Abnormal prediction error processing in schizophrenia and depression

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Abstract
To make adaptive decisions under uncertainty, individuals need to actively monitor the discrepancy between expected outcomes and actual outcomes, known as prediction errors. Reward-based learning deficits have been shown in both depression and schizophrenia patients. For this study, we compiled studies that investigated prediction error processing in depression and schizophrenia patients and performed a series of meta-analyses. In both groups, positive t-maps of prediction error tend to yield striatum activity across studies. The analysis of negative t-maps of prediction error revealed two large clusters within the right superior and inferior frontal lobes in schizophrenia and the medial prefrontal cortex and bilateral insula in depression. The concordant posterior cingulate activity was observed in both patient groups, more prominent in the depression group and absent in the healthy control group. These findings suggest a possible role in dopamine-rich areas associated with the encoding of prediction errors in depression and schizophrenia.

KEYWORDS
depression, dopamine, fMRI, meta-analysis, prediction error, reward, schizophrenia

INTRODUCTION

Significant theoretical evidence has accumulated to suggest that dopaminergic neurons within the striatum play a critical role in reinforcement learning. Originally revealed by single-unit recordings of dopaminergic neurons in the monkey brain, the discrepancy between firing rates of reward reception and its predicted value was suggestive of a prediction error signal (Schultz, Dayan, & Montague, 1997). Prediction errors can occur from receiving positive and negative feedback, colloquially expressed as “better than expected” or “worse than expected” prediction errors, and can also be distinguished in both gain and loss modalities. Prediction error signals have become rather prominent in clinical populations such as schizophrenia and major depressive disorder. The interest in these specific clinical populations is partially based on the notion that patients with schizophrenia and depression have significant aberrant putative dopamine disturbance (Breier et al., 1997; Laruelle et al., 1996). Anhedonia is one of the common symptoms in both depression and schizophrenia (Cooper, Arulpragasam, & Treadway, 2018; Strauss, 2013), characterized by an inability to experience pleasure and believed to have significance in the role of dopaminergic neurons in the brain (Dunlop & Nemeroff, 2007). Specifically, patients with depression have been shown to be less responsive to pleasure by rewarding stimuli compared with healthy controls (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008). In schizophrenia patients, putative dopamine disturbance has also been linked to positive symptoms including delusions and hallucinations (Gray, 1998).

The incentive salience hypothesis states that dopamine mediates the attribution of “incentive salience” to conditioned cues that predict
reward (McClure, Berns, and Montague 2003). It has been proposed that increased chaotic or stress-associated firing of dopaminergic afferents to the striatum of schizophrenia patients attributes increased incentive salience to otherwise irrelevant stimuli. This over attribution of meaning to otherwise irrelevant cues can play a prominent role in delusional thinking and mood by promoting aberrant perceptions and the formation of delusions. Abnormal prediction error-mediated learning of associations has been hypothesized to be mechanistically related to observed symptoms in both schizophrenia and depression. Abnormal encoding of neural prediction error signals could underlie anhedonia in depression and perhaps positive and negative symptoms in schizophrenia by disrupting learning and blunting the salience of rewarding events (Gradin et al., 2011).

Several functional magnetic resonance imaging (fMRI) studies have actively used different reinforcement learning algorithms, such as State-action-reward-state-action (SARSA) and Q-learning in healthy humans. For example, a previous meta-analysis by Garrison and colleagues reported prediction error signals encoded in the striatum and insula (Garrison, Erdeniz, & Done, 2013). A recent meta-analysis on the neural representation of prediction error signals in substance users concluded that substance users showed blunted activity in the striatum, medial-frontal gyrus, and insula in comparison with controls (Tolomeo, Yable, & Yu, 2020). With respect to the neuroimaging data in schizophrenia and depression, inconsistencies have been reported. While many studies revealed reduced brain activity associated with prediction error signals in schizophrenia (Gradin et al., 2011; Polli et al., 2008; Schlagenhauf et al., 2014; Waltz et al., 2018) and major depressive disorder patients (Chase et al., 2013; Gradin et al., 2011; Greenberg et al., 2015; Kumar et al., 2008; Kumar et al., 2018; Liu, Valton, Wang, Zhu, & Roiser, 2017; Segarra et al., 2016), others have either reported enhanced prediction error signals (Walter, Kammerer, Frasch, Spitzer, & Abler, 2009; White, Krugljac, Reid, & Lahti, 2015), no differences between groups (Culbreth, Westbrook, Xu, Barch, & Waltz, 2016; Rothkirch, Tonn, Köhler, & Sterzer, 2017; Walter, 2010), or a mix of reduced and enhanced activity depending on the lateralization of the striatum (Morris et al., 2012). Moreover, it is important to emphasize that many studies attribute prediction error signals to regions within the striatum (Culbreth et al., 2016; Gradin et al., 2011; Greenberg et al., 2015; Kumar et al., 2018; Morris et al., 2015; Murray et al., 2008; Rothkirch et al., 2017; Schlagenhauf et al., 2014; Ubl et al., 2014), while many others have reported reduced prediction error signals associated with the anterior cingulate cortex (ACC) (Chase et al., 2013; Kumar et al., 2008; Polli et al., 2008; Waltz et al., 2018). Furthermore, few have clearly distinguished the activity between groups for positive and negative correlates of prediction errors (i.e., PPE/NPE; Waltz et al., 2018; Dowd, Frank, Collins, Gold, & Barch, 2016), despite a meta-analysis on reward and punishment prediction error (Fouragnan, Retzler, & Philastides, 2018). Notably, because schizophrenia and depression are specifically associated with motivational deficits, such as negative symptoms in schizophrenia and anhedonia in depression, understanding the mechanisms underlying reinforcement learning is a crucial priority in psychiatry research. To this end, we find it necessary to perform a meta-analysis on fMRI studies to determine the concordance of brain regions most likely associated with prediction errors in schizophrenia and major depressive disorder patients. We further aim to compare and conjunct meta brain maps of these clinical populations with healthy controls. For this article, we aim to extract articles that reported positive and negative t-scores separately or reported a linear signed prediction error. Using effect-size seed-based differential mapping we assign the positive and negative t-score to attain stereotaxic brain maps of PPE and NPE.

2 | METHODS AND MATERIALS

2.1 | Selection of studies

A series of searches for fMRI studies that report prediction errors in patients with schizophrenia and depression was performed by entering keywords: (a) “prediction error” OR reinforcement AND “fMRI” AND schizophrenia; (b) “prediction error” OR reinforcement AND “fMRI” AND depression; (c) “prediction error” OR reinforcement AND “fMRI” AND depressive into the web of knowledge database (http://www.webofknowledge.com) and Pubmed database (https://www.ncbi.nlm.nih.gov/pubmed). These searches include articles up to March 1, 2019, which yielded a total of 154 articles and which were screened for eligibility. To identify eligible research articles, we screened those that: (a) did not report fMRI foci; (b) did not report foci in standard stereotactic coordinate space (either Talairach or Montreal Neurological Institute, MNI); (c) articles that did not use whole-brain analysis; (d) articles not from schizophrenic or depressed patients; (e) articles isolated from nonhumans; and (f) articles that did not include prediction error-related foci. The total number of eligible studies was 20 articles, 10 articles reported 11 schizophrenia groups with 17 contrasts and 10 articles reported 11 depression groups with 16 contrasts; of which reported within-group whole-brain results from patients with schizophrenia and depression in MNI or Talairach space. See Figure 1 for PRISMA flowchart illustrating the screening procedure. The data that support the findings of this study are available from the corresponding author upon reasonable request.

2.2 | Software and analysis

Effect-size seed-based differential mapping (ES-SDM) meta-analysis software (http://www.sdmproject.com) was used to perform the meta-analyses. Based on activation likelihood estimation, this analysis creates statistical parametric t-maps by combining peak coordinates of clusters with t-scores from multiple studies to increase statistical power (Radua et al., 2012). Effect-size brain maps and variances are derived from reported t-statistics, or converted to t-statistics from z-scores using an in-built statistical converter. We assigned prediction error contrasts as PPE or NPE, depending on the sign of the t-score. Essentially, positive prediction error and negative prediction error are
equivalent to activations and deactivations of prediction error, respectively.

The full width at half maximum (FWHM) in SDM was set at the default (20 mm) to control for false positives (Radua et al., 2012). To optimally balance sensitivity and specificity resulting statistical maps were thresholded at $p = 0.005$ to control for family-wise error rate, as indicated by the developers of the software (Radua et al., 2012). Conjunction analysis, as well as contrast analysis, was performed to compare activation of prediction error between groups (schizophrenia and healthy controls; depression and healthy controls and schizophrenia and depression). Analyses for each group were thresholded at $p = 0.005$ before conjunction and contrast analysis, which is consistent with the standard in the literature. SDM values were overlaid onto an anatomical template normalized to MNI space using Mango image viewer software (http://rii.uthscsa.edu/mango/mango.html).

Jackknife sensitivity analysis was performed to assess the replicability of clusters. Jackknife sensitivity analysis is a linear bootstrapping sampling technique which repeats the meta-analysis as many times as the number of studies that have been included, removing each study per analysis. If an area remains significant in all or most of the combinations of studies (> 80%), it is considered highly replicable (Radua & Mataix-Cols, 2009).

3 | RESULTS

Twenty articles were eligible for inclusion in the meta-analyses. Table 1 summaries participant demographics, contrast, and prediction error information for the depression, schizophrenia, and healthy controls groups, respectively. Healthy controls were extracted from both schizophrenia and depression articles. A total of 1,050 participants...
### TABLE 1 Information on prediction error studies included in the meta-analysis

| Article                      | n   | Age mean (SD) | Gender male/female | Foci | Task                  | Contrast type       | PE valence       | PE clinical group versus control |
|------------------------------|-----|---------------|--------------------|------|-----------------------|---------------------|------------------|---------------------------------|
| **Depression**               |     |               |                    |      |                       |                     |                  |                                 |
| Bradley et al., 2017         | 22  | 16.3 (2.32)   | 12/10              | 13   | Reward flanker        | Positive only       | Reward only      | Intact             |
| Chase et al., 2013           | 40  | 31.04 (8.04)  | 9/31               | 16   | Card-guessing         | Both (linear)       | Reward and punishment | Reduced           |
| Gradin et al., 2011a         | 15  | 45.27 (12.32) | 6/9                | 8    | Instrumental reward   | Both (linear)       | Reward only      | Reduced            |
| Greenberg et al., 2015       | 78  | 38.47 (13.21) | 97                 | 7    | Monetary reward       | Both (linear)       | Reward and punishment | Reduced           |
| Kumar et al., 2008           | 15  | 45.3 (12.3)   | 6/9                | 4    | Pavlovian reward      | Both (linear)       | Reward only      | Reduced            |
| Kumar et al., 2018           | 25  | 25.25 (5.46)  | 6/19               | 35   | Instrumental reward   | Both (linear)       | Reward and punishment | Reduced           |
| Liu et al., 2017             | 21  | 30.7 (8.9)    | 9/12               | 7    | Instrumental reward   | Both (linear)       | Reward and punishment | Reduced           |
| O’Sullivan et al., 2011      | 24  | NA            | NA                 | 13   | Reinforcement learning | Positive only       | Reward only      | Enhanced           |
| Rothkirch et al., 2017       | 28  | 36.32 (11.88) | 14/16              | 15   | Reinforcement learning | Both (separately)   | Reward and punishment | Intact             |
| Ubl et al., 2014             | 30  | 46 (11.85)    | 14/16              | 1    | Monetary reward       | Both (linear)       | Loss only        | None               |
| **Schizophrenia**            |     |               |                    |      |                       |                     |                  |                                 |
| Culbreth et al., 2016a       | 58  | 37 (8.6)      | 39/16              | 27   | Reversal learning     | Both (linear)       | Reward only      | Intact             |
| Dowd et al., 2016            | 38  | 35 (9.25)     | 24                 | 72   | Reversal learning     | Both (separately)   | Reward only      | Intact             |
| Gradin et al., 2011a         | 14  | 42.5 (12.27)  | 11/3               | 4    | Instrumental reward   | Both (linear)       | Reward only      | Reduced            |
| Insel et al., 2014           | 26  | 39.54 (9.17)  | 18/8               | 87   | Reinforcement learning | Both (linear)       | Reward and punishment | Intact/reduced    |
| Morris et al., 2012          | 16  | 33            | 9/7                | 14   | Card-guessing         | Both (linear)       | Reward only      | Intact/enhanced    |
| Polli et al., 2008           | 18  | 42 (11)       | 11/4               | 16   | Saccade               | Negative only       | Reward only      | Reduced            |
| Schlagenhauf et al., 2014    | 24  | 27.5 (5.2)    | 22/2               | 3    | Reversal learning     | Both (linear)       | Reward and punishment | Reduced           |
| Walter et al., 2010          | 12  | 36.7 (7.8)    | 5/7                | 5    | Monetary reward       | Both (linear)       | Reward only      | Intact             |
| Walter et al., 2009          | 16  | 38 (9)        | 8/8                | 4    | Monetary reward       | Both (linear)       | Reward only      | Enhanced           |
| Watz et al., 2017            | 27  | 38.1 (11.9)   | 17/10              | 10   | Reinforcement learning | Both (separately)   | Reward only      | Reduced            |
| **Healthy control**          |     |               |                    |      |                       |                     |                  |                                 |
| Chase et al., 2013           | 37  | 33.09 (6.23)  | 25/12              | 5    | Card-guessing         | Both (linear)       | Reward and punishment |                  |
| Culbreth et al., 2016a       | 40  | 36.6 (9.2)    | 36.6% (9.2)        | 23   | Reversal learning     | Both (linear)       | Reward only      |                  |
| Dowd et al., 2016a           | 37  | 36.43 (8.44)  | 43.2               | 72   | Reversal learning     | Both (separately)   | Reward only      |                  |
| Gradin et al., 2011a         | 17  | 40.64 (11.87) | 7/10               | 16   | Instrumental reward   | Both (linear)       | Reward only      |                  |
| Kumar et al., 2008b          | 18  | 42 (12.8)     | 7/11               | 12   | Pavlovian reward      | Both (linear)       | Reward only      |                  |
| Kumar et al., 2018           | 26  | 26.31 (7.96)  | 7/19               | 31   | Instrumental reward   | Both (linear)       | Reward and punishment |                  |
| Liu et al., 2017             | 17  | 28.3 (5.2)    | 7/10               | 7    | Instrumental reward   | Both (linear)       | Reward and punishment |                  |
| Morris et al., 2012          | 16  | 32.9          | 8/8                | 64   | Card-guessing         | Both (linear)       | Reward only      |                  |
| Polli et al., 2008           | 15  | 37 (10)       | 11/4               | 17   | Saccade               | Negative only       | Reward only      |                  |
| Rothkirch et al., 2017       | 30  | 36.13 (11.96) | 8/22               | 15   | Reinforcement learning | Both (separately)   | Reward and punishment |                  |
| Schlagenhauf et al., 2014    | 24  | 27.2 (4.9)    | 22/2               | 14   | Reversal learning     | Both (linear)       | Reward and punishment |                  |
| Ubl et al., 2014             | 28  | 43.96 (12.85) | 13/15              | 2    | Monetary reward       | Both (linear)       | Reward only      |                  |
| Walter et al., 2010          | 12  | 36.2 (11.2)   | 13                 | 13   | Monetary reward       | Both (linear)       | Reward only      |                  |
| Walter et al., 2009          | 16  | 33 (10.2)     | 7/9                | 5    | Monetary reward       | Both (linear)       | Reward only      |                  |
| Watz et al., 2018            | 27  | 38.3 (12.6)   | 18/9               | 6    | Reinforcement learning | Both (separately)   | Reward only      |                  |

**Abbreviations:** n, sample size; NA, not available; SD, standard deviation.

*Article includes both schizophrenia and depression groups.

*Article includes at least two groups.*
(including healthy controls) were included in the meta-analyses yielding equivalent population sizes (see Table 1 for further details). One study reported both depression and schizophrenia groups (Gradin et al., 2011). See Table S1 for more clinical information, such as illness duration, illness severity, and medication for the depression and schizophrenia patients included in this meta-analysis.

The analysis of positive scores of prediction error for schizophrenia revealed five activated clusters: right striatum, left striatum, left precuneus, left supramarginal gyrus, and left posterior cingulate cortex (PCC). All regions except the left supramarginal gyrus were present in at least 80% of the jackknife analyses. The largest cluster was the right striatum which also overlapped with the right amygdala, insula, and putamen. The left striatum overlapped with the left amygdala and left putamen. For the positive scores of prediction error in the depression group, five clusters were at least 80% replicable were reported. These clusters include: the left precuneus, right caudate nucleus, left striatum, right middle occipital gyrus, and right postcentral gyrus. Negative scores of prediction error in schizophrenia revealed two relatively large clusters within the right superior and inferior frontal lobes. Negative scores of prediction error for depression included the medial prefrontal cortex and bilateral insulae. Positive scores of prediction errors for the healthy control group revealed bilateral striatum and right angular gyrus, and while negative scores of prediction error included three clusters within the prefrontal cortex (inferior and superior frontal gyrus), all reported as significant for at least 80% of all studies. Bilateral striatum activity overlapped with the bilateral caudate nucleus, bilateral amygdala, and bilateral insula. See Figure 2 for 3D maps of brain activity and Table 2 for the results of the main analysis for each group.

Contrast analysis was performed between groups (see overlay maps in Figures 3 and 4; Table 3). Contrast analysis revealed no significant regions in neither schizophrenia > control contrast nor the reverse contrast. Comparing meta-analyses across patients with depression and healthy individuals revealed greater concordant activity within the left inferior frontal gyrus yet reduced concordant activity within the right striatum for patients with depression. For the depression > schizophrenia contrast, depressed participants appear to reveal several frontal clusters (i.e., right superior/middle/inferior and left middle frontal gyrus). However, these clusters may be due to the large frontal hypoactivated clusters in schizophrenia, which appear absent in the depression group. Other clusters include the right caudate nucleus. Interestingly, the reverse contrast revealed more activity within the right putamen for schizophrenia compared with depression, suggesting that the right striatum is strongly affected by both depression and schizophrenia.

Conjunction analysis between healthy control and depression participants demonstrated bilateral striatum clusters with larger concordant activity within the right caudate and putamen. Comparing healthy controls with schizophrenia patients, two clusters within the left and right striatum were found. Both of these clusters overlapped with the putamen and lacked concordant activity within the caudate. The conjunction analysis between patients with depression and schizophrenia patients revealed only right-lateralized putamen activity. See Table 3 for results of the conjunction analysis.
DISCUSSION

This meta-analysis investigated positive and negative correlates of prediction error signals in major depressive disorder and schizophrenia, which we interpret as PPE and NPE, respectively. Previously the encoding of prediction error signals in depression and schizophrenia revealed some inconsistencies associated with the specific region and polarity of fMRI activation. Many studies seem to point to a reduction of concordant activity in the striatum, yet others have reported either no differences or enhanced activation of the striatum and/or ACC between healthy and patient groups. We justify the necessity to compile studies isolating the processing of prediction errors and perform a series of meta-analyses among these clinical populations to determine which regions are most likely to become active.

With respect to the healthy control group, bilateral striatum was reduced in the depression and schizophrenia groups, particularly the left dorsal striatum. The schizophrenia group revealed greater activation of the right putamen compared with patients with depression, yet a more focalized right caudate nucleus for the depression group. The striatum is particularly involved in prediction error as well as reward-related stimulus–response learning (Delgado, 2007; O’Doherty, 2004). For example, while the putamen responds to unexpected gains that encode prediction error (O’Doherty, 2004), and predicts procedural adjustments after receiving rewarding stimuli (Wrase et al., 2007), the caudate nucleus responds to unpredicted rewards.

| Brain region | BA  | Volume | x   | y   | z   | SDM-Z | Jackknife (%) |
|--------------|-----|--------|-----|-----|-----|-------|---------------|
| Depression   |     |        |     |     |     |       |               |
| Positive t-map |     |        |     |     |     |       |               |
| Caudate nucleus | 2,529 | 10 | 22 | –2 | 4.145 | 100<sup>c</sup> |
| L cingulate gyrus | 23 | 2040 | 0 | –42 | 46 | 2.421 | 100<sup>c</sup> |
| R angular gyrus | 39 | 309 | 48 | –70 | 26 | 2.306 | 90.9<sup>5</sup> |
| R Supramarginal gyrus | 48 | 138 | 66 | –24 | 30 | 2.086 | 72.7 |
| L inferior frontal gyrus | 44 | 25 | –50 | 6 | 24 | 1.823 | 54.5 |
| Negative t-map |     |        |     |     |     |       |               |
| L Supramarginal gyrus | 6 | 934 | –8 | 16 | 52 | 4.479 | 81.8<sup>c</sup> |
| R insula | 47 | 498 | 32 | 24 | –4 | 1.482 | 81.8<sup>c</sup> |
| L insula | 47 | 238 | –32 | 24 | –6 | 1.439 | 81.8<sup>c</sup> |
| Schizophrenia |     |        |     |     |     |       |               |
| Positive t-map |     |        |     |     |     |       |               |
| R striatum | 1988 | 24 | 2 | 0 | 4.590 | 100<sup>c</sup> |
| L striatum | 850 | –20 | 0 | –4 | 24 | 4.624 | 100<sup>c</sup> |
| L precuneus | 23 | 197 | –4 | –60 | 24 | 2.765 | 90<sup>c</sup> |
| L supramarginal gyrus | 2 (48) | 111 | –56 | –26 | 36 | 2.637 | 70 |
| L median cingulate | 51 | –8 | –20 | 42 | 2.754 | 90<sup>c</sup> |
| Negative t-map |     |        |     |     |     |       |               |
| R superior frontal gyrus | 8 (6) | 2,213 | 4 | 30 | 56 | 2.685 | 100<sup>c</sup> |
| R inferior frontal gyrus | 45 (48) | 1857 | 40 | 22 | 12 | 2.290 | 100<sup>c</sup> |
| Healthy control |     |        |     |     |     |       |               |
| Positive t-map |     |        |     |     |     |       |               |
| R striatum | 4,820 | 20 | 2 | –4 | 4.599 | 100<sup>c</sup> |
| R angular | 39 | 778 | 52 | –60 | 32 | 2.345 | 93.7<sup>c</sup> |
| Negative t-map |     |        |     |     |     |       |               |
| L inferior frontal gyrus | 38 | 908 | –48 | 18 | –8 | 2.341 | 93.7<sup>c</sup> |
| R superior frontal gyrus | 8 | 317 | 12 | 26 | 58 | 2.128 | 81.2<sup>c</sup> |
| R inferior frontal gyrus | 48 | 130 | 58 | 18 | 6 | 2.120 | 87.5<sup>c</sup> |

Note: depression n = 16; schizophrenia n = 17; healthy control n = 16. Jackknife replicability is represented as percentage; foci represented in MNI space. Abbreviations: BA, Brodmann area; L, Left; R, Right; SDM-Z, signed differential mapping z-score.  
<sup>a</sup>Peak coordinates with overlapping BA areas (in brackets).  
<sup>b</sup>2 mm × 2 mm × 2 mm.  
<sup>c</sup>Regions greater than 80% replicability.
when participants believe that outcome is dependent on their actions (Tricomi, Delgado, & Fiez, 2004). According to these findings, a reduction of the dorsal striatum may be detrimental to the processing of prediction error as well as learning associations between rewarding stimuli and motor responses (Haruno, 2004; Pizzagalli, 2014). Although this claim has been supported in schizophrenia patients showing reduced caudate nucleus activity in response to procedural (Zedkova, Woodward, Harding, Tibbo, & Purdon, 2006) and instrumental learning (Sheffield, Ruge, Kandala, & Barch, 2018), no evidence has been shown to demonstrate differences in striatum activity during motor-related associations in patients with depression (Naismith et al., 2010). The lack of evidence for patients with depression suggests an alternative mechanism. Therefore, further empirical studies to discern these neural and functional differences are encouraged.

An explanation for the reported differences in striatal activity across studies has been suggested to be caused by the differences in medication or severity of symptoms (Dowd et al., 2016; Kapur, 2003). However, this further clarification may be unwarranted since studies have demonstrated reduced striatum activity in both medicated (Gradin et al., 2011; Insel et al., 2014; Segarra et al., 2016; Waltz et al., 2018) and unmedicated (Juckel et al., 2006; Murray et al., 2008; Reinen et al., 2016; Schlaginhaufen et al., 2014) schizophrenic patients, while other studies report enhanced striatum activity in medicated patients (Walter et al., 2009; White et al., 2015). A similar trend can be found among patients with depression; reduction of striatum has been shown in medicated patients (Gradin et al., 2011; Kumar et al., 2008) as well as unmedicated patients (Greenberg et al., 2015; Kumar et al., 2018; Pizzagalli et al., 2009). Moreover, enhanced striatal activity was demonstrated in unmedicated patients (Liu et al., 2017), while no differences in striatum activity were found between medicated (Chase et al., 2013) or unmedicated (Rothkirch et al., 2017) depression and healthy control groups. Therefore, further investigations are necessary to determine whether striatal activity depends on the type and dosage of medication, comorbidity, or whether samples include “treatment-resistant” or “non-treatment-resistant” patients (Vanes, Mouchlianitis, Collier, Averbeck, & Shergill, 2018).

Analyses of both schizophrenia and depressed groups revealed activation of the precuneus and overlapping PCC reflecting enhanced activation compared with controls. When comparing schizophrenia and depression, schizophrenia patients appear to have slightly enhanced PCC activity. Dysfunction of the PCC is often associated with rumination and distortion of self-experience in depression.

**FIGURE 3** Positive prediction error in three groups. Positive correlates of prediction error signals
Berman et al., 2011) and schizophrenia (Holt et al., 2011), respectively. Multiple functional roles of the PCC have been attributed to internally-directed cognition (Buckner, Andrews-Hanna, & Schacter, 2008; Raichle et al., 2001), conscious awareness (Cavanna, 2007; Vogt & Laureys, 2005), mediation between internal and external states (Mesulam, 1998), as well as change detection (Hayden, Nair, McCoy, & Platt, 2008; Hayden, Pearson, & Platt, 2009; Pearson, Hayden, Raghavachari, & Platt, 2009; Pearson, Heilbronner, Barack, Hayden, & Platt, 2011). More recently a dynamic systems approach was proposed (Leech & Sharp, 2014), which suggests that depending on how broad or narrowly focused and how internally or externally driven the attentional state, the activation or deactivation of the PCC may signal connecting regions associated with other networks.

To our knowledge, only two articles have made inferences to explain PCC activity in association with prediction errors (Chase et al., 2013; Reinen et al., 2016). The former attributed PCC activity in patients with depression to changes in hedonic evaluation (Chase et al., 2013), while the latter article declared that the PCC processes value associated with positive stimuli (Reinen et al., 2016). No other explicit inferences on PCC activity on the processing of prediction errors have been reported, despite ample examples of reported PCC activity (Culbreth et al., 2016; Dowd et al., 2016; Insel et al., 2014; Murray et al., 2008; Rothkirch et al., 2017; Segarra et al., 2016; Walter et al., 2009). Therefore, we find that the PCC in these clinical groups is widely unexplored and deserves more attention in future empirical studies. The notion that the PCC was involved in both the schizophrenia and depression groups is indicative of an important process for these clinical populations. One possibility of reduced reward learning may be explained by the dynamic systems approach which would suggest that the increase in PCC activity while processing prediction errors may be due to the inability or decreased tendency to switch between attentional states (Leech & Sharp, 2014). Direct evidence has been demonstrated in depressed and schizophrenic patients showing impaired ability to use internal value estimations (Horan, Foti, Hajcak, Wynn, & Green, 2012; Llerena, Wynn, Hajcak, Green, & Horan, 2016; Rupprechter, Stankevicius, Huys, Douglas Steele, & Seriès, 2018; Takeda et al., 2018).

Note that no ACC activation was found across studies, despite multiple articles reporting the ACC as a key region in depression (Chase et al., 2013; Kumar et al., 2008) and schizophrenia (Koch et al., 2010; Polli et al., 2008; Walter et al., 2009; Waltz et al., 2018). As the result of splitting PPE and NPE, ACC activity may have been
neutralized. This notion concords with theoretical representations of ACC functioning; unsigned prediction errors regardless of valence (i.e., absolute prediction error) have been shown to elicit ACC activity (Manza et al., 2016).

A meta-analysis was also calculated for NPEs across all three groups. For both schizophrenia and healthy control groups, these analyses revealed clusters only within the prefrontal (PFC) lobe, such as the superior and inferior PFC. Specifically, while the healthy control group yielded concordant activity within the left inferior PFC and bilateral supplementary motor area, the schizophrenia group yielded two relatively larger clusters within the medial PFC and right middle frontal cortex. Although both the healthy and the schizophrenia group displayed deactivated frontal activity, the PFC clusters of the schizophrenia group were relatively larger. On the other hand, the meta-analysis of NPE in the depression group revealed a large cluster within the medial PFC (overlapping with the medial PFC of the schizophrenia group) as well as the bilateral insula. Together these results suggest alternative networks affected by NPE in depression and schizophrenia.

A few explanations for the functional role of the PFC have been offered in prior studies. These explanations differentiate between negative and positive symptoms. One possibility is that the dysfunctional frontal lobe activity may be associated with negative symptoms of schizophrenia such as anhedonia or avolition. However, reports on anhedonia in association with frontal activation appear to be inconsistent. For example, prior reports showing reduced responses of the PFC to PPEs in schizophrenia patients have attributed these alterations to anhedonia/avolition (Chung & Barch, 2016; Cohen, Barch, Carter, & Servan-Schreiber, 1999; Dowd et al., 2016; Dowd & Barch, 2012), while others show enhanced activation of PFC regions in association with the severity of anhedonia (Becerril & Barch, 2011; Harvey, Pruessner, Czechowska, & Lepage, 2007). Further, the severity of

| Brain region                        | BA  | Volume (mm³) | x  | y  | z  |
|-------------------------------------|-----|--------------|----|----|----|
| Schizophrenia > healthy controls    |     |              |    |    |    |
| No suprathreshold clusters          |     |              |    |    |    |
| Schizophrenia < healthy controls    |     |              |    |    |    |
| No suprathreshold clusters          |     |              |    |    |    |
| Depression > healthy controls       |     |              |    |    |    |
| L inferior frontal gyrus            | 47  | 153          | -48| 24 | -6 |
| R caudate nucleus                   | 18  | 18           | 26 | 8  |    |
| L inferior longitudinal fasciculus  | 11  | -30          | -58| -10|    |
| Depression < healthy controls       |     |              |    |    |    |
| R striatum                          | 421 | 22           | 2  | -2 |    |
| Inferior longitudinal fasciculus    | 25  | 30           | 30 | -4 |    |

Note: Foci represented in MNI space; depression n = 16; schizophrenia n = 17; healthy control n = 16. Abbreviations: BA, Brodmann area; L, left; R, right.

*Peak coordinates with overlapping BA areas (in brackets).

2 mm x 2 mm x 2 mm.
Within the frontal lobe may reflect NPE; hence our decision to define deactivations of PPE as activations than zero, NPE were valued less than zero), few reported only PPE or of the eligible studies calculated neural correlates of prediction error (Yeung et al., 2018), and reversal learning (Yaple and Yu, 2010), social norm violation (Zinchenko and Arsalidou, 2018), affective value (Yeung et al., 2018), and reversal learning. This pattern of concordant activity seems to reflect a similar network activated concordant clusters within the bilateral insula and medial PFC. Hence, it is unclear how abnormal prediction error signals in the brain determine whether the PFC has a specific functional role in association with anhedonia.

Another interpretation of PFC activity relates to positive symptoms of schizophrenia such as delusional beliefs since delusions have been hypothesized to be caused by faulty prediction error calculations (Corlett et al., 2007; Corlett, Frith, & Fletcher, 2009; Griffiths, Langdon, Le Pelley, & Coltheart, 2014; Heinz, 2002; Iwashiro et al., 2019; Kapur, 2003; Lee et al., 2019). For instance, in one study the right PFC in psychotic patients was shown to respond to prediction errors and was anti-correlated with delusional beliefs (Corlett et al., 2007), while another study reported a significant correlation between delusional behavior and right PFC responses to negatively valenced auditory stimuli (Iwashiro et al., 2019). On the other hand, others have reported left PFC activity associated with delusion severity (Lee et al., 2019), suggesting inconsistencies across the literature. Moreover, it is important to acknowledge that few of the articles included in the meta-analysis reported specific symptoms of each participant. Hence, the presence of delusional beliefs in schizophrenia patients in the current meta-analysis cannot be determined and therefore these explanations cannot rule out other possibilities.

The inconsistencies of enhanced and reduced PFC activity between studies may be due to the notion that most reports do not distinguish between “better than expected” versus “worse than expected” prediction errors. In the current meta-analysis, while most of the eligible studies calculated neural correlates of prediction error using a linear coefficient (PPE were prediction error values greater than zero, NPE were valued less than zero), few reported only PPE or NPE; hence our decision to define deactivations of PPE as activations of NPE, and vice versa. Using this perspective, the clusters found within the frontal lobe may reflect changes in activation associated with NPE in schizophrenia patients when compared with healthy controls. To our knowledge, few whole-brain studies isolated both PPE and NPE (Dowd et al., 2016; Ha usler, Artigas, Trautner, & Weber, 2016; Spoormaker et al., 2011). While two of these articles reported increased activation in the ventromedial and dorsolateral PFC in response to NPEs in healthy controls (Ha usler et al., 2016; Spoormaker et al., 2011), another study demonstrated robust PFC activity in association with NPEs and deactivated PFC clusters for PPEs in schizophrenia patients (Dowd et al., 2016). Nevertheless, due to the low number of studies further investigations isolating PPE and NPE is necessary to further explore the functional role of the PFC while processing NPEs.

Another important observation is that the depression group activated concordant clusters within the bilateral insula and medial PFC. This pattern of concordant activity seems to reflect a similar network demonstrated in prior meta-analyses on risk-taking (see Mohr et al., 2010), social norm violation (Zinchenko and Arsalidou, 2018), affective value (Yeung et al., 2018), and reversal learning (Yaple and Yu, 2019). It is possible that these common networks reflect a salience network composed of bilateral insula and medial frontal regions capable of detecting salient events and switching between large-scale networks to attend to these salient events (Menon and Uddin, 2010). This premise agrees with the results obtained from the prior studies aforementioned, as well as the current meta-analysis results, yet specifically for the depression group.

Others have declared that executive networks such as “cingulo-opercular” network and a frontal network may account for multiple executive operations independently or may operate together during a single cognitive process (Dosenbach et al., 2007; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Fair et al., 2009; Gratton et al., 2017; Velanova, Wheeler, & Luna, 2008). While the frontal network is relevant for rapid adaptive control, the cingulo-opercular network is thought to be more relevant for long-term stable set-maintenance (Fair et al., 2009). This distinction may shed light on the mechanistic differences between depression, schizophrenia, and healthy controls associated with NPE. For example, perhaps schizophrenic patients are more prone to recruit frontal regions for NPE due to the hyper-activation of the regions (Glahn et al., 2005). However, what is undetermined is whether the salience/cingulo-opercular network is commonly active during NPE in depressed patients as a result of (a) a failure to switch between executive networks; (b) an overcompensation of the salience network due to a decreased reaction to saliency, presumably coincides with anhedonia; or (c) a preference to maintain mental representations of executive control due to apathy associated with novel stimuli. These ideas have yet to be tested in an empirical setting and thus, further work is necessary.

Notably, the literature concerning the relationship between reward learning deficits in schizophrenia and depression has been mixed and has been confounded with distinct mechanisms of PPE and NPE. Thus, while the present meta-analysis cannot rule out the possibility that differential motivational deficits can exacerbate these abnormal learning effects, here we have demonstrated that the PPE and NPE clusters in schizophrenia and depression include the neural systems responsible for the core clinical underlying psychopathology.

One potential confound for the interpretation of the results is medication usage. No studies directly compared the prediction error activation in medicated patients with non-medicated patients, making it difficult to discern whether the activity across studies is due to the differences in medication usage. Other heterogeneity measures between patients that could not be incorporated into the current results include illness duration, dosage amount and duration, and diversity of symptoms between patients. Finally, consistent behavioral changes in prediction error were not reported in many of the studies. Hence, it is unclear how abnormal prediction error signals in the brain are related to changes in performance.

5 | CONCLUSIONS

Previously published studies reporting the encoding of prediction error signals in major depressive disorder and schizophrenia patients reported inconsistent results. A series of the meta-analysis was performed to determine whether consistent neural substrates are
associated with the processing of prediction errors in major depressive disorder and schizophrenia patients. Both patient groups exhibited abnormalities in neural prediction errors, but the spatial pattern of abnormality differed: reduced striatum activity for PPE in depression and enhanced PCC and PFC activity for both patient groups. Although many have interpreted reduced and enhanced activity to be associated with positive and negative symptoms, we encourage future interpretations to acknowledge the variety of results exhibited by the versatility of patient characteristics such as medication use comorbidity, or presence or absence of co-existing symptoms as well as the valence of prediction errors.

DECLARATION OF INTEREST
Serenella Tolomeo has no conflict of interest with regard to the current work. However, unrelated to this project she has received funding from Indivior, Merck Serono, and Lundbeck. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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