Precision-weighting of superior frontal cortex unsigned prediction error signals benefits learning, is mediated by dopamine, and is impaired in psychosis.

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Abstract (150 words)

Recent theories of cortical function construe the brain as performing hierarchical Bayesian inference. According to these theories, the precision of cortical unsigned prediction error (i.e., surprise) signals plays a key role in learning and decision-making, to be controlled by dopamine, and to contribute to the pathogenesis of psychosis. To test these hypotheses, we studied learning with variable outcome-precision in healthy individuals after dopaminergic modulation and in patients with early psychosis. Behavioural computational modelling indicated that precision-weighting of unsigned prediction errors benefits learning in health, and is impaired in psychosis. FMRI revealed coding of unsigned prediction errors relative to their precision in bilateral superior frontal gyri and dorsal anterior cingulate, which was perturbed by dopaminergic modulation, impaired in psychosis, and associated with task performance and schizotypy. We conclude that precision-weighting of cortical prediction error signals is a key mechanism through which dopamine modulates inference and contributes to the pathogenesis of psychosis.

Introduction

A common theme in contemporary theories of brain function, ranging from perception (Rao & Ballard, 1999) to reinforcement learning (Mathys et al., 2011), is an emphasis on the critical role played by prior predictions in inference (Rao & Ballard, 1999; Friston, 2009; Bastos et al., 2012; Adams et al., 2013; Mathys et al., 2011 & 2014; Iglesias et al., 2013; Clark, 2013 & 2015; Hohwy, 2013). According to these theories, predictions and incoming sensory input each have an associated precision (inverse variance), reflecting their confidence or reliability. Predictions and sensory input are thought to be compared against one other, generating a discrepancy signal termed the prediction error which indicates the difference between the expectation and sensory input. Such prediction error signals update prior beliefs in a manner that is weighted by their associated precision, such that more is learned from precise and reliable prediction errors compared to noisy and unreliable prediction errors (Friston, 2009; Bastos et al., 2012; Mathys et al., 2011 & 2014; Iglesias et al., 2013). Several theorists have suggested that neuromodulator systems, including dopamine, play an important role in mediating the precision of these prediction errors, and that impaired precision-weighting of prediction errors (through dopaminergic or other neuromodulator dysfunction) may be part of the cascade that result in psychotic symptoms (Bastos et al., 2012; Adams et al., 2013; Friston, 2009; Mathys et al., 2014; Fletcher & Frith 2009). However, to the best of our knowledge no direct evidence for these hypotheses exists. Specifically, whilst several neuroimaging studies have indicated abnormal brain prediction error signals in schizophrenia and related psychoses (Corlett et al 2007, Murray et al 2008, Schlagenhauf et al 2014, Ermakova et al 2018), none of these studies have addressed precision-weighting of prediction errors in patients.

In the context of reinforcement learning models, a distinction can be made between two types of prediction errors. First, the signed prediction error indicates whether an outcome is better or worse than expected, and thereby plays a crucial role in changing the value allocated to cues, thereby guiding future decisions (Schultz et al., 1997; O'Doherty et al., 2003 & 2004; Pessiglione et al., 2006; D'Ardenne et al., 2008; Diederen et al., 2016 & 2017, Tian et al., 2016). A second type of prediction error, the unsigned prediction error, signals the degree of surprise, without indicating valence (better/ worse than expected). In addition to signed prediction errors, unsigned prediction error are included in various reinforcement

learning models to control how much should be learned from new information. Large unsigned prediction errors signal that the brain's model of the world is inaccurate, thereby increasing the amount that is learned from new information. This can be achieved in various ways, including a non-Bayesian approach by using a dynamic learning rate parameter (Pearce & Hall, 1980; Sutton & Barto, 1998) or a Bayesian approach by decreasing the precision of prior beliefs (Courville et al., 2006; Gershman, 2015) across different levels in the hierarchy so that new sensory information has more of an impact on learning (Mathys et al., 2011 & 2014; Iglesias et al., 2013). In these hierarchical models both signed and unsigned prediction errors are weighted by their precision. Whilst evidence has been provided for a dopamine-mediated precision-weighted signed prediction error in learning (Diederen et al., 2015, 2016 & 2017), no such evidence exists for dopaminergic modulation of the precision-weighting of unsigned prediction errors. This is despite many computational theorists hypothesizing a role for neuromodulator systems in precision-weighting of unsigned prediction errors (Bastos et al., 2012; Adams et al., 2013; Mathys et al., 2014), and that the dysfunctional precision-weighting is a key contributor to the pathogenesis of psychosis (Fletcher & Frith 2009; Adams et al 2013, Sterzer et al 2018, Heinz et al 2018).

Here we therefore studied whether unsigned prediction errors are indeed coded relative to their associated precision; whether dopamine modulates the precision of these prediction errors; where precision-weighted prediction errors are represented in the cortex and whether and how precision weighting of cortical prediction error signals is disrupted in psychosis. Our methods elicit reliable measures of prediction error, as we use a task where prediction error is directly observable, rather than inferred as a latent variable as is common in many paradigms. To probe the role of precision-weighted prediction errors in learning, and the influence of dopamine, we employed pharmacological modulation in healthy volunteers, combined with fMRI, associative learning and computational modelling. We next examined how individual differences in computational learning signals and brain precision weighting signals relate to clinical psychosis, and psychotic-like thinking in health (schizotypy). We show that unsigned prediction errors are coded in superior frontal cortex, where the unsigned prediction error signal is coded relative to the precision of environmental outcomes; that the degree of precision-weighting benefits learning, is

mediated by dopamine, is perturbed in first episode psychosis, and relates to schizotypy in a health.

Results

Participants undertook a cognitive task in which they were presented with rewards/monetary outcomes on each trial that were drawn from distributions with specific degrees of precision (i.e. inverse variance). They were instructed to best-predict drawn rewards, with the most accurate prediction corresponding to the mean of the reward distribution. Crucially, we manipulated the precision of reward information by including distributions with different degrees of precision. We first examined the role of precision weighting of unsigned prediction errors on learning and the effect of dopaminergic modulation, by applying a novel, theoretically motivated, analysis to a dataset from an experiment (Diederen et al 2017) in which healthy volunteers were randomised to receive either placebo, sulpiride (a dopamine D2 receptor antagonist), or bromocriptine (a dopamine receptor agonist) and undertook the task in the MRI scanner. Subsequently, we repeated the same fMRI task in patients with early psychosis and matched controls. Finally, we also examine inter-individual differences in trait psychosis "schizotypy" in relation to precision-weighting.

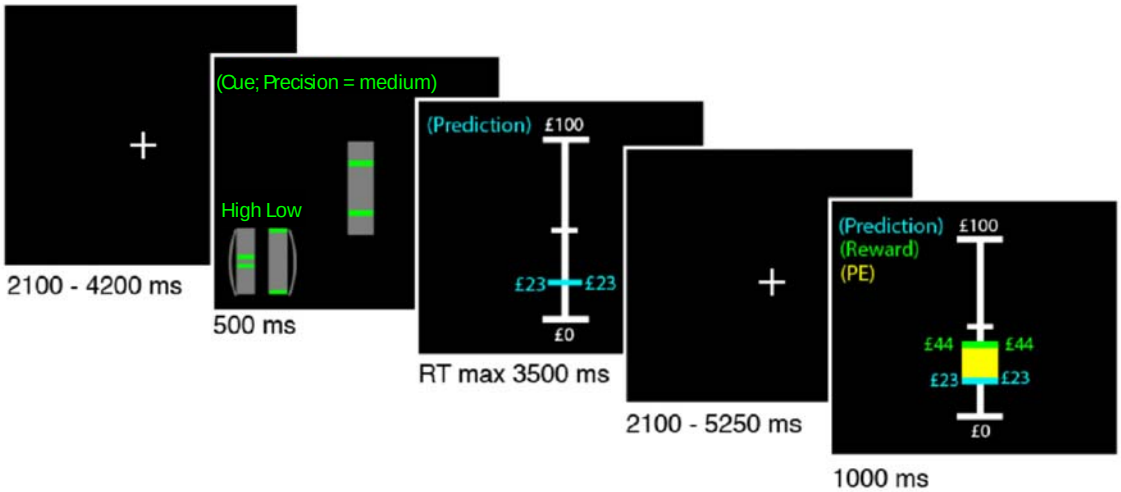

Figure 1: Example of a trial. The participants were instructed to learn the mean of a reward distribution. First a fixation cross was presented after which the participants were informed about the standard deviation (which indicated the precision) of the reward distribution. Subsequently the participants were asked to make a prediction regarding the upcoming reward, which was presented to the participant in combination with the prediction error (in yellow) after an anticipation period.

Study 1: Dopamine modulation study

Environmental precision and dopamine D2 receptor antagonism modulate task performance.

In the dopamine modulation study we explored the influence of precision and dopaminergic medication on performance, which was defined as the distance between the participants prediction and the mean of the distribution, as the latter corresponds to the most accurate prediction. We found that participants' performance increased when the precision of the reward distributions increased, and reduced average performance under sulpiride (a dopamine D2 receptor antagonist). Trial-by-trial analysis revealed lower performance in low-precision conditions at the start of the experiment, but no significant group differences. We studied whether dopaminergic modulation influenced scrolling distance, missed trials and reaction times as this might explain differences in performance. However, dopaminergic modulation did not affect scrolling distance or missed trials, although reaction times were increased under sulpiride (see Fig. 2 and supplementary information).

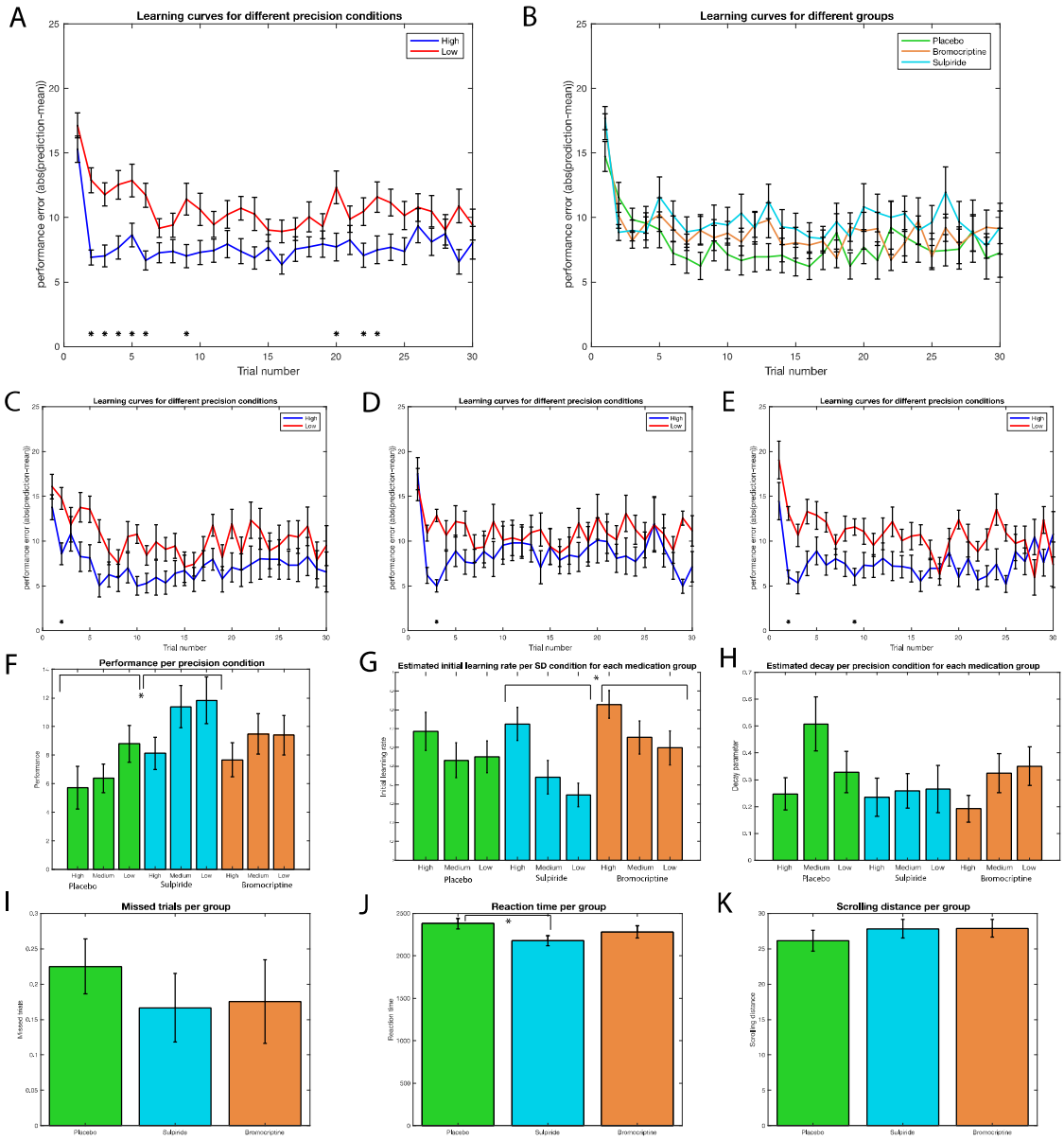

Figure 2: A. *Behavioural results for the dopamine study. A-E display the average learning curves , reflecting the absolute distance between the actual mean of the distribution and the participants estimate of the mean distribution over 30 trials averaged over the 3 sessions for each participant. Asterisks indicate Bonferoni corrected significant differences across conditions. A: Performance was significantly higher in the high precision condition compared to the low precision condition when combing all participants, especially at the beginning of the experiment. B: There were no clear differences between groups when analysing trial-by-trial performance. C-E: The placebo, Sulpiride and Bromocriptine group showed only a significant difference between the precision conditions on or two trials in the beginning of the experiment. F: Averaging performance across all trials, we see overall better performance in the placebo condition compared to the Bromocriptine condition, and higher performance in more precision conditions. G: Learning rates were higher in the Bromocriptine condition compared to the Sulpiride condition. H: Precision and group did not affect the learning rate decay parameter. I: No differences were found in number of missed trials, and K: scrolling distance.. J: Reaction times were quicker in the Sulpiride group.*

Reinforcement learning modelling of behavioural data indicates precision-weighted unsigned and signed prediction errors

We used two complementary approaches to demonstrate the contribution of unsigned prediction errors. First we used a general linear model with signed and unsigned prediction errors and their interaction term as independent variables and learning – defined as the change in predicted reward from one trial to the next – as the dependent variable. Here we showed that the unsigned*signed prediction error interaction term was highly significant in predicting learning (F{1,10763}=51.7, p<.0001), demonstrating the importance of unsigned prediction errors (for more details, see supplementary results). In addition, we fitted various reinforcement learning models to the participants' trial-wise predictions to investigate whether participants were likely to make use of precision-weighted unsigned and signed prediction errors. In all three medication groups a Pearce-Hall model with separate estimated precision weighted signed and unsigned prediction errors best predicted participants' predictions (model comparison using AIC to penalize models for the number of free parameters; see table 1 for an overview of the model (free) parameters and models' fits and comparisons). These results indicate that both unsigned and signed prediction errors are precision-weighted to facilitate efficient learning under uncertainty. By simulating data using the estimated model parameters and correlating this with the acquired data, we show that the correlation between the simulated and the real data is comparable across groups (R^2 placebo: .20 (SE= .035), sulpiride: .18 (SE= .034), bromocriptine: .19 (SE= .026), similar to other studies (e.g. Powers et al., 2017).

Table 1: Overview of AIC values for each learning model per medication group. The lowest AIC, which indicates the best performing model, is printed in bold. RW: Rescorla-Wagner. PH – Pearce-Hall.

	Free parameters	AIC overall	Placebo	Sulpiride	Bromocriptine
RW	1	894.7	824.2	935.9	924.0
RW scaled	1	903.2	829.0	947.3	933.4
PH not scaled	2	884.2	808.2	931.1	913.4
PH both scaled	2	883.6	807.3	930.1	913.4
PH-estimated precision-weighting	3	882.7	806.1	928.9	914.1
PH-estimated precision-weighting separate for signed and unsigned prediction error	4	**879.4**	**803.1**	**926.3**	**910.4**

Bromocriptine increases learning rates

The best-performing computational model contained 4 free parameters (initial learning rate, decay parameter, precision-weighting of signed prediction error and unsigned prediction error - see methods for details). As the model with a precision-weighting parameter outperformed the models without, precision is expected to affect the learning rate and decay parameters in the model. In order to explore this question further, we fitted the data to each precision condition separately for each participant and tested for an effect of precision on the model parameters. We tested for a main effect of group and precision on the initial learning rate and decay parameter (see methods), and their interactions. We found a significant effect of precision on the initial learning rate in the winning model, reflecting higher learning rates when reward information was more precise ($F\{1,52\}=16.83$, $p<.001$). In addition we found a small, but significant, effect of group ($F\{2,52\}=3.252$, $p=.047$), which was driven by higher learning rates in the bromocriptine group compared to the sulpiride group ($F\{1,36\}=7.266$, $p=.011$). However, no significant interaction was found $F\{2,52\}=1.348$, $p=.27$). We also explored the effects of precision and medication group on the decay parameter, and found no significant main effect of precision $F\{1,52\}=2.48$, $p=.12$), medication group $F\{2,52\}=1.80$, $p=.18$), or interaction $F\{2,52\}=.44$, $p=.65$) (see Fig. 2 G-H).

Unsigned prediction errors are coded in the SFC and pre SMA/dACC

Trial-by-trial unsigned prediction error (absolute difference between predicted and observed rewards) was included as a parametric modulator in our fMRI model. Whilst correcting for whole brain comparisons, unsigned prediction errors were coded in various regions within the frontal cortex, and parietal cortex (see Table 2). We used the left and right SFC and dACC clusters as ROIs, as informed by previous work, to take forward our analysis of dopaminergic effects on precision weighting. Secondary analyses examined these effects in occipital and parietal regions (supplementary materials).

Table 2: Regions coding unsigned prediction error voxelwise whole brain corrected <.05. SFC = Superior frontal cortex. SMA/dACC=supplementary motor area/dorsal anterior cingulate cortex. sOC= superior occipital cortex. FWE: family-wise error corrected.

Region	MNI	Voxels	T	Z	*p*FWE
Right SFC	27 8 54	145	8.43	7.68	<.001
Left SFC	-26 0 54	32	7.66	7.09	<.001
Pre SMA/ dACC	-7 12 50	6	5.32	5.10	=.002
Right sOC	24 -74 34	21	7.24	6.75	<.001
Parietal cortex	34 -48 38	18	5.69	5.43	<.001
Parietal cortex	20 -60 26	4	5.24	5.03	=.003

Precision-weighting of unsigned prediction errors is mediated by dopamine in the SFC/dACC

To test whether precision and dopaminergic perturbations affected the coding of unsigned prediction errors, we extracted the parameter estimates (betas) of the unsigned prediction error parametric modulators from the left and right superior frontal cortex (SFC) and dACC cluster that showed a main effect of unsigned prediction error coding at whole brain corrected *p*FWE<.01. We used a two-factor mixed model ANOVA with medication group as the between-subjects variable and precision condition as the within-subjects variable, using a linear contrast across precision conditions for the main effect of precision and interaction.

In the left SFC cluster, there was a significant interaction across precision conditions and medication group, suggesting that medication had a significant effect on precision-weighting of unsigned prediction errors ($F\{2,56\}=4.025$ $p=.023$; Fig.6B). We then explored whether the effect was driven by bromocriptine or sulpiride compared to placebo. We found a significant interaction between medication group (placebo vs sulpiride) and precision condition (F{2,37}

= 5.44, p=.025), with less precision-weighting in the sulpiride than in the placebo group, which suggests that sulpiride dampens precision-weighting of unsigned prediction errors. Comparing the placebo and bromocriptine group, there was a significant effect of precision (F{1,37} = 14.93, p<.001), but no significant effect of medication group (placebo vs bromocriptine) (F{1,37} = 2.781, p=.104) or interaction between medication group and precision (F{2,36} = 0.02, p=.894). This finding suggests that left SFC unsigned prediction error signals are precision-weighted, but relatively unaffected by bromocriptine.

In the right SFC we did not find a significant interaction between medication and precision condition (F{2,56}=1.70, p=.193; Fig. 3C). However, signal changes in the right SFC are largely the same as in the left SFC (see Fig. 3B). We did find a significant main effect of medication (F{2,56}=3.65, p=.032). This effect was driven by a stronger main effect of unsigned prediction error in the bromocriptine group compared to the placebo group (F{1,37}=6.740, p=.013), whereas the difference was only trend-level significant between the sulpiride and placebo group (F{1,38}=3.55, p=.067).

In the dACC we found a trend-level significant interaction between precision and medication (F{2,56}=2.81, p=.069; Fig. 3D). Post-hoc tests between the placebo and sulpiride group revealed a trend-level interaction between precision and medication (F{1,38}=3.043, p=.089). Testing the placebo and bromocriptine group revealed a significant effect of precision (F{1,37}=9.32, p=.004), but no effect of group (F{1,37}=1.17, p=.29) or interaction (F{1,37}=.172, p=.68). A similar pattern was thus found in the dACC as in the left SFC (see Fig. 3B+D).

The degree of precision-weighting in the left and right SFC and dACC correlated with task performance (controlling for group), such that higher precision-weighting relates to better performance (Left Rho=-.45, p<.001; Fig. 7A, Right: Rho=-.37, p=.005; Fig. 7B, dACC: Rho=-.25, p=.057). Performance was quantified as the mean performance error (*abs*(actual mean – predicted mean)) on the last three trials in each session (Fig. 4).

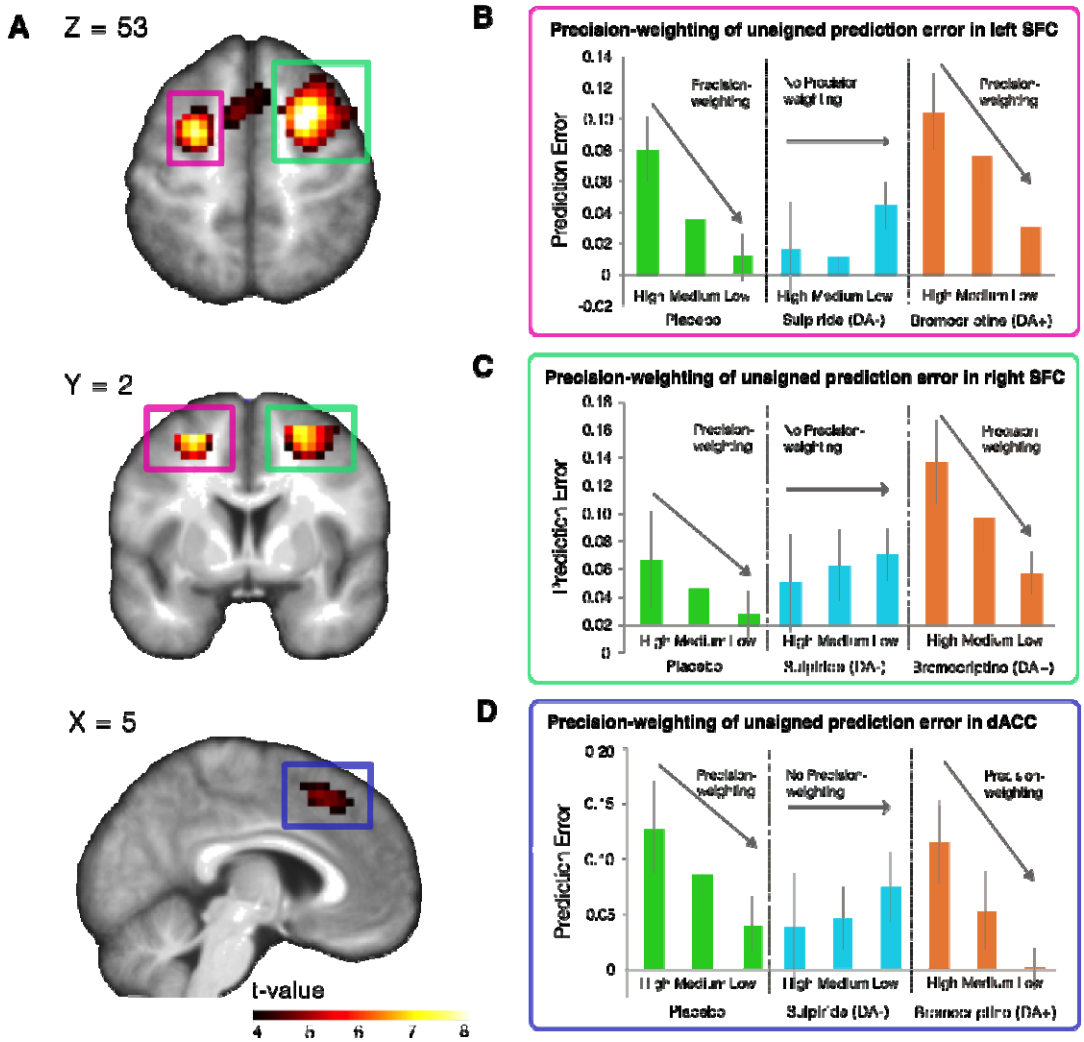

Figure. 3: A. Unsigned prediction errors were coded in bilateral superior frontal cortex and dorsal anterior cingulate cortex. The left side of the brain is the left side of the image. B-D. When exploring these regions further, we find that unsigned prediction errors are coded in a precision-weighted fashion as indicated by the strong unsigned prediction error signal in the high precision condition which declines over the medium and low precision condition in the placebo and bromocriptine group. Importantly, sulpiride perturbed precision-weighting significantly in the left SFC. Error bars represent standard error of the mean.

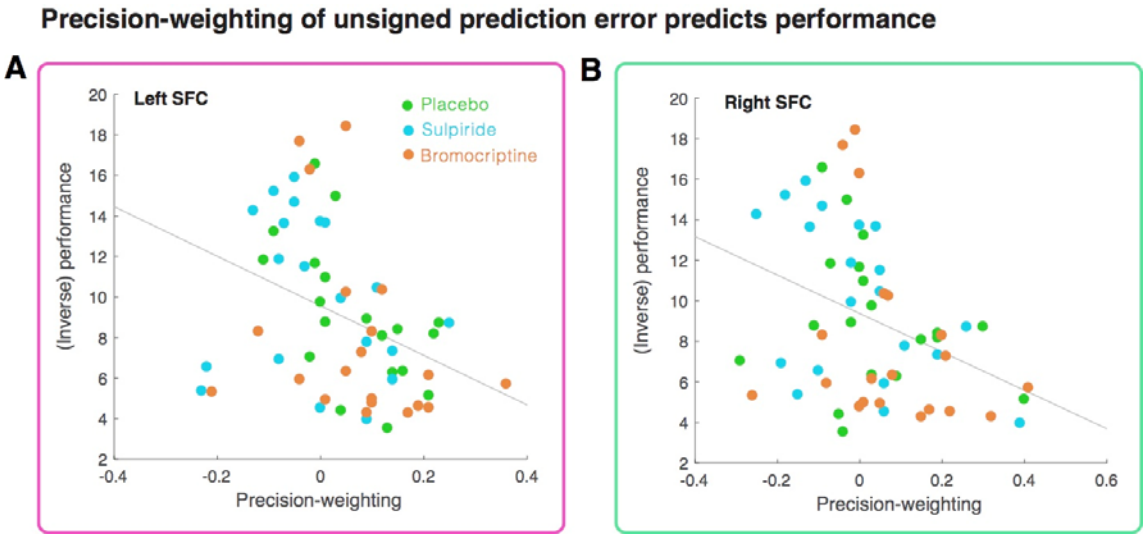

Figure. 4: Precision-weighting of unsigned prediction errors in the A. left SFC and B. right SFC correlates with performance (i.e. difference between mean of the reward distribution and predicted mean) on the task.

Study 2: Psychosis study

Having established the role of dopamine in the precision-weighting of cortical unsigned prediction errors, we tested whether precision-weighting is perturbed in psychosis by using the same experimental paradigm – in a slightly altered form – to assess a group of healthy controls (HCS), patients with first episode psychosis (FEP) and current psychotic symptoms (as assessed by scoring over 3 on the PANSS rating scale for the delusions or hallucinations items P1&P3, Kay et al., 1987), and a help-seeking group of people at risk for psychosis (At Risk Mental State, ARMS, Yung et al., 2005).

First Episode Psychosis (FEP) is associated with decreased overall performance and less benefit from more precise information

We explored the difference between participants' estimates of the mean and the actual mean across trials, and tested for significant differences across groups and precision conditions while correction for multiple comparisons using a Bonferonni correction. We found increased performance when precision was high in healthy control participants and ARMS individuals but not in people with FEP. We also found decreased performance in the FEP group compared to controls. There were no significant differences in missed trials,

reaction times and scrolling distances between the groups (see Fig. 5 and supplementary results).

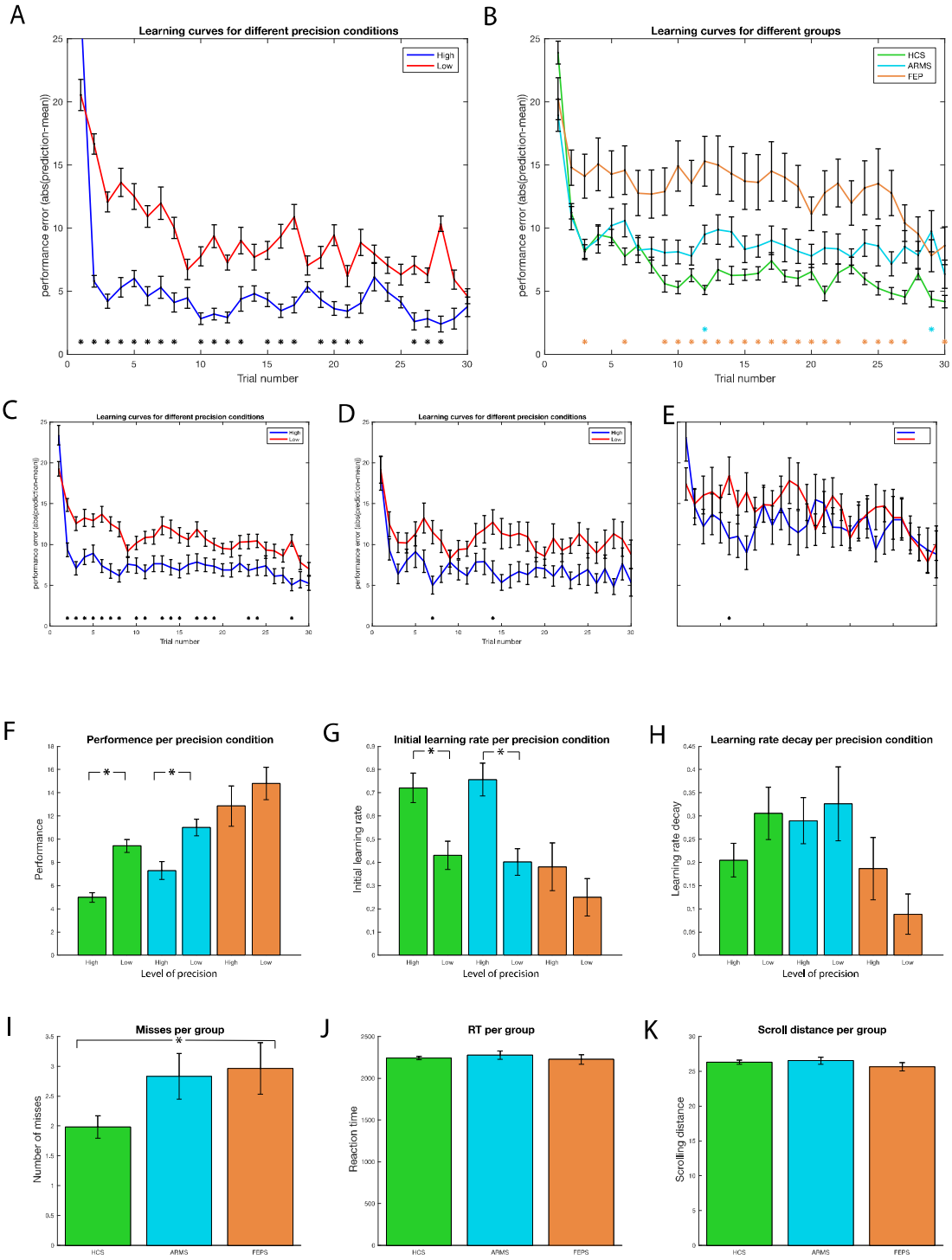

Figure. 5: Behavioural results for the patient study. A-E display the average learning curves , reflecting the absolute distance between the actual mean of the distribution and the participants estimate of the mean distribution over 30 trials averaged over the 3 sessions for each participant. Asterisks indicate Bonferoni corrected significant differences across conditions. A: Performance was significantly higher in the high precision condition compared to the low precision

condition when combing all participants, especially at the beginning of the experiment. B: HC performed better than FEPs, but not compared to ARMS. The colour of the asterisk indicates a significant difference of the patient group with HC. C-E: Healthy controls showed a significant difference between the precision conditions, whereas the patient groups did not. F: Averaging performance across all trials, HC and ARMS perform better than FEP, and benefitted from more precise information, whereas FEP did not. G: Learning rates were higher in the high precision condition compared to the low precision condition in HC and ARMS, but not for FEPS, although an interaction was not significant. H: Precision did not affect the learning rate decay parameter. I: HC had slightly fewer missed trials than FEP. J: Reaction times were equal across groups. K: Scrolling distance was equal across groups.

FEP is associated with a lack of precision-weighting as revealed by computational modelling

As before, we compared two different families of computational models; two Rescorla-Wagner reinforcement learning models and four Pearce-Hall learning models. We found that for the HCS and ARMS participants the best model was the Pearce-Hall model with a precision-weighting parameter for both the signed and unsigned prediction error term. However, the FEP group followed a simple RW-learning rule without precision-weighting of prediction error. This suggests that the FEP group specifically is not precision-weighting prediction errors (Table 3).

To confirm the lack of precision-weighting in the FEP group compared to control participants, we modelled the data separately for the high precision and low precision condition, and compared the model parameters between the two conditions. We found that both the HCS group T{29}=4.26, p<.001) and the ARMS group T{22}=4.99, p< .001) presented with significantly higher learning rates in the high precision condition compared to the low precision condition. By contrast, the FEP group did not show such a significant difference between high and low precision conditions (T{18}=1.5, p=.15). However, when we tested the precision by group interaction using a mixed (3x2) two-way ANOVA we did not see a significant interaction (F{2,76}=1.68 , p=.193) (Fig. 5G). We found no differences in learning rate decay between precision conditions for the HC group (T{29}=1.52, p= .14), ARMS group (T{22}=-.26, p= .74), and FEP group (T{18}=-1.39, p= .18) (Fig. 5H).

Table 3: Overview model comparisons

	Free parameters	AIC overall	HC	ARMS	FEP
RW	1	1365.5	1316.1	1375.5	1077.1
RW scaled	1	1364.8	1311.7	1376.5	1077.3
PH not scaled	2	1359.8	1298.7	1362.0	1094.2
PH both scaled	2	1361.4	1299.7	1362.9	1096.5
PH-estimated precision	3	1355.6	1292.9	1356.7	1097.1
PH-estimated precision separate for signed and unsigned PE	4	1349.8	1288.6	1348.5	1087.8

Unsigned prediction-errors are precision-weighted bilaterally in the SFC

In bilateral SFC (see methods for ROI derivation) there were brain signals that encoded unsigned prediction error (Right: T=7.33, voxels: 150, p<.001, [24 4 52]; Left: T=6.78, voxels: 149, p<.001, [-24 6 52], small volume correction). Importantly, there was significantly stronger encoding of unsigned prediction errors in the high precision condition compared to the low precision condition in both the right and left SFC, demonstrating precision-weighting (Right: T=3.82, voxels: 66, p=.011, [22 12 52]; Left: T=3.52, voxels: 45, p=.025, [-21 -2 52]; small volume corrected), and replicating the effect observed in the dopaminerigc modulation study.

In a whole brain analysis, additional regions demonstrated precision weighting of prediction error: bilateral superior frontal cortex, right lateral frontal cortex, and medial parietal lobe (see Table 3).

Table 4: Overview significant clusters precision-weighting of unsigned prediction error

Region	MNI	N-voxels	T	*p*
Medial parietal lobe	[-9 -61 48]	383	5.59	<.001
Occipital	[-12 – 101 2]	87	5.29	.011
Right SFC	[24 12 58]	171	4.53	<.001
Right PFC	[36 52 24]	171	4.46	<.001
Left SFC	[-21 -2 52]	94	4.20	.007

FEP is associated with diminished precision-weighting in the right SFC

There was a significant difference in precision-weighting of prediction error between the FEP group and the control group in the right SFC (T=3.38, voxels: 9, *p*=.035,[24 9 48]; small volume corrected) (see Fig. 6A). Importantly, group differences were not driven by medication as precision-weighting in medicated psychosis patients was not significantly different from patients who non-medicated (T{18}=.14, p=.89; analysis conducted on voxels that showed a FEP v control group difference), and there was no correlation between medication dose and precision-weighting (r=.17, p=.52). No voxels differentiated the groups on whole-brain analysis, or left SFC ROI analysis, corrected for multiple comparisons. We tested whether precision-weighting in these 9 voxels (that differentiated the first episode psychosis and control groups) correlated to symptom severity. To increase the number of participants for this analysis with a wide variety of symptoms we included both the ARMS group the FEP group. This revealed a significant relationship with positive symptoms (F{1,49}=5.21, *p*=.027), however this became trend-level after controlling for group (F{1,49}=3.42, *p*=.07).

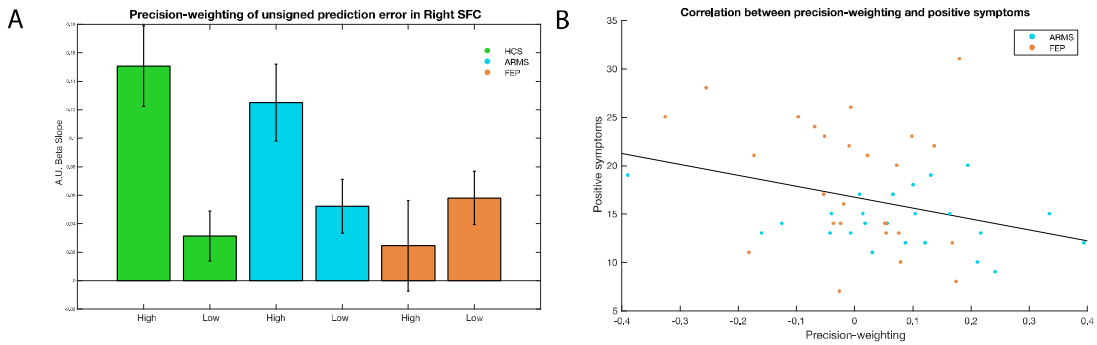

Figure 6: A: Precision-weighting of prediction error in ROI. Precision-weighting is significantly diminished in first episode psychosis. B: Diminished precision-weighting of prediction error is correlated with positive symptoms.

Higher SPQ scores is related to decreased performance and diminished precision-weighting of cortical prediction errors in a separate healthy sample

We next examined the relationship between psychotic-like symptoms and precision-weighting of prediction error in health, free from the possible confounds of medication or illness duration driving effects. For this purpose we pooled the participants in the dopaminergic modulation study (N=59) and the participants of a previously published normative sample (N=27) (Diederen et al., 2016). From these participant measures of schizotypy (trait levels of schizophrenia-like thoughts and behaviour that occur on a continuum in the general population) were taken around the time of scanning (Schizotypal Personality Questionnaire, SPQ (Raine et al., 1991)). We tested for a relationship between SPQ scores and precision-weighting of prediction error, while controlling for experimental group. There was a significant correlation between performance and SPQ scores (Rho=-.23, p=.034). This was mirrored by a significant brain signal-schizotypy correlation between SPQ scores and the extracted right SFC precision-weighting parameter estimates (Rho=-.25, p=.024)(Figure 6C). The higher schizotypal personality, the less the participants exhibited cortical precision-weighting of prediction errors. Importantly, no relationship was observed between schizotypy and the main-effect of prediction error (p>.3), suggesting that the effect is specific to the precision-weighting of prediction error.

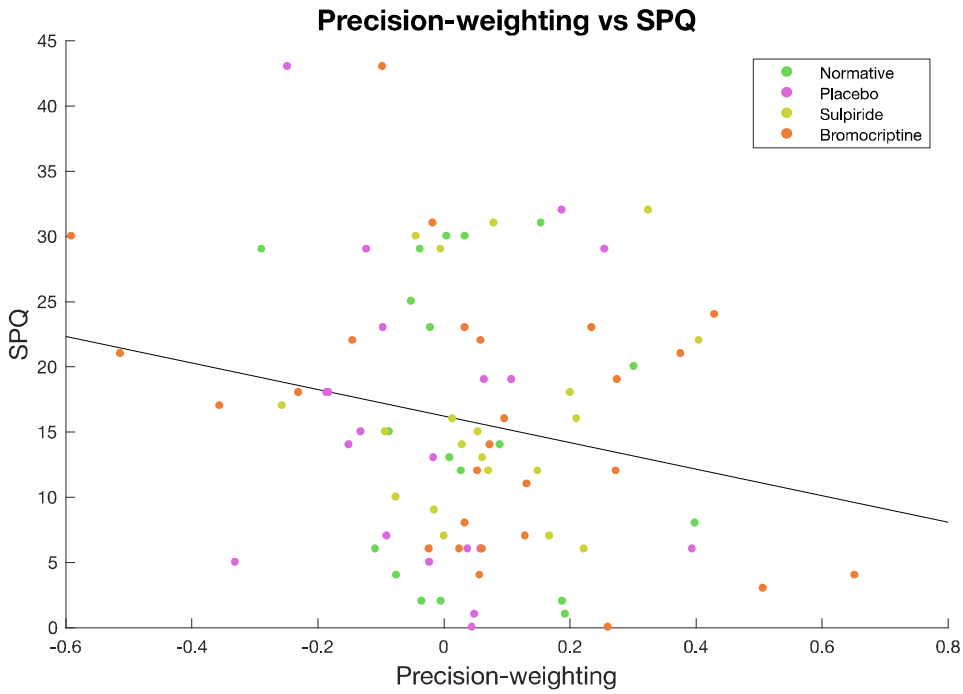

FIgure 7: Higher SPQ scores were correlated with less precision-weighting in the right SFC, including when controlling for experimental group

Discussion

Recent theories (Friston, 2009; Bastos et al., 2012; Adams et al., 2013; Fletcher & Frith, 2009; Sterzer et al., 2018) have hypothesised that precision-weighting of cortical prediction errors is mediated by neuromodulators (including dopamine), and link a malfunctioning dopamine system to psychosis through aberrant precision-weighting of these prediction errors. However, to our knowledge, no direct evidence for any of these claims exists. Here we showed that separately estimated precision-weighted signed and unsigned prediction errors provided the best description of the behavioural data, thus suggesting that both precision-weighted and unsigned prediction errors should be represented in the brain. The representation of precision weighted *signed* prediction errors in subcortical areas was confirmed previously by fMRI in humans (Diederen et al., 2016). In the present study, we tested the prediction that unsigned prediction errors would be represented in the brain, and found evidence for a precision weighted cortical representation of unsigned prediction in the bilateral superior frontal cortex and dorsal anterior cingulate cortex/pre-supplementary motor area (that we collectively referred to as SFC). Importantly, this precision weighting was significantly diminished in the sulpiride (dopamine D2 receptor antagonism) group in comparison to the other groups in the right SFC; there was marginal evidence of a medication effect in the dACC. This finding suggests that the dopamine D2 receptor plays a key role in the mechanisms underlying precision-weighting of unsigned prediction errors. We furthermore found that a greater degree of superior frontal precision-weighting of unsigned prediction error was significantly correlated to performance on the task, where an increase in precision-weighting resulted in more accurate predictions of upcoming rewards. These results confirm the hypothesis that there exist cortical unsigned prediction error signals, which influence performance and are precision weighted by dopamine.

The coding of unsigned prediction errors in the superior and middle frontal gyri and dACC is in line with earlier findings by Hayden (et al., 2011) who found unsigned prediction errors in the dACC of monkeys, and with prior fMRI studies in humans (Fletcher et al 2001, Turner et al 2004, Fouragnan et al., 2017; Fouragnan et al 2018; Metereau et al., 2013; Ide et al., 2013). Our findings are consistent with those of Katthagen et al 2018, who used reaction time data (rather than choice data) from a human fMRI reversal learning study to derive a

relevance weighted unsigned prediction error signal, which was also represented in the dACC. Our data in both the dopaminergic modulation dataset, and in the psychosis study dataset show that SFC prediction error signals based on choice data are precision-weighted in humans. We note that dopaminergic innervation of cortex is greatest in superior frontal regions (Lewis et al., 1987; Berger et al., 1991; Paus, 2001), compatible with the hypothesis that precision weighting is influenced here by dopaminergic input.

If the precision-weighting of prediction errors is important in learning, we can expect aberrant learning to occur when prediction errors are not scaled optimally to the environmental statistics determining the precision of available information. We tested whether this mechanism could be of importance to psychosis, which is characterized by delusional beliefs and hallucinatory perception (Fletcher & Frith et al., 2009). Previous work showed aberrant cortical and subcortical prediction error coding in people with psychosis (Murray et al., 2008; Corlett et al., 2007, Ermakova et al., 2018). As psychosis has consistently been associated with dopamine dysfunction (Howes et al., 2009), it is likely that a dopamine mediated precision-weighting process would be impaired in psychosis. Indeed, it has been suggested that dopamine dysregulation causes psychosis due to affecting the brains capacity to precision-weight prediction error (Adams et al., 2013). That is, if unreliable prediction errors were given excessive weight, they could have an exaggerated influence on driving changes in the brain's model of the world, thereby contributing to the formation of abnormal beliefs.

We extended previous studies showing abnormal brain prediction error signals in psychosis by testing the degree of precision-weighting of unsigned prediction errors in a clinical psychosis population. Here we found several lines of evidence suggesting that FEP in particular is associated with a failure to precision-weight prediction errors. First, FEP was associated with decreased performance on the task. Furthermore, the FEP group did not benefit as much from more precision reward information than the healthy controls and ARMS group did. This could potentially be driven by a ceiling effect, where the performance in the FEP group is so poor that the difference between the high precision and low precision condition is attenuated. However, this is unlikely: the distance between the participants predictions and actual mean of the distribution towards the end of the experiment (the

measure of performance used in the present study) were below 14 points in both precision conditions, which is better than expected from random guessing on a 100 point scale. Secondly, computational modelling suggests that the FEP group does not precision-weight prediction errors, as they follow a simple RW learning rule without precision-weighted prediction errors. By contrast, controls and ARMS follow a Pearce-Hall learning rule with precision-weighted prediction errors. This invites the question whether the poor performance of the FEP group might have more to do with the failure to diminish their learning rate appropriately over time (as this is what characterizes a Pearce-Hall model). However, subsequent analysis revealed that whereas controls and ARMS show a clear effect of precision on learning rate, the FEP group does not. In contrast, no differences were found for the decay parameter, suggesting that the differences lie in how much prediction errors are used in different precision conditions. Thirdly, neural evidence suggests that the FEP group does not precision-weight cortical prediction errors to the extent that healthy controls do, and that the degree of neural abnormality may relate to positive psychotic symptom severity.

Although we demonstrate that in health, dopaminergic modulation influences precision weighting of the prediction error signal in the superior cortex, and we demonstrate abnormal SFC precision weighting in psychosis, we cannot conclude that the abnormalities in patients were of dopaminergic origin, as we make no neurochemical measures in patients. Such inference would require either a pharmacological design in patients, or the use of neurochemical imaging such as PET. One possible confound in the patient study is the use of anti-psychotic medication in some patients, given that we showed that precision-weighting of prediction errors is diminished after healthy controls take a dopamine D2-receptor antagonist in controls. We addressed this issue by showing that there are no differences in precision-weighting within the participants who take anti-psychotics and those who do not. We furthermore showed that there is no relationship between anti-psychotic dosage and the degree of precision-weighting in this study. Furthermore we demonstrated evidence for aberrancies in cortical precision-weighting of prediction errors, and impaired task performance, relating to schizotypal personality in the healthy population, where medication cannot be a confound. We thus conclude that there is no evidence in the

present study that the reported effects in patients are driven by the use of anti-psychotic medications.

Several other studies have used this computational framework to study learning in individuals with psychosis that imply a failure to precision weight prediction errors. For example in a pharmacological model of psychosis, Vinckier (et al., 2015) found that ketamine modulated a confidence parameter in a reinforcement learning model, which controls the degree to which prediction errors influence learning. Confidence might be implicated in the brain through a precision-weighting process, where prediction errors are coded as less precise when confidence increases, so less is learned from new prediction errors. Furthermore, Deserno (et al., 2017) and Powers (et al., 2017) have used hierarchical Bayesian models to make inferences about the way individuals with schizophrenia and psychosis respectively form beliefs about the environment. Critically in these models a prediction error is weighted by the precision of beliefs regarding cue-outcome contingencies, and the volatility of these relationships (Mathys et at., 2011 & 2014; Iglesias et al., 2013). As such, these models imply precision-weighting of prediction, however they do not test the degree to which these prediction errors are precision-weighted explicitly. Our results complement these studies and provide an additional direct test of the degree of precision weighting of prediction errors in psychosis.

A previous study has reported differences between healthy controls and individuals with schizophrenia in the degree to which they adapt the coding of value to the variability in the environment (Kirschner et al., 2016). This process of adaptive coding is similar to precision weighting of unsigned prediction errors, as it reflects the brains capacity to scale neural signals to what is referred to as economic 'risk', in other words the spread of possible reward outcomes. In combination with the present findings, psychotic disorder might be associated with a broader failure to adapt neural signals to the statistics of the environment. We thus conclude that there is evidence for a diminishment in precision-weighting of unsigned prediction errors in individuals with first episode psychosis. This was most strongly related to the intensity of the positive symptoms experienced by the patients in this study. Our current study provides evidence for a key hypothesis in the field of predictive coding theories of psychosis, which is that psychosis is associated with a failure to accurately take

into account the reliability of new information, leading to the formation of aberrant inferences about the world, predisposing to delusional beliefs.

Our findings are in line with the wide literature on adaptive coding of neural signals to context. Adaptive coding seems to be a feature of many neural systems (Brenner et al., 2000; Fairhall et al., 2001; Barlow et al., 1961; Laughlin et al., 1981), ranging from the perceptual system (Ohzawa et al., 1982; Smirnakis et al., 1997) to reward systems (Tobler et al., 2005; Park et al., 2012). Indeed, previous studies that used the present paradigm have framed these questions in terms of adaptive coding of signed reward prediction errors rather than precision-weighting of unsigned prediction errors (Diederen et al., 2016 & 2017). However, adaptive coding of neural signals to the statistics of the environment follows directly from predictive coding models of neural functioning which suggest that prediction errors should be weighted by their precision (Srinivasan et al., 1982). Here the adaptive coding of prediction errors equals precision-weighting. Therefore, we believe that the framework of adaptive coding and precision-weighting do not constitute competing interpretations of the data, but rather that adaptive coding is a feature that follows from predictive coding models.

In the present study, no differences were found with regards to the ARMS group. This is in line with recent work showing intact cortical prediction error responses in ARMS (Ermakova et al., 2018). There might be different reasons for this. First, considering that the effects were correlated with severity of symptoms, and the symptoms in the ARMS group were significantly lower, the lack of a significant finding for the ARMS group might be a matter of severity. Indeed, if we separate the ARMS group and FEP group and correlate the degree of precision-weighting with positive symptoms, we find comparable r values for both groups (ARMS: r=-.30, FEP: r=-.36), although neither is significant in isolation due to the small N. An alternative is that the aberrancies are disease category specific, which could be relevant as only a minority of ARMS patients will go on to develop psychotic illness (Morrison et al 2012 BMJ). Future studies with more power, ideally including longitudinal follow-up, would clarify these issues.

In conclusion, we found evidence of precision-weighted unsigned prediction errors in the superior frontal and dorsal anterior cingulate cortices. Furthermore, we found that the precision-weighting of prediction errors was modulated by the dopaminergic antagonist sulpiride, and we found that the degree of precision-weighting in this area was correlated to performance on the task, providing evidence for the first time that dopamine plays a role in precision-weighting of unsigned prediction error signals during learning. We demonstrate the clinical relevance of the unsigned prediction error signal by showing that it is, as predicted, abnormal in psychotic illness, and that it relates to trait levels of schizotypy in the healthy population.

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Methods

Table 5: Demographics for dopamine and schizotypy study

	Normative		Dopamine study						
			Placebo		Sulpiride		Bromocriptine		p-value
N	27		20		20		19		
Male	10 (17)		9 (11)		12 (8)		10 (9)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age	24.2	5.4	23.9	4.8	24.8	4.5	23.7	4.3	
Schizotypy	16.0	10.1	16.6	10.1	15.4	11.5	15.6	11.2	*p*=.99

Table 6: Demographics for psychosis study

Group	HCS		ARMS		FEP		
N	30		24		26		
	Mean	SD	Mean	SD	Mean	SD	p-value
Age	22.57	3.53	21.00	3.48	24.7	4.90	*p*=.007
Male	16		18		21		*p*=.07
IQ	118.8	10.5	118.7	11.65	105.8	19.8	*p*=.002
PANSS positive	7.20	0.76	14.00	2.97	19.27	6.45	*p*<.001
PANSS negative	7.23	.94	13.50	6.22	15.46	8.05	*p*<.001
Taking antipsychotic medication	0/30		4/24		14/26		*p*<.001
Antipsychotic dosage	0	0	55.5	64.3	328.2	181.54	*p*=.010

Participants - psychosis study

Healthy volunteers (HCS, n=30, average 22.6 years, 15 female) without a history of psychiatric illness or brain injury were recruited as control subjects. Healthy volunteers did not report any personal or family history of neurological, psychiatric or medical disorders. Participants with first episode psychosis (FEP, n=26, average 24.8 years, 6 female) or at-risk (ARMS, n=24, average 21.5 years, 8 female) were recruited from the Cambridge Early

intervention service North and South. In addition, psychosis-prone participants were recruited on the basis of belonging to a help-seeking, low-mood, high schizotypy sub-group following a latent class analysis on the Neuroscience in Psychiatry Network (NSPN) cohort (Davis et al., 2017) or through advertisement via posters displayed at the Cambridge University counselling services. Individuals at-risk for psychosis were identified by meeting At-Risk-Mental-State (ARMS) criteria on the CAARMS interview in the past six months. All participants had normal hearing and normal or corrected to normal vision. All participants gave written informed consent. The study was approved by the West of Scotland (REC 3) ethical committee. See Table 1 for details on demographics and symptom scores.

Participants - dopamine and schizotypy study

Healthy volunteers were recruited for a normative study and a pharmacology study exploring adaptation of reward prediction errors to context variability (see Diederen et al., 2016 & 2017). 28 participants were recruited for the normative study (one excluded due to scanning issues). A further 63 participants were recruited, of which 4 were excluded due to feeling unwell during scanning and/or a failure to complete the paradigm, or side-effects of the medication. All participants were recruited via the distribution of flyers in Cambridge and advertisements on Gumtree. Drug screenings were all negative. After receiving detailed information about the study, all participants gave written informed consent. Schizotypy was measured on these participants using the Schizotypal Personality Questionnaire.

Pharmacological dopaminergic challenge

Participants received a single dose of the D2-antagonist sulpiride (600mg), the dopamine agonist Bromocriptine (2.5 mg), or placebo, in a double-blind fashion. Domperidone was added to prevent potential nausea, as it would be an indicative factor of having taken a drug, and could thus influence the blinding procedure, as well as making people feel unwell (see Diederen et al., 2017 for a detailed description of the dopaminergic manipulation).

Task design

During functional (f)MRI data acquisition, participants predicted the magnitude of upcoming rewards. Optimal performance on this task required the participant to estimate the mean of the distribution from which the rewards were drawn. The task consisted of three sessions of

10 minutes each. The rewards were drawn from six different pseudo-Gaussian distributions that differed with respect to their precision (i.e. inverse variance) and expected value (i.e. mean of the distribution; EV). For the dopamine and Schizotypy study, the standard deviations from the distributions were 5, 10 & 15, corresponding to precision of .01, .04 and .004. For the psychosis study, the standard deviation of the distributions were either 5 or 15, corresponding to precision of .01 and .004. Distributions were counterbalanced to ensure that the two conditions within each session differed with respect to the EV and precision. The conditions were presented in short blocks, each including 4-6 trials. Each distribution consisted of 31 trials, which resulted in a total number of trials of 62 per session. The participants were informed beforehand that each distribution (of which two per session) had a different level of precision, which could be one of three levels: low, medium or high precision, corresponding to precisions of 0.004, 0.04 and 0.01 although the exact precisions were not revealed to the participants (in the psychosis study there was no medium condition). Each trial started with a fixation cross that was presented between 2100 and 4200ms. The fixation cross was followed by a cue that was presented for 500ms. This cue informed the participant from which of two distributions (high, medium or low) in that block the upcoming reward was being drawn. After the cue was presented the participants were required to predict the magnitude of the upcoming reward. They had 3500ms to make this prediction. Making the prediction involved scrolling a mouse ball with their fingers up and down, and clicking the left mouse button to state their prediction. This resulted in moving a bar up and down the screen on a scale that ranged from 0 to 100. The starting point on the bar was randomized throughout the experiment, to ensure that scrolling distance did not correlate with participants' predictions. The participants were instructed to minimize the prediction error, i.e. the difference between the expected and the actual obtained reward. After the prediction, another fixation cross was presented for duration between 2100 and 5250ms. Thereafter, the obtained reward was presented in addition to the prediction and the reward prediction error for 1000ms (see Fig. 7 for an example trial).

Pay-off

If the participants would always receive the amount of money drawn by the computer, this might have reduced their motivation to reveal their true prediction. Therefore, the participants were rewarded according to their accuracy (i.e., proximity to the mean of the

reward distribution) on 20% of the trials in order to keep them motivated to predict as well as possible.

Behavioural analyses

Behavioural data was analysed in Matlab. In order to test the performance of the participants, we analysed whether the predictions of the participants approached the mean of the distribution (or expected value (EV)), during the experiment. We calculated the absolute difference between the EV and the prediction in across all trials and averaged across the 3 sessions. We computed bonferonni corrected paired t-tests to test the effect of precision across and within groups and the differences across groups (see figure 2&5A-E). We also tested for an effect of group and precision on average distance across the experiment. In addition, we analysed differences in scrolling distance to exclude the possibility that drug effects influenced willingness to do the task, resulting in a decrease in scrolling distance. We also analysed differences in reaction times and missed trials for the same reason.

Linear regression model

In order to explore the contribution of signed and unsigned prediction error to learning we used a linear regression model with belief-updating as dependent variable and both unsigned and signed prediction error as independent variables. Belief updating here is defined as the change in value estimate from t_n to t_{n+1}. That is, when the participant expects a value of 20 on t_1 and expect as value of 30 on t_2 there was a belief update of 10, which is expected to be explained by a prediction error experienced at t_1. Since signed prediction errors, but not unsigned prediction errors inform the participant about the direction of learning, we expect the former but not the latter to have a main effect on belief-updating. Furthermore, since formal learning models like the Pearce-Hall model (Pearce & Hall, 1980), suggest that unsigned prediction errors increase learning, we expect an interaction between unsigned and signed prediction error on belief-updating. In order to visualise the effect of signed and unsigned prediction errors on belief-updating, we will create bins on the basis of signed prediction errors and plot belief-updating on the y-axis. If unsigned prediction errors interact with signed prediction error in predicting belief-updating we should expect to see a logit or sigmoid relationship between signed prediction error and belief updating.

Behavioural modelling

To investigate learning, we fitted several reinforcement learning models to participants' prediction sequences. Each model used a common updating rule in which predictions on trial *n* depended on the prediction error and the learning rate on trial *n-1:*

$$\mathbf{y_n = y_{n-1} + k_n\, \delta_n} \qquad \textbf{Equation 1}$$

Here, y_n is the prediction made on trial *n*, k_n refers to the learning rate and δ_n denotes the size of the prediction error. This is a standard reinforcement learning model, and allows to estimate to which degree prediction errors are being used by the participant by estimating the learning rate parameter (Sutton & Barto et al., 1998).

The first model consisted of a Rescorla-Wagner (RW) reinforcement learning model with a fixed learning rate. A fixed learning rate prescribes that each prediction error is weighted equally during learning (e.g., independent of whether a prediction error occurred at the start, or the end of a session):

$$\mathbf{k_n = \alpha} \qquad \textbf{Equation 2}$$

The second model consisted of a Pearce-Hall (PH) model with a trial-wise, dynamic, learning rate, which prescribes higher weighting of prediction errors (i.e., more learning) at the start of a task session compared to later trials (Pearce et al., 1980). In uncertain environments, it is more optimal to decrease the weighting of prediction errors as learning progresses (once participants become more certain of their predictions) as prediction errors will continue to occur as a result of the imposed uncertainty. The PH learning rate decays as trial progress, as a function of the previous learning rate and the experienced prediction error, which allows for fast updating of predictions at the beginning of each task session:

$$\mathbf{k_n = \alpha C|\delta_{n-1}| + (1 - \alpha)\, k_{n-1}} \qquad \textbf{Equation 3}$$

in which $|\delta|$ is the absolute prediction error, C is an arbitrary scaling coefficient and α is the learning rate decay.

We additionally explored whether scaling prediction error to the reliability of the environment (i.e., precision–weighting) benefitted learning by comparing models that scaled the prediction error term and models that did not. We both explored models that simply precision-weighted the prediction error by a constant term ω (equation 4&5), and models that estimated the degree υ of precision-weighting for each individual (equation 6). The precision here is the true precision, and not the trial-by-trial estimated precision as participants were informed prior to the experiment which of the cues indicated the high, medium and low variance condition. We estimated both models that had a single estimated υ for both signed and unsigned prediction errors and a model that had a separate variable for signed and unsigned prediction errors. In contrast to earlier studies (Diederen et al., 2015, 2016 & 2017) we used a more simplified model that utilised a linear precision-weighted model to ease interpretation.

$$y_n = y_{n-1} + k_n (\delta / \omega)_n \qquad \textbf{Equation 4}$$

$$k_n = \alpha C |(\delta_{n-1} / \omega)| + (1 - \alpha)\, k_{n-1} \qquad \textbf{Equation 5}$$

$$\omega = 1 - \upsilon + \upsilon * (SD) \qquad \textbf{Equation 6}$$

For the Pearce-Hall model we explored the scaling of the signed and unsigned prediction error separately, as well as combined.

We fitted the free parameter ϕ to the subjective predictions Y by maximizing the likelihood $p(Y|\phi) = \Pi_m^M p(y_m|\phi)$, where $p(y_m|\phi) = N(\mu_m, \hat{\sigma}^2)$, and $Y = [y_1\ y_2 \cdot \cdot y_m]$ are the subjective predictions. We used a combination of nonlinear optimization algorithms implemented in MATLAB to estimate the free parameters to each participant's full dataset over the trials of all conditions.

We used the Akaike Information Criterion (AIC) to estimate the model evidence in favour of each of the two models. The model with the lowest AIC was used for further analyses.

fMRI pre-processing steps

All pre-processing steps were performed using SPM8 (available at http://www.fil.ion.ucl.ac.uk; Wellcome Department of Cognitive Neurology, London, England) in combination with the Donders matlab (dmb) toolbox for combining data from different echo acquisition times. Data was acquired at 4 different echo times (TE's) of 12,

27,91, 43,82 and 59,73 ms. Corrections for slice timing was not applied considering the relatively fast repetition times (TR) of 2100ms. Using SPM8 the functional images were realigned first, after which the four different echoes were summed and averaged in order to minimize signal intensity inhomogeneity due to differences in T2* relaxation times across the brain (Poser et al., 2006). The functional images were subsequently coregistered to the T1-weighted anatomical image in native-space by first coregistering one averaged functional image, after which the coregistration parameters of this registration were applied to the all the functional images in order to registered to native space. Unified segmentation was used in order to achieve the normalization of the functional and anatomical images to MNI space (Ashburner et al., 2005). Unified segmentation is a single iterative model that combines segmentation, bias correction and normalization in order to achieve optimal results. The segmentation step was omitted for one of the participants; since it gave erroneous segmentation parameters resulting in distortions in the normalized anatomical T1 scan. The segmentation step was later conducted using a different template, namely the East-Asian template, which resulted in a correct segmentation. Spatial smoothing was performed using 8mm Gaussian kernels. The time series in each session were high-pas filtered at 128 Hz. These pre-processing steps were the same for all studies, with the exception that the patient study did not use a multi-echo sequence.

1st-level analysis

fMRI analyses were conducted using SPM8. We used a single statistical linear regression model for our main analyses. We modelled for each trial the onset of the cue as an event (i.e. a delta function of zero duration), the onset of the prediction event (i.e., when participant could start making their prediction) as a single epoch lasting until they indicated their prediction. Each event was convolved by the standard canonical haemodynamic response function in SPM8. Importantly, we used parametric modulation to identify neural correlates of unsigned prediction error responses by specifying for all outcome events the unsigned prediction errors. The signed prediction error was not included in the 1st-level model, as it is uncorrelated with unsigned prediction error. The reward events were separately modelled for the different precision conditions in order to test for differences in precision-weighting of prediction errors as evidences by different sizes of slopes for the coding of unsigned prediction errors under different levels of certainty. Contrast were

created on the 1st-level which combined the two EV conditions for each precision condition in order to leave a single contrast for each precision conditions which could be taken to the 2nd-level (i.e., group-level).

2nd-level analysis dopamine study

For the analysis of the main effect of unsigned prediction errors we first created 1st-level contrast in which we combined the 2 EV's for each separate precision condition, resulting in 3 contrasts corresponding to the 3 different precision conditions (high, medium, low). We modelled these 3 precision contrasts for each pharmacological condition separately specifying the effects to be dependent, and having equal variance. We subsequently tested for a main effect of prediction error by doing a positive 2nd-level contrast on the parametric modulators for the unsigned prediction error.

To test for an effect of precision on the coding of unsigned prediction error and the effect of pharmacological group, we extracted the parameter estimates (beta's) for all precision conditions for each medication group separately from the left and right superior frontal cortex clusters and dACC cluster surviving FWE<.01 coding unsigned prediction errors; for each cluster we used the mean values per cluster per participants in a mixed-2-factor-ANOVA with a 3-level within subject factor (high, medium, low) and a 3-level between subject factor (medication), and tested for main effect of precision and interaction between precision conditions and medication using a mixed-model ANOVA in SPSS (version 21). Specifically we used a linear contrast (termed "linear polynomial contrast" by SPSS) across precision to examine the main effect of precision and interaction between group and precision. When a significant interaction was found we explored this further to see which group was driving the interaction.

2nd-level analysis psychosis study

For the analysis of the main effect of unsigned prediction errors we first created 1st-level contrasts in which we combined the 3 EV's for each separate precision condition, resulting in 2 contrasts corresponding to the 2 different precision conditions (high, low). We modelled these 2 precision contrasts for each pharmacological condition separately specifying the effects to be dependent, and having equal variance. We subsequently tested for a main effect of prediction error by doing a positive 2nd-level contrast on the parametric modulators

for the unsigned prediction error. We tested for a main effect of precision by doing a 2nd-level contrast on the two precision conditions. A small volume correction was implemented as follows: these tests were performed wholebrain uncorrected <.005, after which we used an ROI on the basis of the peak coordinates of the dopamine study [27 8 54] in form of a 10mm sphere, which was used to do a small-volume correction. We subsequently tested for differences in precision-weighting by creating a 1st-level contrast which subtracted the low-precision condition from the high-precision condition as a measure of precision-weighting. On 2nd-level we contrasted precision-weighting in the ARMS and FEP group against the HC group to test for significant differences in precision-weighting, again at <.005 uncorrected, after which we used the same ROI to test for differences in precision-weighting.

2nd-level analysis schizotypy study

In order to test for a relationship between schizotypy and precision-weighting of prediction error, we extracted the betas from the precision-weighting contrast from a cluster which showed a significant main effect of unsigned prediction error at FWE<.01 in the dopamine study (which is the same criteria used for testing the effect of medication). In addition we re-analysed an existing normative data-set consisting of 27 healthy controls (pre-processing and 1st level analysis is the same as in the dopamine study). We used an ROI (10mm sphere) based on the peak-voxel of the dopamine study [27 8 54], and tested for a main effect of prediction error at FWE<.01. Again we subtracted from these voxels the betas reflecting precision-weighting. Subsequently we used a general linear model to test for a relationship between SPQ scores and the extracted precision-weighting betas whilst controlling for medication group and study.

Data availability: the data analysed in this study are available from the corresponding author on reasonable request.

Supplementary results

Study 1: Dopamine study

Environmental precision and D2 antagonism modulate task performance.

First, we explored whether performance increases when environmental precision is high (i.e. when the standard deviation of rewarding outcomes is low). We measured performance by investigating how close participants' predictions were to the actual mean of the distribution on average (i.e., the average difference between the mean of the reward distribution). We used a two-factor mixed model ANOVA with medication group as the between-subjects variable and precision conditions as the within-subjects variable, using a linear contrast across precision conditions for the main effect of precision and interaction between precision and medication. We found that performance increased when the precision increased ($F\{1,56\}=11.3$, $p=.001$), but there was no significant interaction between precision and medication group ($F\{2,56\}=1.3$, $p=.27$). However, there was a trend-level effect of group on average final performance ($F\{2,56\}=2.5$, $p=.094$). Post-hoc tests indicated reduced overall performance in the sulpiride group compared to placebo ($F\{1,38\}=5.10$, $p=.030$), but no significant interaction with precision ($F\{1,38\}=.18$, $p=.68$). Comparing the bromocriptine group to placebo there was no significant overall difference ($F\{1,37\}=2.01$, $p=.17$) and no significant interaction ($F\{1,37\}=1.70$, $p=.20$) (See Fig.2).

Elimination of possible confounding by effects on motivation

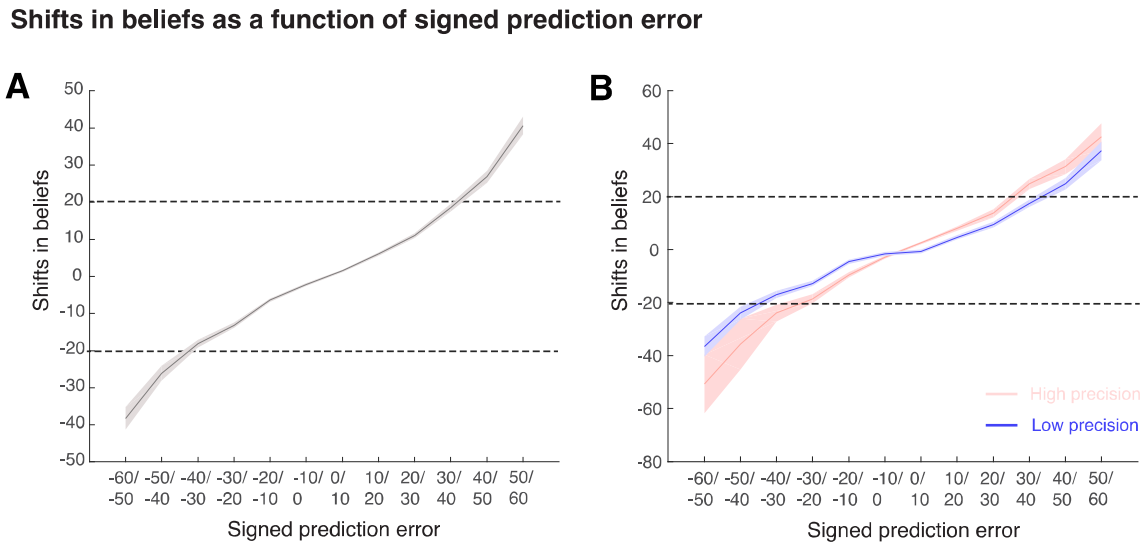
Since dopamine also plays an important role in motivation, we explored whether the dopaminergic manipulation influenced measures of motivation, such as response times (Crespi, 1942; Niv, 2007), how much the participants moved the mouse ball to state their prediction (Fig. 3B; see methods section for more detail), and the number of missed trials (Fig. 3D). Using one-way ANOVAs, we found that only response times were significantly different across medication groups, with the sulpiride group being faster than placebo (RT: $F\{2,55\}=4.21$, $p=.019$; Misses: $F\{2,55\}=0.33$, $p=.72$; Scrolling distance: $F\{2,55\}=0.56$, $p=.57$; Fig. 3B-D). Differences in response times remained significant when controlling for scrolling distance: $F\{2,55\}=3.32$, $p=.044$. More rapid reactions in the sulpiride condition render it unlikely that any performance deficit secondary to sulpiride could be driven by motivational impairments. In the clinical psychosis study we also tested for differences in reaction times,

scrolling distance, and missed trials, to see whether there could have been motivational and/ or motor/movement differences between groups. Using one-way ANOVA's, we found that none of these measures were different across groups (RT: $F\{2,75\}=1.77$, $p=.17$; Misses: $F\{2,75\}=0.1$, $p=.91$; Scrolling distance: $F\{2,75\}=0.12$, $p=.89$) (Figure 2I-K).

Unsigned and signed prediction errors contribute to belief updating

In order to explore whether signed and unsigned prediction errors contribute to learning, we fitted a simple regression model to the behavioural data, where the extent of learning, defined as the change in predicted reward from a trial to the next, was the dependent variable and signed and unsigned prediction errors were the independent variables. Signed prediction errors are defined in this task as the signed difference between predicted and received reward. Unsigned prediction errors are defined as the absolute difference between predicted and received reward. Both of these prediction errors can be observed directly in our task, and thus in contrast to many other experimental paradigms, do not have to be inferred as a latent variable using a modelling procedure. We expected a main effect of signed prediction error on learning, but not of unsigned prediction as the former informs the participants about the direction of belief updating, whereas the latter does not, and can therefore not drive learning directly. However, Pearce-Hall reinforcement learning models suggest that unsigned prediction errors increase the amount of attention devoted to a stimulus. Thus we expect that when unsigned prediction errors are high, the effect of signed prediction errors on learning is higher. That is, we expect there to be an interaction between unsigned and signed prediction errors. In line with this expectation, we found a significant interaction between signed and unsigned prediction errors ($F\{1,10763\}=51.7$, $p<.0001$), suggesting that learning is a function of both the signed and unsigned prediction error. In addition, we observed a significant effect of signed prediction errors on learning ($F\{1,10763\}=246.95$, $p<.0001$), whereas the effect of unsigned prediction errors was insignificant ($F\{1,10763\}=.95$, $p=.33$). We furthermore tested whether the precision condition interacted with signed prediction errors on belief updating. Although there was no main-effect of precision ($F\{2,10761\}=.25$, $p=.78$), there was indeed a significant interaction between precision and signed prediction error ($F\{2,10761\}=25.8$, $p<.0001$). The significant interaction between signed and unsigned prediction errors predicts a pseudo logit-function amplifying the contribution of signed prediction error on belief updating when the unsigned

prediction errors are highest (i.e. when signed prediction errors are highly positive or highly negative). To visualise the interaction between signed and unsigned prediction error we binned signed prediction errors and plotted learning on the y-axis (Fig.4A). We indeed find the predicted pseudo-logit shape between the relationship between signed prediction errors and learning such that the line is steeper when signed prediction errors are higher, indicating that unsigned prediction errors contribute to learning in addition to signed prediction errors. We furthermore visualised the effect of precision, where we see that signed prediction errors have a stronger effect on learning in the high precision condition compared to low precision condition (Fig. 4B). The significant interaction predicts a stronger effect of signed prediction error on belief updating in the high precision condition compared to the low precision condition. We thus conclude that signed prediction errors contribute more to learning when reward information is more precise.



Supplementary Figure 1: Here we show the relationship between signed prediction errors (x-axis) and belief-updating (y-axis) collapsed for the high, medium, and low precision conditions (A) and separate for high and low precision (B) (The medium precision condition is not plotted for clarity purposes). The shaded area is one standard error of the mean. In A the interaction effect between unsigned prediction error and signed prediction is shown (above the top and below the bottom dotted line unsigned prediction errors are strongest, amplifying the effect of the signed prediction error). In B the effect of precision is shown, revealing a stronger effect of signed prediction error in the high precision condition compared to low precision.

Secondary outcome variable analyses

In addition to the analyses we conducted in our primary regions of interest, i.e. SFC and dACC, we also tested for an interaction between precision conditions and medication in the remainder of clusters that coded unsigned prediction errors. There were no significant

precision by medication interactions: superior occipital cortex cluster, ($F\{2,56\}=1.60$, $p=.21$), larger parietal cluster ($F\{2,56\}=.82$, $p=.45$), smaller parietal cluster ($F\{2,56\}=1.53$, $p=.23$).

Study 2: Psychosis study

No evidence for an effect of antipsychotic medication on precision-weighting in patients

We found no significant difference between FEP participants who take antipsychotic medication and those who do not in terms of precision weighting of the prediction error ($T\{18\}=.14$, $p=.89$; analysis conducted on voxels that showed a group difference). There was no significant relationship between anti-psychotic medication dosage and degree of precision-weighting in the 14 participants who took antipsychotic medications ($r=.17$, $p=.52$).

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