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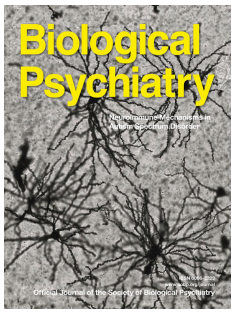


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Manuscript Title:

# Glutamateric contribution to probabilistic reasoning and jumping-to-conclusions in schizophrenia: a double blind, randomized experimental trial.

Running Title: Impaired probabilistic reasoning in schizophrenia linked to NMDA-R

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**Abstract**

**Background**: Impaired probabilistic reasoning and the jumping-to-conclusions reasoning bias (JTC) are hallmark features of schizophrenia (SCZ), yet the neuropharmacological basis of these deficits remain unclear. Here we test the hypothesis that glutamatergic neurotransmission specifically contributes to JTC and impaired probabilistic reasoning in SCZ.

**Methods**: 192 healthy participants received either N-methyl-D-aspartate-receptor (NMDA-R) agonists/antagonists (D-cycloserine/dextromethorphan), dopamine-2-receptor (D2-R) agonists/antagonists (bromocriptine/haloperidol), or placebo, in a randomized, double-blind between-subjects design. In addition, we tested 32 healthy controls matched to 32 psychotic inpatients with SCZ – a state associated with compromised probabilistic reasoning due to reduced glutamatergic neurotransmission. All experiments employed two versions of a probabilistic reasoning ('beads') task, which required participants to either sample individual amounts of sensory information to infer correct decisions, or provide explicit probability-estimates for presented sensory information. Our task instantiations assessed both information-sampling and explicit probability-estimates in different probabilistic contexts ('easy' vs. 'difficult' conditions) and changing sensory information through random transitions between easy, difficult, and ambiguous trial-types.

**Results:** Following administration of D-cycloserine, haloperidol, and bromocriptine, healthy participants displayed data-gathering behavior that was normal compared to placebo and adequate in context of all employed task conditions and trial level difficulties. However, healthy participants receiving dextromethorphan displayed a JTC bias, abnormally increased probability estimates and over-weighting of sensory information. These effects were mirrored in SCZ patients performing the same versions of the beads task.

**Conclusions:** Our findings provide novel neuropharmacological evidence linking reduced glutamatergic neurotransmission to impaired information sampling, and to disrupted probabilistic reasoning, namely to over-weighting of sensory evidence, in patients with SCZ.

**Trial name**: "Behavioral investigation of the influence of impaired neurotransmission on perceptual and decision-making processes using computer-assisted mathematical model systems in people with schizophrenia and depression."

**URL**: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00019012

**Registration Number**: DRKS00019012

## Introduction

Impaired information processing and decision-making are key behavioural manifestations of schizophrenia (SCZ) (1-3). One striking phenomenon is the tendency to make premature decisions when probabilistic judgments are required (4-7). This 'jumping-to-conclusions' (JTC) reasoning bias has been widely demonstrated by the so called 'beads task' (4, 6, 8, 9). In this experimental paradigm, participants are presented with two jars containing colored beads, and asked to sample random sequences of these beads until feeling certain to decide from which of two potential source jars a sequence was drawn. By varying the information about the source jars' contents and/or the information contained within presented sequences, the beads task can be used to manipulate the degree to which participants can infer the correct jar (10). Patients with SCZ typically show JTC behavior in this task, especially in the psychotic state (6, 7, 9, 11-15). Further, SCZ patients tend to overestimate the significance of new sensory information and overlook the context in which new information is encountered (16-20). While these abnormalities in decision-making have long been proposed to stem from impaired probabilistic reasoning, only recently have psychotic symptoms been more formally connected to both JTC behavior and probabilistic reasoning impairments (21, 22), whereby the overweighting of sensory information seems to be of particular importance for JTC in SCZ.

However, the underlying pathophysiology of these behavioral abnormalities and reasoning impairments common in SCZ remains poorly understood (4, 8). Current theoretical frameworks have linked two neurotransmitter systems to the impaired probabilistic reasoning in SCZ: first, hypo-activity of N-methyl-D-aspartate receptor (NMDA-R) related neurotransmission, and second, hyper-activation through increased signaling of dopamine type-2 receptors (D2D-R) (4, 18, 19, 21, 23-25). We sought to investigate the role of these candidate neurotransmitter systems by comparing three probabilistic beads task conditions, together with pharmacological manipulations of glutamatergic and dopaminergic neurotransmission in healthy participants. To relate our findings to SCZ, we additionally tested patients diagnosed with paranoid SCZ with the same tasks, while they were in a psychotic state, as this symptom domain has been correlated to decision-making impairments (6, 12, 26-31). On the basis that disturbances of glutamatergic and dopaminergic signaling are proposed to contribute to impaired probabilistic reasoning, we hypothesized that decreased glutamatergic and increased dopaminergic neurotransmission would both result in overweighting of sensory information and JTC in healthy subjects, whereas increased glutamatergic and reduced dopaminergic neurotransmission would induce opposite effects. Further, given the proposed association between impaired probabilistic reasoning and psychotic symptoms in SCZ, we hypothesized that the task performance in psychotic patients with SCZ would mirror the behavioral and reasoning impairments

seen in healthy participants with pharmacologically decreased glutamatergic and increased dopaminergic neurotransmission.

## Methods and Materials

*Study Population*

Our study consisted of three experiments at two different study sites (University College London / University of Munich) involving a total of 256 participants. Participants provided written informed consent prior to inclusion and our study was approved by the local ethics committees. The protocol for sample size calculation, inclusion, randomization, and drug administration is specified in Supplement 'Methods'. According to a randomized, double-blind, and placebo-controlled between-subjects design, 192 healthy participants received dopaminergic or glutamatergic manipulations and assessments of delusional ideation with Peter's delusional inventory (PDI, (32)). In **experiment I,** we administered 120mg Dextromethorphan (NMDA-R antagonist, DXM), or 250mg D-cycloserine (NMDA-R agonist, DCS), or placebo (PLC-1). In **experiment II,** we used 2.5mg haloperidol (D2-R antagonist; HAL), or 2.5mg bromocriptine (D2-R agonist; BRO), or placebo (PLC-2). Drug doses were selected in line with previous studies which had reported distinct neuropharmacological and behavioural effects (33-42). In **experiment III**, 32 psychotic inpatients with SCZ and 32 healthy control participants (HC) were tested. Patients underwent PANSS interviews and diagnoses were confirmed by two independent clinical interviewers based on ICD-10 criteria. Socio-demographic, clinical and neuropsychological characteristics – including attention span (d2) and executive functioning (TMT-A/TMT-B) – are presented in Table 1.

*Beads task*

The complete design is detailed in Supplement 'Methods'. Our variant of the beads task included two 'draws-to-decision' conditions (2x18 trials) (43-46), which allow participants to gather sensory evidence until they feel certain to decide for one of two potential source jars. Participants also undertook a 'probability-estimates' condition (12 trials), which obtains probability-estimates and disconfirmatory-evidence-scores (which quantify cumulative changes of probability-estimates following changes of bead color of ≥2 preceding beads) (13, 21, 47). The draws-to-decision conditions differed regarding their pre-specified probabilistic distributions ($P_{80/20}$/$P_{60/40}$), while the probability-estimates condition used only the $P_{80/20}$ distribution. Further, despite participants being instructed that random bead sequences would be presented, pre-specified trial sequences were applied based on a probabilistic task design (10, 43, 47). The resulting bead sequences subdivided into three difficulty levels: (I) easy trials with a likelihood of 80% for one predominant bead color, (II) difficult trials with a likelihood of 60%, and (III) ambiguous trials with a likelihood of 50% (Figure 1). We

hypothesized that SCZ patients would generally be able to distinguish between trial types and conditions, and would not display reduced information sampling as a trait. Further, we hypothesized that SCZ patients would display reduced information sampling due to overweighting of sensory evidence. Regarding our neuropharmacological interventions in healthy subjects, we hypothesized that these assumed reasoning and behavioral impairments would be mimicked following DXM and BRO, while DCS and HAL would induce opposite effects (see also Supplement 'Methods').

*Statistical analyses*

Analyses were conducted using IBM SPSS 25 with a level of significance set to $\alpha$=0.05. Draws-to-decision (DTD), probability-estimates (PE), and disconfirmatory-evidence-scores (DES) were defined as main outcome variables. Group level comparisons of socio-demographic, clinical and neuropsychological characteristics were conducted using one-way analysis of variance (ANOVA), independent samples t-tests and chi²-tests. As the assumptions of normal distribution were fulfilled according to Kolmogorov-Smirnov tests (without Lilliefors correction) for 38 of the 39 main outcome variables (single exception: disconfirmatory-evidence-scores of ambiguous trials; experiment III) parametric tests were computed. In addition to parametric analyses, non-parametric tests were performed for control purposes (see Supplement 'Results II'). To account for the numerous conditions and trial types, multivariate analyses of covariance (MANCOVAs) were performed for each dependent variable across trial-types and conditions (DTD: 2 conditions ($P_{80/20}$/$P_{60/40}$) × 3 trial-types (easy/difficult/ambiguous); PE: 1 condition ($P_{80/20}$) × 10 probability-ratings × 3 trial-types; DES: 1 condition ($P_{80/20}$) × 3 trial-types). Main independent factor was 'group'. To adjust for intervening variables, between-subject factor 'gender' and covariates 'educational attainment' and 'PDI' (Peter's delusional inventory scores (32) available only for experiments I and II) were included. In case of significant 'group' effects, subsequent univariate analyses (ANCOVAs, adjusted for 'gender' (fixed-factor), 'educational attainment' and 'PDI' (covariates)) were performed for each variable of the MANCOVA separately, assuming homogeneity of variances (Levene's tests $p \geq 0.05$). If significant univariate group effects were observed, post hoc SIDAK tests were computed to adjust for multiple comparisons (see Supplement 'Results I' for detailed tables). To assess within-subjects differences in response behavior between conditions ($P_{80/20}$/$P_{60/40}$) and between trial-types (easy/difficult/ambiguous), repeated-measures ANOVAs (RM-ANOVAs) were computed with the within-subjects factors 'condition' and 'trial-type'. Following a mixed-model approach, 'group' was defined as a fixed-factor (experiment I: DXM/DCS/PLC-1; experiment II: HAL/BRO/PLC-2; experiment III: SCZ/HC). Sphericity was assessed using the Mauchly's test and, where necessary (Mauchly's test < 0.05), Greenhouse-Geisser correction was applied. In case of significant effects, post hoc

comparisons were computed using SIDAK tests (see Supplement 'Results I' for respective test statistics).

**Results**

In total, data from 252 participants are reported (experiment I: n=92, experiment II: n=96, experiment III: n=64), as four participants from experiment I were excluded from analysis due to uniform response behavior regardless of trial-type or condition. We assume a sufficient quality of blinding as we observed no significant differences between the actual interventions (verum/placebo) and the assumptions of participants (see Supplement 'Methods'). Average $PANSS_{total}$ scores of our schizophrenia sample (mean: 77.4±18.1; median: 78.5; see Table 1) were within the range of pharmacological studies (e.g. (48) investigating the effectiveness of antipsychotics in psychotic SCZ patients). Based on $PANSS_{total}$ scores and the observation that all patients apart from one scored ≥4 points on at least 2 symptoms or ≥6 for one symptom of the $PANSS_{positive}$ subscale (minimum threshold definition) (49), our sample can be considered to represent psychotic patients.

**Draws-to-decision measures and jumping-to-conclusions**

MANCOVAs across both DTD conditions and across trial-types yielded significant 'group' effects for **experiment I** ($F_{(12,160)}$=3.21, p<0.001), but no significant effects for **experiment II** ($F_{(12,168)}$=0.74, p=0.708), and **experiment III** ($F_{(6,54)}$=1.49, p=0.200). No significant effects were observed for 'gender' (all p≥0.246), 'educational attainment' (p≥0.180) or 'PDI' (p≥0.693). For **experiment I**, ANCOVAs for the $P_{80/20}$ condition indicated significant group differences for easy and difficult trials (all $F_{(2,84)}$≥3.61, all p≤0.031), which were explained by significantly lower draws-to-decision in DXM compared to PLC-1 (easy trials: p=0.041) and trend level fewer draws-to-decision in DXM compared to DCS (easy trials: p=0.077; difficult trials: p=0.063). No differences were found between DCS and PLC-1 (all p≥0.983) (see Supplement 'Results I' for complete test statistics). For the $P_{60/40}$ condition no group differences were observed (Figure 2A).

Based on our hypothesis that neuropharmacological manipulations in healthy controls would mirror the impairments seen in SCZ, we subsequently compared draws-to-decision of SCZ patients and of participants in experiments I. Explorative ANCOVAs (DXM/DCS/PLC-1/SCZ) with the fixed-factor 'gender' and the covariate 'educational attainment' revealed significant group differences for easy and difficult trials of the $P_{80/20}$ condition (all $F_{(3,115)}$≥3.01, all p≤0.033), which SIDAK tests explained by lower draws-to-decision of SCZ compared to DCS on a significant or trend level (easy trials: p=0.061, difficult trials: p=0.029, ambiguous trials: p=0.060) and PLC-1 (easy trials: p=0.109, difficult trials: p=0.063, ambiguous trials: p=0.049). At the same time, no differences were observed between DXM and SCZ (all p≥0.719) (Supplement 'Results I'). By comparison, analyses of the $P_{60/40}$ condition

indicated no group differences (all $F_{(3,115)} \leq 2.30$, all $p \geq 0.081$) (see Supplement 'Results I', Table S6-S10).

To additionally assess jumping-to-conclusions behavior, we computed JTC rates based on the established criterion (6, 9, 50), where ≤ 3 draws-to-decision in a trial define JTC (Supplements 'Results I'). This approach obtained significantly higher JTC rates of DXM and SCZ compared to all other groups (all $p \leq 0.031$; Figure 2B) (Supplement 'Results I', first section). Consistent JTC behavior in SCZ was found to relate to higher $PANSS_{positive}$ scores ($p<0.001$) and higher $PANSS_{positive}$ factor (51) scores ($p=0.006$). However, higher $PANSS_{positive}$ scores and higher $PANSS_{positive}$ factor scores did not correlate with lower draws-to-decision (all $p \geq 0.071$, Supplement 'Results I').

**Probability-estimates**

In the probability-estimates (PE) condition, participants were asked to provide explicit probability estimates on 10 consecutive bead views on an analogue-scale (ranging from 0-100%) (see Figure 1 and Supplement 'Methods'). On the first bead rating of each trial, the cursor was positioned at "0% probability" for both potential source jars. With each additionally bead view ($2^{nd}$ to $10^{th}$ bead rating), participants were asked to move the cursor on the rating scale to the probability value that represented their perceived level of probability for one preferred jar being the source of the currently viewed bead sequence. In case participants felt uncertain about the source jar, they could move the cursor back to "0% probability" (Figure 1 and Figure 3, A).

MANCOVAs across trial-types obtained significant 'group' effects in **experiment I** ($F_{(60,112)}=3.12$, $p<0.001$) and **experiment III** ($F_{(30,30)}=2.43$, $p=0.009$), while no significant 'group' effects were observed in **experiment II** ($F_{(60,120)}=0.98$, $p=0.524$). Further, there were no significant effects for 'gender' (all $p \geq 0.160$), 'educational attainment' (all $p \geq 0.294$) or 'PDI' (all $p \geq 0.865$). For **experiment I**, subsequent ANCOVAs revealed significant group-level differences for the $5^{th}$ to $8^{th}$ bead ratings in easy trials (all $F_{(2,84)} \geq 4.59$, all $p \leq 0.013$), and for each of the $4^{th}$ to the $8^{th}$ bead ratings in difficult trials (all $F_{(2,84)} \geq 4.98$, all $p \leq 0.009$). Subsequent SIDAK tests revealed no differences between probability-estimates of DCS and PLC-1 (easy trials: all $p \geq 0.869$; difficult trials: all $p \geq 0.289$). By contrast, we observed significantly higher probability-estimates in DXM compared to DCS (easy trials: all $p \leq 0.012$; difficult trials: all $p \leq 0.011$) and PLC-1 (easy trials: all $p \leq 0.036$; difficult trials: all $p \leq 0.034$) (Supplement 'Results I'). For ambiguous trials, no significant probability-estimates differences were observed (all $F_{(2,89)} \leq 2.48$, all $p \geq 0.089$). In **experiment III**, ANCOVAs revealed significant differences for the $2^{nd}$ to $9^{th}$ bead rating of easy trials (all $F_{(1,62)} \geq 7.07$, all $p \leq 0.010$), and the $2^{nd}$ to $10^{th}$ bead rating of difficult trials (all $F_{(1,62)} \geq 4.43$, all $p \leq 0.039$). Significant differences were only observed for the $2^{nd}$ rating in ambiguous trials ($F_{(1,62)}=6.69$, $p=0.012$; all other: $F_{(1,62)} \leq 2.83$, $p \geq 0.098$).

We then assessed whether drug interventions in healthy participants lead to similar response patterns as those seen in SCZ. Explorative ANCOVAs adjusted for gender and educational attainment (DXM/DCS/PLC-1/SCZ) revealed significant effects for the 2nd to 8th rating in easy trials (all $F_{(3,115)} \geq 3.82$, all $p \leq 0.012$) and for the 4th to 10th rating in difficult trials (all $F_{(3,115)} \geq 3.10$, all $p \leq 0.030$). SIDAK tests revealed significantly higher probability-estimates in SCZ compared to DCS (easy trials: all $p \leq 0.043$; difficult trials: all $p \leq 0.017$) and compared to PLC-1 (easy trials: all $p \leq 0.041$). By contrast SCZ's probability-estimates did not significantly differ from DXM (easy trials: all $p \geq 0.232$; difficult trials: all $p \geq 0.605$). For ambiguous trials, significant effects were only observed for the 2nd rating ($F_{(3,115)}=3.92$, $p=0.011$) and explained by significantly higher probability-estimates in SCZ compared to DCS and PLC-1 (all $p \leq 0.021$; SCZ vs. DXM: $p=0.157$) (see Supplement 'Results I', Table S11-S28).

**Overweighting of sensory evidence**

Patients with SCZ frequently display over-adjustments of their beliefs following changes in sensory information (16, 22, 27, 29, 52). Thus, we computed disconfirmatory-evidence-scores as an additional measure to quantify changes of probability ratings following switches of bead color compared to ≥2 preceding beads (21).

MANCOVAs across trial-types revealed significant 'group' effects in **experiment I** ($F_{(6,166)}=2.64$, $p=0.018$) and **experiment III** ($F_{(3,57)}=5.59$, $p=0.002$), while no significant 'group' effects were observed in **experiment II** ($F_{(6,174)}=0.61$, $p=0.720$). Again, there were no significant effects for 'gender' (all $p \geq 0.074$), 'educational attainment' (all $p \geq 0.329$) or 'PDI' (all $p \geq 0.438$). For **experiment I**, ANCOVAs revealed significant disconfirmatory-evidence-score differences in case of easy ($F_{(2,84)}=6.65$, $p=0.002$) and difficult trials ($F_{(2,84)}=6.51$, $p=0.002$), while no differences were found for ambiguous trials ($F_{(2,84)}=0.24$, $p=0.790$). SIDAK tests showed these effects were driven by significantly higher disconfirmatory-evidence-scores in DXM compared to DCS (all $p \leq 0.003$) and compared to PLC-1 (all $p \leq 0.040$), while no differences were observed between DCS and PLC-1 (all $p \geq 0.723$). For **experiment III**, ANCOVAs obtained significant differences between SZC and HC for easy ($F_{(1,59)}=10.75$, $p=0.002$), difficult ($F_{(1,59)}=9.10$, $p=0.004$), and ambiguous trials ($F_{(1,59)}=8.34$, $p=0.005$).

Subsequent explorative ANCOVAs adjusted for gender and educational attainment for **experiment I** (DXM/DCS/PLC-1/SCZ) showed significant effects for all trial-types (all $F_{(3,115)} \geq 6.16$, all $p \leq 0.001$), with significantly higher disconfirmatory-evidence-scores in SCZ compared to DCS (all $p \leq 0.002$) and PLC-1 (all $p \leq 0.013$). In contrast, DXM showed no disconfirmatory-evidence-score differences from SCZ in easy ($p=0.944$) and difficult trials ($p=0.994$), but only in ambiguous trials ($p<0.001$) (Figure 3, B) (see Supplement 'Results I', Table S29-S33).

**Response Behavior**

We compared response behavior between conditions ($P_{80/20}$/$P_{60/40}$) and between trial-types (easy/difficult/ambiguous). For all three experiments, RM-ANOVAs on draws-to-decision revealed significant main effects of 'condition' (all $p<0.001$) and 'trial-type' (all $p<0.001$) as well as significant interactions for 'condition × trial-type' (all $p\leq0.003$), but no significant 'condition × group' interactions (Supplement 'Results I'). Subsequent SIDAK tests indicated that these effects related to significant gradual increases of draws-to-decision between the $P_{80/20}$ and $P_{60/40}$ condition as well as between levels of trial difficulty (draws-to-decision: easy < difficult < ambiguous) within and between conditions. Further, RM-ANOVAS for the PE condition revealed significant main effects on 'trial-type' (all $p<0.001$), on 'probability-estimates' (all $p<0.001$), and significant 'trial-type × probability-estimates' interactions (all $p<0.001$) for all three experiments. Subsequent SIDAK tests explained the effects on 'trial-type' through significantly decreased probability-estimates with increasing trial difficulty (probability-estimates magnitudes: easy > difficult > ambiguous trials) (Figure 3, A). Additionally, we observed 'trial-type × group' interactions for experiment II and III, which were due to the aforementioned increased probability estimates of DXM and SCZ, compared and DCS/PLC-1 and HC (see also Supplement 'Results I'). Taken together, these results suggest that all participants and patients were able to adequately distinguish between different difficulty levels of task conditions and trial-types.

**Discussion**

Here we provide novel neuropharmacological evidence in support of theories associating impaired data-gathering and probabilistic reasoning in patients with SCZ with reduced glutamatergic neurotransmission (4, 19, 21, 24, 26, 53, 54). We base this conclusion on the close resemblance between the data-gathering impairments (significantly increased JTC) displayed by SCZ patients and healthy participants following DXM intervention (down-regulating NMDA-R activity). Moreover, in the probability-estimates condition, DXM participants reported elevated probability-estimates and significantly higher disconfirmatory-evidence-scores compared to all other interventional groups. No differences were observed comparing DXM to SCZ, who displayed the outlined behavioral abnormalities even more clearly. As we did not obtain group level effects in experiment II we were not able to relate dopaminergic neurotransmission to behavioral or reasoning alterations. By comparison, our results following DXM suggest that JTC and overweighting of sensory evidence in SCZ might be conveyed by abnormal glutamatergic neurotransmission. Further, as our task setup allowed systematic assessments of probabilistic reasoning through the experimental modulation of sensory data (via different trial-types) in the context of different contextual information ($P_{80/20}$ and $P_{60/40}$), we were able to link our behavioral findings not only to alterations at the neurotransmitter

level but also to corresponding impairments of probabilistic reasoning as proposed by current theoretical frameworks for SCZ (4, 19, 23).

Here, data-gathering impairments stem from overweighting of new sensory information (or more precisely reduced stability of prior beliefs, e.g. (21, 55)) owing to a decrease in the formation of probabilistic predictions regarding the context of previously encountered sensory data (18, 19). With respect to the neuropharmacological correlates, NMDA-R hypofunction is viewed as one key causative contributor of these probabilistic reasoning impairments (4, 19, 21, 24, 26, 56). Translating this to our experimental framework, new sensory data (i.e. every new bead view) would be given increased significance, whereas the context of previous sensory experiences (i.e. previous beads) would be down-weighted (5, 18, 19, 24, 26, 53, 57). Consequently, identifying the correct source jar of a given bead sequence would depend less on the sensory context (i.e. the overall compilation of the bead sequence) but more on the currently observed bead. As a consequence, less information (i.e. fewer bead samples) would be viewed before participants feel confident and make a decision about the jar from which they believe beads were drawn. These proposed mechanisms could explain the development of delusions in the clinical context (18) and open a window for the development of novel compounds targeting treatment-resistant positive symptoms.

Against this background, our findings in the probability-estimates condition support previously observed impairments in probabilistic reasoning through over-weighting of sensory information and reduced stability of prior beliefs (21). In the present study, participants reported significantly elevated individual probability-estimates for a favored source jar following DXM intervention. Additionally, participants in the DXM group displayed significantly higher disconfirmatory-evidence-scores compared to all other healthy participants, further indicating reduced stability of prior beliefs following down-regulation of NMDA-R activity. These changes of probabilistic reasoning were even more pronounced in patients with SCZ and our explorative comparisons showed no significant differences between DXM participants and patients with SCZ, both for probability-estimates and disconfirmatory-evidence-scores (in easy and difficult trial-types). These observations further support an association between reduced glutamatergic neurotransmission, increased significance assigned to sensory data, and reduced stability of prior beliefs. In that regard, over-weighting of sensory evidence should result in reduced information sampling. Indeed, we observed numerically, but not significant, reduced data-gathering and significantly increased JTC rates both following DXM intervention and in patients with SCZ. Together these observations support the hypothesis that over-weighting of sensory information is associated with reduced data-gathering, and that impaired glutamatergic neurotransmission might be contributory to these complex processes.

Notably, our finding of impaired probabilistic reasoning appeared not to be a stable trait but rather context-dependent. This notion is supported by our observation that significant JTC was only

obtained in a context with an easily distinguishable bead distribution ($P_{80/20}$). By comparison, in the case of the $P_{60/40}$ condition, appropriately higher draws-to-decision and fewer JTC rates were observed in all experimental groups including SCZ patients, although the same trial difficulty levels (easy/difficult/ambiguous) were applied. Prior information about the jar distributions therefore leads to distinct forms of response behavior. With respect to proposals that unstable formation of probabilistic predictions underpins JTC (19, 21, 24), our results in the $P_{80/20}$ condition suggest the subjective level of certainty about the correct source jar would increase, thereby effectively reducing the need to sample information until feeling certain about a source jar. Correspondingly, jar distributions of the $P_{60/40}$ condition, as well as ambiguous sensory information ('ambiguous' trial-type), appear to reduce the level of certainty resulting in reduced JTC and probability-estimates. As our task layout did not include feedback regarding the correctness of a decision, the consequence of reduced data-gathering remained unknown to our participants. We thus propose that the individually perceived level of certainty depended more on prior information and trial difficulty than on feedback learning, which could otherwise have prompted our participants to continuously update their levels of certainty (5, 20, 23). In sum, our findings suggest that patients with SCZ are able to appropriately consider the context and ambiguity of presented sensory information. Hence, probabilistic reasoning impairments in SCZ might not represent stable traits but rather context-dependent states. This novel aspect is of essential importance for the future development of psychotherapeutic interventions (e.g. meta-cognitive interventions), as it shows that patients with SCZ in a psychotic state in principle still have the capabilities to integrate contextual information and to modify their reasoning about perceptions.

*Limitations and Outlook*

As all patients with SCZ included in this study received different antipsychotics, effects of the medication on our results must be assumed. However, a previous review has subsumed that the data-gathering and reasoning biases investigated in our study are likely to be independent from symptom improvement due to antipsychotic medication (58). Further, our study design compared SCZ patients exclusively to healthy controls. As we did not investigate a matched sample of non-psychotic patients with schizophrenia, we cannot specify to what extent e.g. psychotic symptoms are associated with the observed behavioral and reasoning impairments nor determine the contributory roles of other schizophrenia symptom domains. While we tried to minimize the influence of potential biases, such as gender, attention span, working memory capacity, and IQ as recommended by previous studies (4, 12, 59), in light of new findings (20), the possible influence of socio-economic status may also play in important role, which could only be estimated here in terms of educational attainment. Finally, regarding the doses of neuropharmacological interventions used, we based our

selection on previous studies that showed distinct behavioural effects (33-42). Although 250 mg DCS is consistent with the listed references, DCS is classically considered to work as an agonist at doses of 50mg to 100mg and as an antagonist at doses above 500mg (60-63). Collectively, these points may be addressed in future work. Despite these limitations, specific advantages of our large-scale randomized study are that we could demonstrate the contributory roles of glutamatergic neurotransmission to specific disturbances of probabilistic reasoning through pharmacological interventions in a strictly randomized and controlled design. Moreover, by also investigating clinically well-characterized patients with SCZ using the same task design we were able to relate our findings of interventionally reduced glutamatergic neurotransmission to impaired data-gathering and overweighting of sensory evidence in patients with SCZ, hence showing that the results from the pharmaco-behavioral experiments are clinically meaningful.

*Conclusions*

In summary, our results provide novel confirmatory neuropharmacological evidence for an association between impaired data-gathering, aberrant probabilistic reasoning and disrupted glutamatergic neurotransmission. By employing a novel probabilistic beads task we obtained interventional evidence linking impaired data-gathering to NMDA-R hypofunction and overweighting of sensory information. While we are aware that the applied neuropharmacological interventions did not selectively target particular neuromodulatory systems, our results offer novel and more direct insights into the complex association of glutamatergic neurotransmission with probabilistic reasoning and data-gathering impairments in SCZ. These insights could inform the development of personalized psychotherapeutic and glutamatergic treatment options and thereby help to overcome issues raised by the failure of foregoing glutamatergic approaches for the treatment of SCZ (64), which have not been effective before now, most likely due to individual disparities of glutamatergic impairments in patients with SCZ.

## Conflict of interest statement

Wolfgang Strube has received a speaker's honorarium from Mag&More GmbH. Peter Falkai was honorary speaker for Janssen-Cilag, AstraZeneca, Eli Lilly, Bristol–Myers–Squibb, Lundbeck, Pfizer, Bayer Vital, SmithKline Beecham, Wyeth and Essex. During the last 5 years, but not presently, he was a member of the advisory boards of Janssen-Cilag, AstraZeneca, Eli Lilly and Lundbeck. Alkomiet Hasan has received a paid speakership from Janssen-Cilag, Otsuka and Lundbeck. He was member of an advisory board of Roche, Janssen-Cilag, Otsuka and Lundbeck. All other authors report no biomedical financial interests or potential conflicts of interest.

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## Author Contributions

Conceptualization: WS SB AH. Formal analysis: WS AH SB. Funding acquisition: WS SB. Investigation: WS CC MU GQ SL. Methodology: WS LM SB. Project administration: WS GQ SL. Software: WS LM SB. Supervision: SB, AH. Visualization: WS LM SB. Writing – original draft: WS AH SB. Writing – review & editing: all authors.

## Open Science Statement

The Matlab code for our experimental beads task instantiation can be downloaded at https://github.com/wstrube/Beadstask. All anonymized study data can be accessed at https://figshare.com, DOI: 10.6084/m9.figshare.11852229.

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594

**Tab. 1**

| **Participant details for experiment I** | | | | | |
|---|---|---|---|---|---|
| | **DXM (n=32)** | **DCS (n=32)** | **PLC-1 (n=28)** | **test statistics** | |
| Gender (number female) | 16 | 16 | 14 | $X^2_{(2)}$<0.001 | p=1.000 |
| Handedness (number right) | 32 | 32 | 28 | - [#] | - [#] |
| Age (Years) | 24.1 (3.3) | 24.9 (4.1) | 22.8 (3.1) | $F_{(2,89)}$=2.76 | p=0.069 |
| TMT-A performance (sec) | 28 (12) | 27 (11) | 27 (7) | $F_{(2,89)}$=0.09 | p=0.912 |
| TMT-B performance (sec) | 62 (28) | 68 (29) | 60 (18) | $F_{(2,89)}$=0.75 | p=0.477 |
| d2-Attention-Task (sec) | 271 (21) | 268 (22) | 261 (23) | $F_{(2,89)}$=1.68 | p=0.192 |
| PDI (total score) | 3.8 (3.9) | 3.2 (3.1) | 4.0 (3.7) | $F_{(2,89)}$=0.45 | p=0.641 |
| Education Years | 12 (0.7) | 12 (0.8) | 12 (0.7) | $F_{(2,89)}$=0.02 | p=0.982 |
| **Participant details for experiment II** | | | | | |
| | **HAL (n=32)** | **BRO (n=32)** | **PLC-2 (n=32)** | **test statistics** | |
| Gender (number female) | 16 | 16 | 16 | $X^2_{(2)}$<0.001 | p=1.000 |
| Handedness (number right) | 32 | 31 | 31 | $X^2_{(2)}$=1.02 | p=0.600 |
| Age (Years) | 23.4 (4.6) | 24.1 (4.4) | 23.7 (3.9) | $F_{(2,93)}$=0.21 | p=0.812 |
| TMT-A performance (sec) | 29 (7) | 29 (10) | 27 (11) | $F_{(2,93)}$=0.23 | p=0.796 |
| TMT-B performance (sec) | 67 (12) | 64 (15) | 61 (18) | $F_{(2,93)}$=1.15 | p=0.322 |
| d2-Attention-Task (sec) | 266 (21) | 264 (32) | 267 (21) | $F_{(2,93)}$=0.13 | p=0.875 |
| PDI (total score) | 3.6 (3.7) | 3.5 (3.4) | 3.4 (3.1) | $F_{(2,93)}$=0.03 | p=0.972 |
| Education Years | 12 (0.7) | 12 (0.7) | 12 (0.6) | $F_{(2,93)}$=0.42 | p=0.660 |
| **Participant details for experiment III** | | | | | |
| | **SCZ (n=32)** | **HC (n=32)** | | **test statistics** | |
| Gender (number female) | 13 | 15 | | $X^2_{(1)}$=2.54 | p=0.614 |
| Handedness (number right) | 28 | 28 | | $X^2_{(1)}$<0.001 | p=1.000 |
| Age (Years) | 36.8 (11.5) | 36.8 (10.5) | | $t_{(62)}$<0.001 | p=1.000 |
| TMT-A performance (sec) | 41 (23) | 27 (11) | | $t_{(62)}$=3.23 | p=0.002 |
| TMT-B performance (sec) | 94 (37) | 66 (23) | | $t_{(62)}$=3.73 | p<0.001 |
| d2-Attention-Task (sec) | 234 (64) | 254 (39) | | $t_{(61)}$=1.44 [*] | p=0.156 |
| PANSS positive (scores) | 21.5 (5.8) | - | | - | |
| PANSS negative (scores) | 17.2 (5.8) | - | | - | |
| PANSS general (scores) | 38.7 (10.2) | - | | - | |
| PANSS total (scores) | 77.4 (18.1) | - | | - | |
| PANSS positive factor | 13.3 (3.6) | | | | |
| GAF | 58.7 (9.2) | - | | - | |
| CGI | 4.4 (0.5) | - | | - | |
| CPZ | 324.3 (295.4) | | | | |
| PDI (total score) | - | 3.2 (4.0) | | - | |
| Premorbid verbal IQ | 105.6 (3.0) | 106.0 (4.0) | | $t_{(62)}$=0.43 | p=0.669 |
| Education Years | 11 (1.6) | 11 (1.8) | | $t_{(62)}$=0.51 | p=0.611 |

595

596 **Figure and Table Legends**

597

598 **Figure 1** Experimental design of the beads task: Subfigures **A** and **B**: the two draws-to-decision (DTD)
599 conditions differed regarding their prespecified probability distributions ($P_{80/20}$: 'easy condition' and
600 $P_{60/40}$: 'difficult condition'); two sets of different colors were used to facilitate distinguishing between
601 the two conditions. Subfigure **C**: the probability-estimates (PE) condition was used to obtain explicit
602 PE for sensory data in different trial-types. Subfigure **D**: bead sequences were generated based on
603 different levels of likelihoods for the sensory data displayed in the three respective trial-types: (I)
604 easy trials with 80% likelihood and (II) difficult trials with 60% likelihood for one predominant bead
605 color, and (III) ambiguous trials with 50% likelihood for both colors. **Note**: *P(A)* denotes the
606 probability for jar 'A' being correct in each new trial; $P(E_n|A)$ represents the likelihood of each
607 cumulative bead sequence to be drawn from jar 'A' (E: sensory evidence, n: number of beads); $P(E_n)$
608 denotes the total probability of the given data and $P(A|E_n)$ the inferred likelihood of jar 'A' to be
609 correct given the sensory evidence accumulated.

610

611 **Figure 2, [A]** Draws-to-decision (DTD) measures subdivided by trial difficulty
612 (easy/difficult/ambiguous). Participants receiving dextromethorphan (DXM) sampled significantly less
613 sensory evidence compared to their respective control groups and did not differ from schizophrenia
614 patients (SCZ) in easy and difficult trails of the $P_{80/20}$ condition. SCZ patients displayed numerically
615 reduced data-gathering compared to HC. **[B]** * Jumping-to-conclusion (JTC) rates quantified the
616 frequencies by which participants decided after ≤ 3 bead views according to the established criterion
617 to define JTC. By comparison, SCZ and DXM displayed significantly elevated JTC rates in easy and
618 difficult trials. Error bars in part [A] represent standard errors of the mean. Legends refer to the
619 experimental groups: DXM: dextromethorphan; DCS: D-cycloserine; PLC-1: placebo group 1; HAL:
620 haloperidol; BRO: bromocriptine; PLC-2: placebo group 2; SCZ: schizophrenia patients; HC: matched
621 healthy controls.

622

623 **Figure 3, [A]** mean probability estimates (PE) on the 10 beads presented in each trial of the PE
624 condition. SCZ and DXM reported significantly higher probability-estimates at earlier bead ratings in
625 case of easy and difficult trials compared to their respective controls, while no differences were
626 observed between SCZ and DXM. **[B] *** Disconfirmatory evidence scores (DES) quantified the
627 cumulative amount by which participants and patients changed their PE following changes in bead
628 color after viewing ≥2 preceding beads of the same color (i.e. following disconfirmatory evidence).
629 DES scores thus quantified participants' responses to surprising (i.e. disconfirmatory) evidence
630 caused by a presenting beads of the color opposite to the participants' belief about the predominant
631 bead color in the presumed source jar. By comparison, SCZ and DXM displayed significantly elevated
632 DES in easy and difficult trials. Error bars represent standard errors of the mean. Legends refer to the
633 experimental groups: DXM: dextromethorphan; DCS: D-cycloserine; PLC-1: placebo group 1; HAL:
634 haloperidol; BRO: bromocriptine; PLC-2: placebo group 2; SCZ: schizophrenia patients; HC: matched
635 healthy controls.

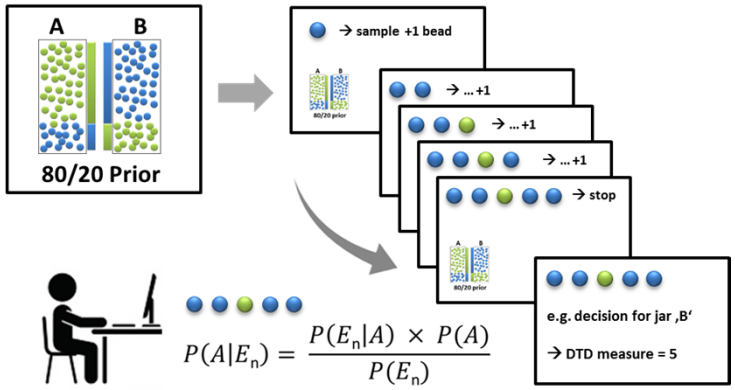
636

637 **Table 1** Socio-demographic, clinical and neuropsychological characteristics for the three separate
638 experiments. Healthy controls were matched to the patient group with respect to age, gender,
639 education-level, handedness, and pre-morbid IQ, since the latter parameter has been demonstrated
640 to impact beads task performance (12). All SCZ patients received assessments of functioning (GAF)
641 (65), clinical global impression (CGI) (66) and psychopathology (PANSS scale and $PANSS_{positive}$ factor)
642 (51, 67). Statistics reflect group comparisons of frequencies and means; standard deviations are
643 juxtaposed to their respective mean values in brackets. Index: n: number of participants (note: in
644 experiment II 4 participants were excluded from our analysis due to indications of inadequate
645 motivation); df: degrees of freedom; $X^2$: chi-square test (df); F: F-statistic of one-way ANOVAs (errors,
646 df); TMT: trail marking task; PDI: Peters et al. delusional inventory; PANSS: positive and negative
647 symptom scale; GAF: global assessment of functioning; CGI: clinical global impression scale; CPZ:
648 chlorpromazine equivalents; (*****) indicates one missing value for the d2 attention task in the SCZ
649 group. ($^{\#}$) As all participants of experiment II were right handed (constant variable), no Chi-Square
650 test were computed.

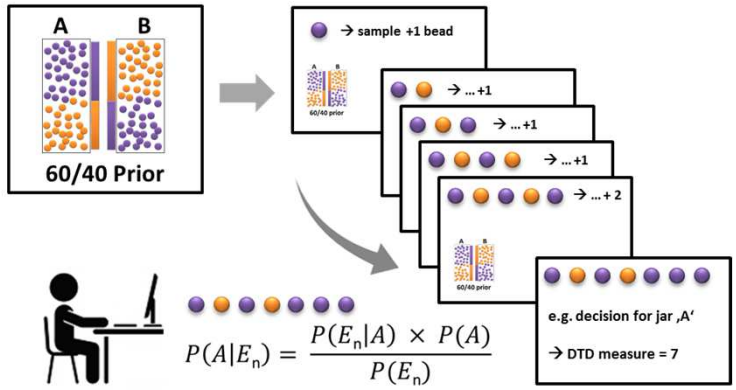
**Fig. 1**

**[1] Task design:**

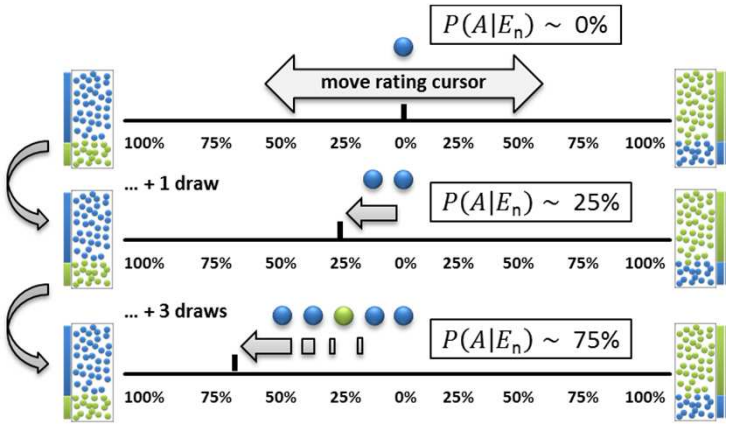
**[A] DTD I** (18 trials)



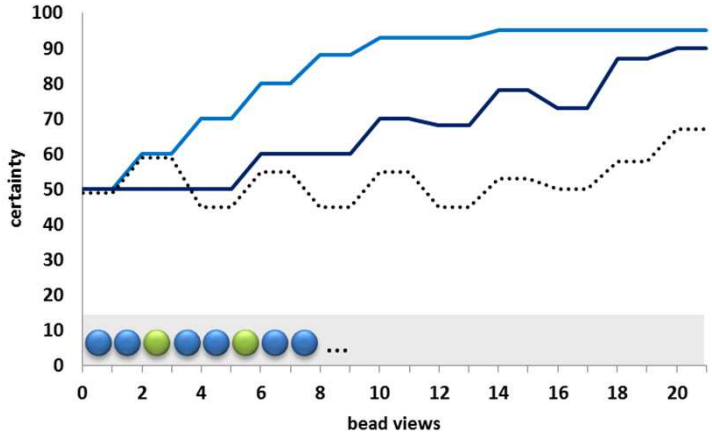

**[B] DTD II** (18 trials)



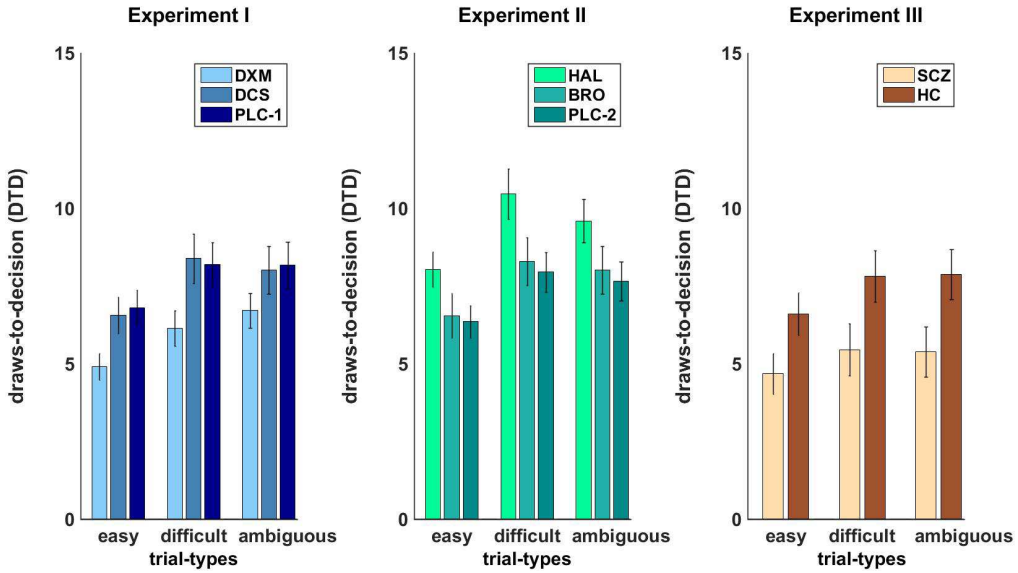

**[C] PE** (12 trials)



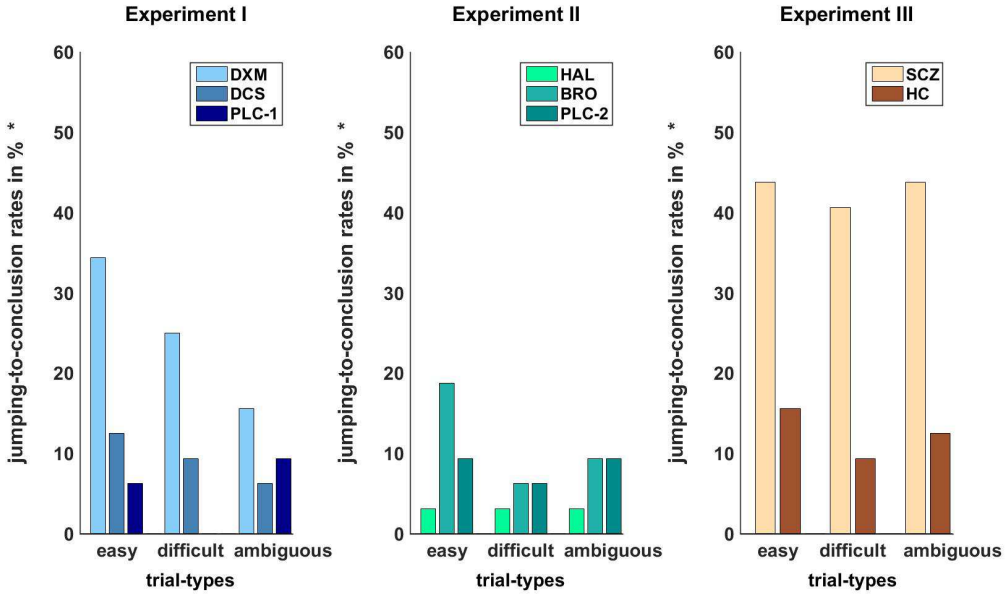

**[D] Trial types**



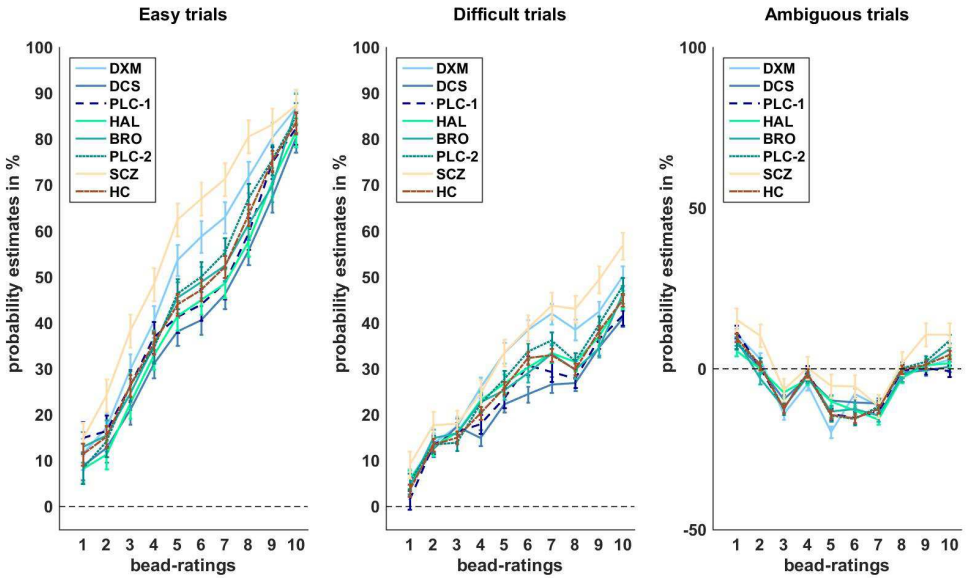
## [A] Reduced information sampling in DXM & SCZ




## [B] Increased JTC rates in DXM & SCZ



## [A] Increased probability estimates in DXM & SCZ




## [B] Overweighting of sensory information in DXM & SCZ