkdown. All data and summary statistics can be reviewed

295 by cloning the Github respository <https://github.com/veithweilnhammer/Ketamin_RDK>

296 and running the file *ketamine\_scz\_frmri\_modes.Rmd*, which will be made public at the time

297 of publication.

298 The stimuli used in the above studies share an important feature: Even though physically

299 ambiguous at all angles of rotation, spontaneous changes in the perceived direction of rotation

300 are limited to overlapping configurations of the stimuli19,20 (see also Supplemental Figure S1

301 and S4). This is because depth-symmetry, which is a prerequisite for changes in subjective

302 experiences during bistable SFM19,20, is limited to timepoints when the bands that compose

303 the stimuli overlap (Supplemental Video S1 and S2).

304 We therefore discretized the perceptual timecourse of all experiments into a sequence of 305overlaps that occur at times *t* (1.5 sec inter-overlap interval for the S-ketamine and fMRI

306 experiment, 3.33 sec inter-overlap interval for the case-control experiment). Each inter-

307 overlap interval is characterized by the primary independent variable *st* = [−1*,* 1] × *SAR* (the

308 SAR-weighted input ranging from maximum information for leftward rotation to maximum

309 information for rightward rotation). As secondary independent variables, we considered

310 block and session index (reflecting the time participants were exposed to the experiment),

311 participant identifiers and, if applicable, treatment or group identifiers. Primary dependent

312 variables were *yt* = [0*,* 1] (the experience of either leftward or rightward rotation), *rt* (the time

313 between the button-press indicating a perceptual event relative to the preceding overlap)

314 and, if applicable, *ct* = [0*,* 1] (low vs. high confidence). As secondary dependent variables,

315 we computed perceptual accuracy (the probability of *yt* ∼= *st*) and perceptual stability (

316 probability of *yt* = *y*(*t* − 1)). We report averages as mean ± s.e.m.

### 317 3.4.1 Conventional statistics

318 The goal of our conventional statistics was to quantify the effect of NMDAR hypofunction,

319 whether due to an antagonism with S-ketamine or due to a diagnosis of Scz, on the inter-

320 pretation of ambiguous sensory information. To this end, we performed standard logistic

321 and linear regression by fitting (general) linear effects models using the R-packages lmer,

322 glmer and afex (see Supplemental Table S2). We predicted *yt*, *ct*, perceptual accuracy and

323 perceptual stability in logistic regression, and *rt* in linear regression. We estimated random

324 intercepts defined within participants in the S-ketamine experiment and nested random

325 intercepts for participants within groups in the case-control experiment. We applied a

326 Bonferroni-correction for the number of main effects and interactions within models. For

327 non-normally distributed secondary dependent variables, we performed rank-based tests to

328 assess correlations (Spearman) and distribution differences (Wilcoxon).

### 329 3.4.2 Computational modeling

330 Having established the effect of NMDAR hypofunction on the interpretation of ambiguous

331 sensory information, we used computational modeling to arbitrate between two mechanistic

332 explanations on how S-ketamine and schizophrenia may alter perceptual inference.

333 **Hypothesis H1: Unimodal inference** In one scenario, NMDAR hypofunction may induce

334 a global increase in the sensitivity to external inputs relative to the stabilizing internal

335 prediction. This unimodal scenario would be reflected by S-ketamine- or Scz-related changes

336 in the weights *w* ≡ {*βS, βP , βB*} of a GLM that predicts percepts *yt* from the input vector *xt*,

337 which consists in the SAR-weighted external input *st*, the stabilizing internal prediction *yt−*1

338 and a constant bias *b*:

*P* (*yt* = 1|*xt*) = 1 + *e−xt×w* (1)

1

*xt* × *w* = *st* × *βS* + *yt−*1 × *βP* + *b* × *βB* (2)

339 According to the unimodal hypothesis 1, NMDAR hypofunction increases *βS* at the expense

340 of *βP* , leading to an increase of ∆*S−P* = *βS* − *βP* .

341 **Hypothesis H2: Bimodal inference** In an alternative scenario, NMDAR hypofunction

342 does not change the weights of the GLM directly, but modulates the transition between

343 latent modes17 or decision-making strategies16 that differ with respect to the balance between

344 external inputs *st* and the stabilizing internal prediction provided by *yt−*1. In the bimodal

345 scenario, perceptual inference is characterized by two latent modes *zt* (i.e., states in a HMM)

346 that alternate at a probability per overlap that is defined by a 2 x 2 transition matrix *A*:

*P* (*zt* = *k*|*zt−*1 = *j*) = *Akj* (3)

347 Each state *zt* is associated by an independent GLM defined by the weights *wk*:

1

*P* (*yt* = 1|*xt, zt*) =

1 + *e−xt×wk*

(4)

*xt* × *wk* = *st* × *βS,k* + *yt−*1 × *βP,k* + *b* × *βB,k* (5)

348 The bimodal hypothesis H2 differs from the unimodal hypothesis H1 in two ways: First,

349 bimodal inference is characterized by two (as opposed to one) GLMs that differ with respect

350 to ∆*S−P* : During external mode, *βS* is increased relative to *βP* , whereas during internal mode,

351 *βP* is increased relative to *βS*. Second, during bimodal inference, NMDAR hypofunction does

352 not alter the weights within the external and internal GLMs, but modulates the transition

353 probability between the two.

354 **Procedure:** To contrast hypotheses H1 and H2, we fitted unimodal and bimodal GLM-HMMs

355 using SSM33 (Supplemental Table S2), compared models via Bayesian Information Criterion

356 (BIC), and assessed the effects of S-ketamine or Scz on the posterior model parameters, i.e.,

357 HMM transition probabilities and the mode-dependent GLM weights *wk*. Model fitting using

358 SSM is governed by the hyperparameters *σ*2 and *α*. *σ*2 denotes the variance of a prior over

359 the GLM weights *wk*. Smaller values of *σ*2 shrink *wk* toward 0, whereas *σ* = ∞ leads to flat

360 priors. We set *σ*2 to 100 for GLMs that predicted group-level data, and to 1 for GLMs that

361 predicted participant- or session-level data, which were initialized with group-level estimates

362 of *wk*. *α* defines the Dirichlet prior over the transition matrix *A* and is flat for *α* = 1. We set

363 *α* to 1 for all group-level and participant-level fits.

364 For each experiment, computational modeling was carried out in a sequence of 3 steps: In a

365 first step, we fitted a unimodal GLM initialized with noisy weights to the group-level data

366 (i.e., data pooled across participants within an individual experiment) for a total of n = 100

367 iterations and computed the average posterior weights *wn*. In a second step, we fitted the

368 group-level data with the unimodal and the bimodal GLM-HMM initialized by *wn*, extracted

369 the posterior parameters *wk*, and compared the models using BIC.

370 In a third step, we fitted the unimodal and the bimodal GLM-HMM to session-level data

371 (S-ketamine experiment) and participant-level data (case-control experiment). Models were

372 initialized by the average weights *wn* of the corresponding group-level model. For all bimodal

373 group-, participant- and session-level GLM-HMMs, we defined the latent mode associated

374 with the higher posterior *βS* estimate as external. Our definition of mode is thus agnostic

375 with respect to *βP* and ∆*S−P* . This allowed us to contrast external-to-internal bimodal

376 inference (hypothesis H2) with a third alternative where perception fluctuates between latent

377 states that differ with respect to decision noise (**hypothesis H0**). Low decision noise is

378 characterized by higher posterior estimates of *βS* and *βP* , whereas high decision noise is

379 characterized by lower posterior estimates of *βS* and *βP* . ∆*S−P* therefore discerns fluctuations

380 in decision noise (H0, no changes in ∆*S−P* ) from external-to-internal bimodal inference (H2,

381 mode-associated changes in ∆*S−P* with higher estimates during external mode).

382 For summary statistics, we extracted the posterior weights *wk* (separately for external and

383 internal mode) and the dynamic posterior probability of external mode *zt* = *e*.

# 384 4 Decleration of interest

385 The authors declare no competing interests.

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395 **6 Figures**

396 **6.1 Figure 1**

397 **Figure 1.**

398 **A.** When inferring whether the world is one state or another (*P* (*yt* = 1) or *P* (*yt* = 0),

399 respectively), the brain integrates ambiguous sensory signals *st* with internal predictions

400 that reflect prior knowledge about the environment. One source of prior knowledge is the

401 temporal autocorrelation of natural stimuli, in which the recent past often predicts the near

402 future. The integration of external inputs and internal predictions depends on the weights

403 assigned to incoming sensory data (*βS* × *st*) and to internal prediction derived from previous

404 experiences (*βP* × *yt−*1, dotted versus solid lines, simulated data), respectively. *βS* determines

405 the slope, and *βP* the shift of the psychometric function that links *st* and *yt*. Importantly,

406 the balance ∆*S−P* = *βS* − *βP* is known to alternate between two opposing modes: During

407 the external mode (left), perception is largely determined by *βS* × *st*, which is reflected by a

408 steep slope and a small shift of the psychometric curve. Conversely, during the internal mode

409 (right), perception is shaped by *βP* × *yt−*1, resulting in a shallow slope and a large shift of the

410 psychometric curve.

411 **B.** We conducted a double-blind placebo-controlled experiments in 28 healthy human partici-

412 pants, who received a continuous infusion with either the NMDAR antagonist S-ketamine or

413 saline. During the infusion, the participants viewed an ambiguous SFM stimulus that was

414 compatible with two mutually exclusive subjective experiences (left vs. rightward rotation of

415 the front surface, red arrows). This induced the phenomenon of bistable perception: While

416 the ambiguous stimulus remained constant, participants perceived only one direction of

417 rotation (blue arrow), before switching to the competing alternative.

418 **C.** Changes in the perceived direction of rotation of the SFM stimulus occur at brief depth-

419 symmetric configurations of the stimulus (Supplemental Video S1). We therefore transformed

420 the behavioral responses into a sequence of states *t* (80 1.5 sec intervals per block), each

421 associated with a combination of the SAR-weighted input *st* and the perceived direction

422 of rotation *yt*. We used GLMs to quantify the weights *βS*, *βP* and *βB*, which reflect how

423 inferences *yt* were determined by the external inputs *βS* × *st* and internal predictions *βP* × *yt−*1.

424 **6.2 Figure 2**

425 **Figure 2.**

426 **A.** The percepts *yt* were more likely to match the stimuli *st* at higher levels of SAR (3*.*01

427 ± 0*.*06, z = 50*.*39, p = 0). The positive effect of SAR on *P* (*yt* ∼= *st*) was more pronounced

428 under S-ketamine (red) relative to placebo (blue; 0*.*45 ± 0*.*08, z = 5*.*6, p = 1*.*71 × 10*−*7).

429 **B.** In the S-ketamine experiment, the HMM identified two modes that differed with respect to

430 the relative weighting of external sensory data and internal predictions: Perception fluctuated

431 between an external mode, determined by the input *st* (upper panel panel, steep slope and

432 small shift of the psychometric curve), and an internal mode, dominated by a stabilizing

433 prediction that biased perception toward previous experiences *yt−*1 (lower panel, shallow slope

434 and large shift of the psychometric curve). Within modes, there was no significant effect of

435 S-ketamine (red) versus placebo (blue) on the relation of *y*(*t*) with *s*(*t*) and *y*(*t* − 1).

436 **C.** ∆*S−P* , the balance between the external input and the stabilizing internal predictions,

437 was larger during external than during internal mode (2*.*8 ± 0*.*29, T(−81) = −9*.*5, p =

438 5*.*22 × 10*−*13). Importantly, we found no significant effect of S-ketamine (red) vs. placebo

439 (blue) on ∆*S−P* within modes (−0*.*03 ± 0*.*29, T(81) = −0*.*1, p = 1).

440 **D.** S-ketamine (red) increased the probability of external mode (1*.*01 ± 0*.*03, z = 30*.*7, p

441 = 4*.*26 × 10*−*206) relative to placebo (blue; left panel). The effect of S-ketamine on mode

442 was present from the start of the session (1*.*77 ± 0*.*07, z = 26*.*9, p = 8*.*88 × 10*−*159, upper

443 panel), with no significant effect of time (−0*.*18 ± 0*.*08, z = −2*.*17, p = 0*.*12). Relative to

444 placebo, S-ketamine increased the probability of external mode across all SARs (0*.*85±0*.*06,

445 z = 14*.*14, p = 8*.*33 × 10*−*45, lower panel). Higher SARs were associated with an increased

446 probability of external mode (1*.*34 ± 0*.*09, z = 15*.*01, p = 2*.*49 × 10*−*50), in particular under

447 S-ketamine (0*.*62 ± 0*.*11, z = 5*.*52, p = 1*.*32 × 10*−*7). Alternations between external and

448 internal mode were found at all SARs: From from full ambiguity to complete

449 disambiguation, the probability of external mode increased by only 0.11 under S-ketamine

450 and 0.07 under placebo.

451 **E.** In patients (red) and controls (blue), percepts *yt* were more likely to match the stimuli *st*

452 at higher levels of SAR (*βS* = 2*.*77 ± 0*.*11, z = 24*.*85, p = 2*.*18 × 10*−*135). Patients followed

453 the external inputs more closely than controls (0*.*75 ± 0*.*15, z = 4*.*96, p = 5*.*6 × 10*−*6).

454 **F.** In analogy to the S-ketamine experiment, the HMM identified two opposing modes in

455 Scz patients (red) and controls (blue). The external mode increased the sensitivity toward

456 *st* (slope of the psychometric function) and weakened the effect of the stabilizing internal

457 prediction *yt−*1 (shift between the dotted and solid line) relative to the internal mode. Within

458 modes, there was no effect of group on the relation of *y*(*t*) with *s*(*t*) and *y*(*t* − 1).

459 **G.** The external mode increased ∆*S−P* , the balance between external inputs and internal

460 predictions, in patients (red) and controls (blue; 1*.*44±0*.*33, T(44) = 4*.*33, p = 3*.*39 × 10*−*4),

461 with no significant effect of group (−0*.*28 ± 0*.*54, T(87*.*97) = −0*.*52, p = 1).

462 **H.** Relative to controls (blue), patients (red) spent more time in external mode (0*.*52 ±

463 0*.*03, z = 16*.*88, p = 1*.*23 × 10*−*63, left panel). In both group, biases toward external mode

464 increased over time after session onset (2*.*41 ± 0*.*11, z = −21*.*37, p = 1*.*02 × 10*−*100; upper

465 panel), with a stronger effect in patients (1*.*84 ± 0*.*14, z = 12*.*97, p = 7*.*09 × 10*−*38). Patients

466 were more likely than controls to be in external mode across all levels of SAR (0*.*51 ± 0*.*03, z

467 = 14*.*56, p = 1*.*89 × 10*−*47, lower panel). External mode increased with SAR (0*.*63 ± 0*.*1, z

468 = 6*.*47, p = 3*.*85 × 10*−*10), with no significant difference between groups (0*.*15 ± 0*.*13, z =

469 1*.*16, p = 0*.*98). As in the S-ketamine experiment, alternations between external and internal

470 mode were found at all SARs: From from full ambiguity to complete disambiguation, the

471 probability of external mode increased by only 0.12 in patients and 0.18 in controls.

# 472 7 Supplemental Information

## 473 7.1 Supplemental Figure S1

### 474 Supplemental Figure S1. The effects of ketamine and bimodal inference on RT.

475 **A.** RT were non-uniformly distributed across the inter-overlap interval (D = 0*.*09, p =

476 5*.*38 × 10*−*9, one-sample Kolmogorov-Smirnov test). This corroborates that changes in

477 perception aligned with the overlapping configurations of the stimulus after S-ketamine (red)

478 and placebo (blue).

479 **B.** RT showed a quadratic relationship with *st* (−6*.*87 ± 1*.*68, T(6*.*2 × 103) = −4*.*1, p =

480 5*.*1 × 10*−*4), indicating faster responses when sensory information was reliable (|*st*| ≫ 0; note

481 that SAR as shown in Figure 2A and 2E is equal to |*st*|). We observed no main effect of

482 S-ketamine (red) vs. placebo (blue) on RT (−3*.*35 × 10*−*3 ± 0*.*01, T(6*.*2 × 103) = −0*.*32, p =

483 1).

484 **C.** We found no additional effect of mode on RT (0*.*02 ± 0*.*03, z = 5*.*96 × 103, p = 0*.*78).

485 **D.** Confidence showed a quadratic relationship with *st* (74*.*83 ± 2*.*39, z = 31*.*32, p =

486 3*.*22 × 10*−*214), confirming that participants were more confident when sensory information

487 was reliable (|*st*| = *SAR* ≫ 0). Relative to placebo (blue), S-ketamine (red) reduced choice

488 confidence (−0*.*21 ± 0*.*04, z = −5*.*9, p = 4*.*36 × 10*−*8), and decreased the quadratic effect of

489 *st* on confidence (−19*.*95 ± 2*.*36, z = −8*.*45, p = 3*.*48 × 10*−*16).

490 **E.** External mode increased confidence globally (0*.*72 ± 0*.*07, z = 9*.*92, p = 7*.*85×10*−*22) and

491 by elevating the quadratic effect of *st* on confidence (242*.*61±18*.*43, z=13*.*16, p=3*.*37×10*−*38).

492 When controlling for mode, the negative effect of S-ketamine (red) vs. placebo (blue) on

493 confidence and on the quadratic relationship of confidence with *st* remained significant.

## 494 7.2 Supplemental Figure S2

### 495 Supplemental Figure S2. Extended data on the effects of S-ketamine and mode

496 **on perceptual inference (related to Figure 2A-C).**

497 **A.** Here, we show psychometric curves (percept *yt* versus input *st*) under S-ketamine (red)

498 and placebo (blue). The plot separates times *t* for which the previous experience was leftward

499 rotation (*yt−*1 = −1, upper panel) and rightward rotation (*yt−*1 = +1, lower panel). As

500 expected, *yt* was driven by both the external input *st* (*βS* = 3*.*01 ± 0*.*06, z = 50*.*39, p <

501 2*.*2 × 10*−*308) and the previous percept *yt−*1 (*βP* = 2*.*06 ± 0*.*03, z = 80*.*58, p < 2*.*2 × 10*−*308).

502 We found no significant interaction between the *st* and *yt−*1 (−0*.*06 ± 0*.*06, z = −1*.*06, p =

503 1). Relative to placebo, S-ketamine caused a shift of *yt* toward *st* (0*.*45 ± 0*.*08, z = 5*.*6, p =

504 1*.*71 × 10*−*7), with no significant effect on *yt−*1 (0*.*08 ± 0*.*04, z = 2*.*39, p = 0*.*13). We found

505 no significant three-way-interaction (drug x *st* x *yt−*1, −0*.*07 ± 0*.*08, z = −0*.*9, p = 1).

506 **B.** This panel shows the data from panel A separately for times *t* where the HMM identified

507 the mode of perceptual inference as external (left panels) or internal (right panels). When

508 the mode of perceptual processing was added to the prediction of *yt* from *st* and *yt−*1, the

509 effect S-ketamine (red) vs. placebo (blue) on *st* disappeared (0*.*24± 0*.*11, z = 2*.*13, p = 0*.*53).

510 Instead, changes in the balance between *st* and *yt−*1 were loaded onto fluctuations between

511 external and internal mode, which caused perception to shift away from external inputs *st*

512 (−4*.*23 ± 0*.*21, z = −20*.*01, p = 7*.*54 × 10*−*88) and toward previous experiences *yt* − 1 (0*.*78

513 ± 0*.*09, z = 8*.*64, p = 8*.*81 × 10*−*17).

514 **C.** Here, we plot the weights from the GLM *yt* = *βS* × *st* + *βP* × *yt−*1 + *βB* × 1, alongside the

515 balance between external inputs and previous experiences ∆*S−P* = *βS* − *βP* during external

516 and internal mode. Colors indicate S-ketamine (red) and placebo (blue). *βS*, the weight

517 associated with the external input *st*, was positive in external mode, but reduced to zero in

518 internal mode (−3*.*55 ± 0*.*23, T(81) = −15*.*44, p = 4*.*78 × 10*−*24). We found no additional

519 effect of S-ketamine (red) versus placebo (blue; −0*.*25 ± 0*.*23, T(81) = −1*.*1, p = 1) and no

520 significant interaction (0*.*21 ± 0*.*33, T(81) = 0*.*65, p = 1). *βB*, the weight associated with the

521 constant response bias *b* toward rightward rotation, was not different from zero (*βB* = 0*.*04 ±

522 0*.*11, T(98*.*36) = 0*.*31, p = 1). We found no effect of drug (−0*.*11 ± 0*.*14, T(81) = −0*.*74, p

523 = 1) or mode (−0*.*02 ± 0*.*14, T(81) = −0*.*12, p = 1) on the bias weight *βB*. *βP* , the weight

524 associated with the previous percept *yt−*1 was not modulated by S-ketamine (−0*.*22 ± 0*.*26,

525 T(81) = −0*.*87, p = 1) or mode (−0*.*75 ± 0*.*26, T(81) = −2*.*92, p = 0*.*29). There was no

526 significant interaction between drug and mode with respect to *βP* (0*.*35 ± 0*.*36, T(81) =0*.*97,

527 p = 1). The balance ∆*S−P* between external inputs and internal predictions was determined

528 by mode (2*.*8 ± 0*.*29, T(81) = 9*.*5, p = 5*.*22 × 10*−*13), with no significant effect of ketamine

529 (0*.*03 ± 0*.*29, T(81) = 0*.*1, p = 1) and no interaction (0*.*14 ± 0*.*42, T(81) = 0*.*34, p = 1).

## 530 7.3 Supplemental Figure S3

### 531 Supplemental Figure S3. Extended data on external and internal mode in Scz

532 **patients and healthy controls (related to Figure 2E-H).**

533 **A.** Here, we show psychometric curves (percept *yt* versus input *st*) in patients (red) and

534 controls (blue). The plot separates times *t* for which the previous experience was leftward

535 rotation (*yt−*1 = −1, upper panel) and rightward rotation (*yt−*1 = +1, lower panel). Perception

536 was driven by *st* (*βS* = 2*.*77 ± 0*.*11, z = 24*.*85, p = 2*.*18 × 10*−*135) and *yt−*1 (*βP*=1*.*5 ± 0*.*03,

537 z = 58*.*2, p < 2*.*2 × 10*−*308), with no significant interaction between *st* and *yt−*1 (−5*.*41 × 10*−*3

538 ± 0*.*11, z = −0*.*05, p = 1). Patients were more sensitive to *st* (0*.*75 ± 0*.*15, z = 4*.*96, p =

539 5*.*6 × 10*−*6). We found no significant three-way-interaction (group x *st* x *yt−*1, −0*.*37 ± 0*.*15,

540 z = −2*.*45, p = 0*.*11).

541 **B.** This panel shows the data from panel (A) separately for time *t* where the HMM identified

542 the mode of perceptual inference as external (left panels) or internal (right panels). When

543 the mode of perceptual processing was added to the prediction of *yt* from *st* and *yt−*1, the

544 difference between patients (red) and controls (blue) in the effect of *st* on *yt* disappeared

545 (−0*.*02 ± 0*.*22, z = −0*.*08, p = 1). Instead, changes in the balance between *st* and *yt−*1 were

546 loaded onto fluctuations between external and internal mode, which caused perception to

547 shift away from external inputs *st* (−3*.*47 ± 0*.*29, z = −11*.*95, p = 1*.*01 × 10*−*31) and toward

548 previous experiences *yt* − 1 (0*.*5 ± 0*.*07, z = 6*.*85, p = 1*.*15 × 10*−*10).

549 **C.** Here, we plot the weights from the GLM *yt* = *βS* × *st* + *βP* × *yt−*1 + *βB* × 1, alongside the

550 balance between external inputs and previous experiences ∆*S−P* = *βS* − *βP* during external

551 and internal mode. Colors indicate the group (patients in red, controls in blue). *βS*, a weight

552 associated with the external input *st*, was positive in external mode, but reduced to zero in

553 internal mode (−2*.*19 ± 0*.*24, T(44) = −9*.*13, p = 4*.*07 × 10*−*11). We found no additional

554 effect of group (−0*.*11 ± 0*.*37, T(87*.*69) = −0*.*3, p = 1) and no significant interaction (−0*.*25

555 ± 0*.*34, T(44) = −0*.*74, p = 1). *βB*, the weight associated with the constant response bias *b*

556 toward rightward rotation, was not different from zero (0*.*05 ± 0*.*18, T(1*.*62 × 10*−*8) = 0*.*29, p

557 = 1). We found no effect of group (−0*.*09 ± 0*.*25, T(1*.*62 × 10*−*8) = −0*.*37, p = 1). There

558 was a trend for a positive effect of internal mode (0*.*6±0*.*24, T(88) = 2*.*47, p = 0*.*06) on the

559 bias weight *βB*. *βP* , the weight associated with the previous percept *yt−*1, was reduced in

560 internal mode (−0*.*75 ± 0*.*26, T(88) = −2*.*92, p = 0*.*02), but not modulated by group (0*.*17

561 ± 0*.*32, T(9*.*88 × 10*−*10) = 0*.*54, p = 1). There was no significant interaction between group

562 and mode with respect to *βP* (0*.*11 ± 0*.*36, T(88) = 0*.*3, p = 1). The balance ∆*S−P* between

563 external inputs and internal predictions was determined by mode (1*.*44 ± 0*.*33, T(81) = 9*.*5,

564 p = 3*.*39 × 10*−*4), with no significant effect of group (0*.*28 ± 0*.*54, T(87*.*97) = 0*.*52, p = 1)

565 and no interaction (0*.*36 ± 0*.*47, T(44) = 0*.*76, p = 1).

## 566 7.4 Supplemental Figure S4

### 567 Supplemental Figure S4. RT and bimodal inference in Scz patients and controls.

568 **A.** RT were non-uniformly distributed across the inter-overlap interval (D = 0*.*22, p <

569 2*.*2 × 10*−*308, one-sample Kolmogorov-Smirnov test against uniformity) in patients (red) and

570 controls (blue). This confirmed that changes in perception were aligned with the overlapping

571 configurations of the stimulus.

572 **B.** RT did not differ between patients (red) and controls (blue; −0*.*07 ± 0*.*08, T(66*.*96)

573 = −0*.*87, p = 1). We found no quadratic relationship between RT and *st* (−3*.*54 ± 2*.*34,

574 T(5*.*33 × 103) = −1*.*51, p = 1).

575 **C.** We found no effect of mode on RT (0*.*03 ± 0*.*04, z = 4*.*89 × 103, p = 0*.*76).

## 576 7.5 Supplemental Figure S5

### 577 Supplemental Figure S5. Scores and Questionnaires.

578 **A.** Responses to Q1 (*How awake do you feel?*) indicated that participants felt more tired

579 under S-ketamine (red) than placebo (blue; −1*.*53 ± 0*.*6, z = −2*.*57, p = 0*.*04), with no

580 significant effect of time or a between-factor interaction. Responses to Q2 (*How intoxicated*

581 *do you feel?*) indicated that participants felt more intoxicated under S-ketamine (3*.*32 ±

582 1*.*44, z = 2*.*3, p = 0*.*09), with no significant effect of time or a between-factor interaction.

583 Responses to Q3 (*How nervous do you feel?*) revealed no effect of S-ketamine (−3*.*01 ±

584 2*.*62, z = −1*.*15, p = 1), time, nor a significant between-factor interaction. CADSS scores

585 were elevated under S-ketamine (1*.*01 ± 0*.*34, T(185*.*32) = 2*.*99, p = 0*.*01) with a borderline

586 trend for an increase over time (0*.*09 ± 0*.*04, T(185*.*61) = 2*.*24, p = 0*.*1) and no significant

587 between-factor interaction.

588 **B.** Q1-3 and CADSS scores were collected after blocks 1, 3, 6 and 9. To assess how the mode

589 of perceptual inference was linked to dissociative symptoms, we separated the participants

590 ratings according to the mode that dominated perception at the very end of the preceding

591 block. While controlling the effect of S-ketamine (red) vs placebo (blue), we found that

592 external mode increased dissociative symptoms (1*.*05 ± 0*.*54, T(208*.*05) = 1*.*95, p = 0*.*05),

593 but had no effect on wakefulness (Q1), subjective intoxication (Q2) or nervousness (Q3).

594 **C.** 5-ASC scores were elevated under S-ketamine (red) relative to placebo (blue; 4*.*89 ± 1*.*59,

595 T(27*.*14) = 3*.*08, p = 9*.*33 × 10*−*3).

596 **D.** Neither PDI, CAPS, nor 5-ASC scores were predictive of the probability of external mode

597 (shown separately for S-ketamine in red and placebo in blue).

598 **E.** Stereodisparity thresholds were not predictive of the probability of external mode (−28*.*73

599 ± 781*.*1, z = −0*.*04, p = 0*.*97). Thresholds did not differ between S-ketamine (red) and

600 placebo (blue; W = 102, p = 0*.*66).

601 **F.** Neither PDI, CAPS (patients in red and controls in blue), nor the PANSS items P1

602 (delusions) or P3 (hallucinations, patients only) predicted the probability of external mode.

603 **G.** In patients (red) and controls (blue), stereodisparity thresholds were not predictive of the

604 probability of external mode (−1*.*88 ± 2*.*05, z = −0*.*92, p = 1). Thresholds did not differ

605 between groups (V = 976, p = 0*.*52).

## 606 7.6 Supplemental Table S1

RESOURCE SOURCE IDENTIFIER

### Deposited data & code

Analyzed data & custom code

### Software

[https://github.com/veithweilnhamme](https://github.com/veithweilnhammer/modes_ketamine_scz) [r/modes\_ketamine\_scz](https://github.com/veithweilnhammer/modes_ketamine_scz)

N/A

**Matlab** <https://www.mathworks.com/> RRID:SCR\_001622 Psychtoolbox 3 <http://psychtoolbox.org/> RRID:SCR\_002881 **R** <http://www.r-project.org/> RRID:SCR\_001905

RStudio <https://www.rstudio.com/> RRID:SCR\_000432

lme4, afex, statConfR, ggplot2, ggridges, gridExtra, tidyr, plyr, readxl

<http://cran.r-project.org/> RRID:SCR\_003005

**Python 3** <http://www.python.org/> RRID:SCR\_008394 Jupyter Notebook <https://jupyter.org/> RRID:SCR\_018315

numpy [http://www.numpy.org](http://www.numpy.org/) RRID:SCR\_008633

pandas [https://pandas.pydata.org](https://pandas.pydata.org/) RRID:SCR\_018214

SSM <https://github.com/lindermanlab/ssm> N/A

607 **Supplemental Table S1. Key resources.**

## 608 7.7 Supplemental Table S2

|  |  |  |  |
| --- | --- | --- | --- |
| Scale | Scope | Condition | mean ± s.e.m. |
| **PDI**27 | Delusion proneness | Global | 46.22 ± 7.19 |
| **CAPS**28 | Hallucination proneness | Global | 23 ± 5.05 |
| **BPRS**29 | Screen for psychotic illness | Global | 0.64 ± 0.27 |
| **5D-ASC**31 | Altered states of consciousness | S-ketamine | 7.11 ± 1.59 |
|  |  | Placebo | 2.2 ± 0.75 |
| **CADSS**23 | Dissociation | S-ketamine | 7.8 ± 0.33 |
|  |  | Placebo | 6.43 ± 0.17 |
| **Q1** | Wakefulness | S-ketamine | 0.41 ± 0.03 |
|  |  | Placebo | 0.48 ± 0.03 |
| **Q2** | Intoxication | S-ketamine | 0.29 ± 0.03 |
|  |  | Placebo | 0.09 ± 0.02 |
| **Q3** | Nervousness | S-ketamine | 0.17 ± 0.02 |
|  |  | Placebo | 0.13 ± 0.03 |
| **Stereovision** | Disparity thresholds | S-ketamine | 2*.*89 × 10*−*3 ± |
|  |  |  | 6*.*18 × 10*−*4 |
|  |  | Placebo | 2*.*75 × 10*−*3 ± |
|  |  |  | 4*.*39 × 10*−*4 |

609 **Supplemental Table S2. Psychometric data for the S-ketamine experiment.**

## 610 7.8 Supplemental Table S3

|  |  |  |  |
| --- | --- | --- | --- |
| Scale | Scope | Condition | mean ± s.e.m. |
| **PDI**27 | Delusion proneness | Patients | 138.83 ± 16.64 |
|  |  | Controls | 21.87 ± 5.75 |
| **CAPS**28 | Hallucination proneness | Patients | 65.17 ± 10.56 |
|  |  | Controls | 7.13 ± 2.2 |
| **P1** | Delusions | Patients | 3.83 ± 0.39 |
| **P3** | Delusions | Patients | 3.35 ± 0.44 |
| **Stereovision** | Disparity thresholds | Patients | 2*.*82 × 10*−*3 ± |
|  |  |  | 5*.*13 × 10*−*4 |
|  |  | Controls | 3*.*46 × 10*−*3 ± |
|  |  |  | 7*.*14 × 10*−*4 |

### 611 Supplemental Table S3. Psychometric data for Scz-control-study.

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