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Review article

Fractionating adaptive learning: A meta-analysis of the reversal learning paradigm

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ABSTRACT

In constantly changing environments, individuals need to overcome old habitual behaviors in order to learn new associations. Neuroimaging studies have focused on prediction errors, reversal errors and reversal switching in the reversal learning paradigm. Due to the inconsistencies of brain functioning across studies, we attempt to shed light on the concordant activity by performing meta-analyses on different components of reversal learning. While all contrasts yielded anterior cingulate and bilateral insulae, specifically prediction errors yielded more concordant activity within the striatum and amygdala, reversal errors yielded more concordant bilateral frontal-parietal activity, and more concordant inferior frontal cortical occurred from reversal switching. These findings suggest that reversal learning is supported by a core saliency network in all aspects of reversal learning as well as other reward and control related regions in distinct stages of this cognitively complex task. Our meta-analyses results provide stereotaxic maps that can be used for further neuroimaging work on adaptive learning.

1. Introduction

Cognitive flexibility is the ability to successfully switch between choice patterns under changing environments which is essential for adaptive learning. Cognitive flexibility has been investigated using both reward-based and non-reward-based paradigms (see Moccia et al., 2017). A popular paradigm for investigating reward-based cognitive flexibility is the reversal learning paradigm which assigns reinforcement contingencies to choices during an acquisition phase, yet during a reversal phase these reinforcement contingencies change, requiring participants to learn new associations and to overcome prepotent ones (Shiu and Chan, 2006).

Reversal learning paradigms are commonly used to investigate the processing of errors associated with learning new associations and subsequent processes related to the adjustments of these errors (Cools et al., 2002). In the deterministic reversal learning task, one option is determined to be correct while the other option is determined to be incorrect. In the probabilistic reversal learning task, the participant chooses one of two stimuli and is probabilistically rewarded for choosing the correct stimulus. For example, selecting one option will yield a reward with an 80% probability and selecting the alternative option will yield a reward with a 20% probability (e.g. Remijnse et al., 2006; Friedel et al., 2015; Boehme et al., 2016). Rule reversals either occur after a fixed determined number or proportion of correct responses (e.g. Dodds et al., 2008) or occur with a probability after the criterion is fulfilled to make reversals less predictable (when 8 of the previous 10 trials are answered, the reversal occurs with a probability of 20%; Boehme et al., 2016). Participants are typically instructed to maximize their outcomes and may be instructed that occasionally the reward contingencies would reverse and the alternative stimulus would be associated with a high probability of reward (e.g. Fouragnan et al., 2017). When this occurs, participants are determined to rediscover the new rule by trial and error, requiring participants to flexibly adjust, i.e. by switching to the alternative option.

Several key contrasts can be computed in fMRI studies using the reversal learning paradigm (see Fig. 1 for task illustration). Negative feedback may occur from selecting the option with the higher probable reward (i.e. the correct trial). These instances are termed as 'probabilistic errors' and may lead to a behavioral switch despite no rule reversal (Cools et al., 2002; Mitchell et al., 2008; Culbreth et al., 2015). During a rule reversal, errors that relate to the processing of learning new associations by trial and error are referred as 'reversal errors' (O'Doherty et al., 2001; Cools et al., 2002; Dodds et al., 2008). If reversal errors are not followed by a switch to the other option on the subsequent trial, these errors are considered 'first/preceding reversal errors'; however, reversal errors that are followed by a switch to the higher probable reward on the following trial are considered to be 'final reversal errors' (Cools et al., 2002; Remijnse et al., 2006; Zeuner et al., 2016). Errors

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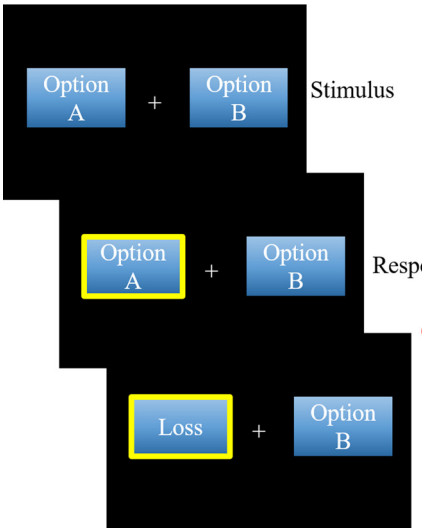

Trial number	Rewarded option	Subject's choice	Feedback	Trial type	Conditions
1	A	B	loss	incorrect	low PE
2	A	A	win	correct	low PE
3	A	A	win	correct	low PE
4	B	A	loss	probabilistic error	high PE
5	A	A	win	correct	moderate PE
6	A	A	win	correct	low PE
7	A	A	win	correct	low PE
8	B	A	loss	reversal error	RE
9	B	A	loss	reversal error	RE
10	B	A	loss	final reversal error	RE
11	B	B	win	correct	RS
12	A	B	loss	incorrect	RS

Fig. 1. Sequence of stimulus events within a trial of the probabilistic reversal learning task (the left panel) and example of a sequence of trials and the categorization of the trials according to the subject's response and the feedback obtained (the right panel). PE = prediction errors. Note PE is a continuous variable and is computed based on computational models. RE = reversal errors; RS = reversal switching.

can also be computed using the relative difference between expectations and actual outcomes, famously known as 'prediction errors' (Rescorla and Wagner, 1972). Different reinforcement learning models, such as the Q-learning algorithm, have been used to capture observed choice behavior and to generate trial-by-trial prediction errors as regressors for the analysis of fMRI data (Gläscher et al., 2010). The final stage of information processing that occurs from the reversal learning paradigm is the reversal switch, instances in which a new rule is learned and then applied (Cohen et al., 2008; Gläscher et al., 2009). Reversal learning in the form of switching may be determined by either comparing post-reversal switches with acquisition trials, trials at the beginning of each trial sequence in which subjects are learning the initial rule (Ghahremani et al., 2010; Hampshire et al., 2012), or by comparing post-reversal switch trials with post-reversal stay trials, in which participants explore rather than continue to repeat erroneous choices (Hampton et al., 2006; Cohen et al., 2008; Culbreth et al., 2015; Lesage et al., 2017). The rationale here is that switching after recognizing the rule reversal reflects the event at which participants learn the new rule. In general, each of these processes of reversal learning capture distinct mechanisms that illustrate the ability to flexibly shift from one stimuli-response mapping to another in order to learn new reward contingencies and to unlearn previous associations. For this article, we aim to determine the concordant activity associated with trial-by-trial prediction errors generated from reinforcement learning models, while final reversal errors are specific to the errors prior to the reversal switch, as well as switching to the alternative option after the reversal.

Many investigating the reversal learning paradigm have revealed activity within the reward network, namely the ventral striatum, ventral lateral prefrontal cortex, bilateral parietal cortex, insula and anterior cingulate cortex (Rogers et al., 2000; de Ruiter et al., 2009; Kringelbach and Rolls, 2003; Ghahremani et al., 2010). Traditionally, the ventral lateral prefrontal cortex has been implicated in the learning aspect of reversal learning since early lesion studies demonstrated diminished reversal learning (Divac et al., 1967; Iversen and Mishkin, 1970; Jones and Mishkin, 1972; Taghzouti et al., 1985; Annett et al., 1989; Stern and Passingham, 1995; Rygula et al., 2010). Later this premise was supported by behavioral manipulations in healthy humans. Using neuroimaging techniques, many have shown increases in activation of the ventral lateral prefrontal cortex when shifting to alternative responses to explore new associations (O'Doherty et al., 2001; Hampton et al., 2006; Shiner et al., 2014; Culbreth et al., 2015; Hauser et al., 2015a; Zhang et al., 2015). In addition, reversal learning paradigms have also explored the role of the ventral striatum (Hampton and O'Doherty, 2007), most notably to explore the neural underpinnings of prediction errors (Robinson et al., 2010; Li et al., 2011; Meder et al., 2016). Prediction errors reflect the degree of unexpectancy by projecting dopaminergic transmission between the striatum and widespread cortical regions such as the prefrontal cortex and parietal cortex (O'Doherty et al., 2003; Tobler et al., 2006). The most profound difference between prediction errors and reversal errors contrasts is that while the former captures the relative difference between actual and expected outcomes (Rescorla and Wagner, 1972), reversal errors capture the exposure to errors while exploring new associations and prior to switching to a correct response, hence reflecting a 'trial and error' aspect of error-related processing (O'Doherty et al., 2001; Cools et al., 2002; Dodds et al., 2008). However, prediction errors and reversal errors not mutually exclusive since these events may overlap (see Table 1).

To our knowledge, no studies have compared neural activity associated with prediction errors and reversal errors. Comparing across studies, there are some inconsistent patterns of functional activity involving the striatum. For example, some studies reveal striatum activity in participants performing the reversal learning task (Dodds et al., 2008; de Ruiter et al., 2009; Ghahremani et al., 2010), while other studies reveal no striatum activity (O'Doherty et al., 2001; Freyer et al., 2009; Mullette-Gillman and Huettel, 2009; Ruge and Wolfensteller, 2016; Zeuner et al., 2016). Perhaps these inconsistencies of striatum activity across studies may depend on the degree of unexpectancy manifested by reversal errors and prediction errors alike. Since reversal errors reflect a 'trial and error' strategy that require multiple attempts to explore novel associations, participants are expected to make errors to discover new rule associations. Therefore, perhaps the difference between reversal errors and prediction errors relates to the degree of expectancy of errors, manifested by the magnitude of striatum activity.

Studies using the reversal learning paradigm also reveal inconsistent patterns of brain activity within the prefrontal cortex, specifically during the reversal phase in which new associations are learned. Reduced reversal learning has been shown in non-human primates with lesions to the ventral part of the frontal cortex (Iversen and Mishkin, 1970; Thorpe et al., 1983; Izquierdo et al., 2004; Rygula et al., 2010), and in humans with lateral orbitofrontal cortical lesions (Hornak et al., 2004). Studies using fMRI in healthy participants have also supported

Table 1
Information on source datasets for prediction errors.

Article	*n*	Mean age (SD)	Age range	Contrast type	Learning model	Probabilities[a]	Stimuli	Foci
Boehme et al. (2016)	85	15.06 (0.05)	13.7–16.4	Model	RL	80/20	Shapes/money	15
Boll et al. (2013)	22	26.9	21–33	Model	PH/RW	Fixed	Fractals	5
D'Cruz et al. (2011)[a]	15	25.4 (4.2)	NA	GLM	–	Various	Shapes	25
				GLM	–	Various	Shapes	25
D'Cruz et al. (2016)[a]	23	18.6 (8.4)	7–38	GLM	–	Various	Shapes	2
				GLM	–	Various	Shapes	27
Fouragnan et al. (2017)	20	21 (2.6)	NA	Model	RL	70/30	Shapes	14
Friedel et al. (2015)	16	38.4 (11.9)	22–61	Model	RW	80/20	Shapes	2
Gläscher et al. (2009)	20	22.3 (4.7)	NA	Model	RL[b]	70/30	Fractals/money	10
Hauser et al. (2015b)	36	20.15	12–29	Model	RW[c]	80/20	Shapes/money	9
Li et al. (2011)	17	NA	18–31	Model	PH/RW	Fixed	Faces	18
Meder et al. (2016)	20	NA	20–40	Model	RL	70/30	Shapes/faces	12
Nickchen et al. (2017)	24	46.8 (11.3)	NA	Model	RL	80/20	Shapes/money	36
Robinson et al. (2010)[a]	16	26 (1)	NA	GLM	–	Fixed	Faces	7
				GLM	–	Fixed	Faces	17
Schiller et al. (2008)	17	NA	18–31	GLM	–	Fixed	Faces	6
Schlagenhauf et al. (2014)	24	27.2 (4.9)	20–41	Model	RW/DSA/HMM	Various	Shapes	14
Tobler et al. (2006)	22	27	19–50	GLM	–	Fixed	Objects	11
Xue et al. (2013)[a]	47	25.36	19–31	GLM	–	Fixed	Fractals	6
				GLM	–	Fixed	Fractals	5

Note: *n* = sample size; SD = Standard deviation; NA = not available.
[a]Article includes more than one contrast; RL = Reinforcement learning; PH = Pearce-Hall (Pearce and Hall, 1980); RW = Rescorla–Wagner (Rescorla and Wagner, 1972); DSA = Double update models; HMM = Hidden Markov models.
[b]Based on RL algorithm (Hampton and O'Doherty, 2007).
[c]Includes other models (see Niv et al., 2012; van den Bos et al., 2012); GLM = General Linear model.

these prior conclusions (O'Doherty et al., 2001; Hampton et al., 2006; Shiner et al., 2014; Culbreth et al., 2015; Zhang et al., 2015); however, contrary to the above findings some studies either report no ventral-medial frontal activity yet activation within other prefrontal regions (Cohen et al., 2008; Linke et al., 2010; Hampshire et al., 2012; Lesage et al., 2017) or report both ventral-medial frontal cortical activity and activity within adjacent prefrontal cortical areas when shifting between responses (Xue et al., 2008; Schlagenhauf et al., 2014; Culbreth et al., 2015; Zhang et al., 2015). Therefore, neuroimaging studies using the reversal learning paradigm seem to reveal inconsistent results with respect to brain activity.

To shed light on these inconsistencies, we aimed to perform an fMRI meta-analysis on the reversal learning paradigm; specifically for reversal errors, prediction errors and switching to correct stimuli-response associations. Our goal was to assess the concordance of the striatum and prefrontal cortex among studies using the reversal learning task. To this end, we aimed to create and compare stereotaxic maps for prediction errors, reversal errors and switching between responses to assess which events comprise of striatum and prefrontal cortex activity. We expected to reveal striatum activity for the meta-analysis associated with prediction errors yet less to no striatum activity for the meta-analysis associated with reversal errors, confirming the notion that reversal errors lack 'unexpectedness' associated with prediction errors. In addition, we hypothesized that the ventral medial prefrontal cortex is involved specifically when participants switch to the new rule associated with the high probable reward option, while simultaneously overcoming associations which have become less optimal. Together, these comparisons allowed us to confirm the neural networks involving the recognition of a rule change and the required switch to learning new associations.

2. Methods

2.1. Literature search and article selection

Our search was performed in Pubmed (https://www.ncbi.nlm.nih.gov/pubmed) and Web of Science (www.webofknowledge.com) using the key terms: "fMRI" AND "reversal learning" on May 21st, 2018. This search yielded 142 studies from Pubmed and an additional twelve non-duplicate articles from Web of Science, bringing a total of 154 articles. These articles were screened for eligibility. Articles were considered eligible if they included whole brain data with random effects analysis, reported coordinates (foci) in Talairach or Montreal Neurology Institute (MNI) space and reported one of the abovementioned contrasts in healthy human participants. For articles including both patient and control groups, contrasts in patients were not included in the meta-analyses. The final dataset included 48 eligible studies. Fig. 2 displays a flowchart representing the steps taken to screen and identify eligible articles. All coordinates were transformed into the same space: MNI coordinates were converted to Talairach space using the Lancaster et al. (2007) transformation algorithm. Three meta-analyses were performed: (a) prediction errors (16 articles; 20 contrasts; 424 participants), (b) reversal errors (21 articles; 25 contrasts; 417 participants), and (c) reversal switches (15 articles; 20 contrasts; 230 participants). See Tables 1–3 for a list of demographic information and contrasts selected for each meta-analysis across eligible studies.

2.2. Software and analysis

To perform the meta-analyses, we used GingerALE version 2.3.6. (http://brainmap.org), a freely available, quantitative meta-analysis method first developed by Turkeltaub et al. (2002), and further developed by Eickhoff et al. (2009, 2017) and Turkeltaub et al. (2012). GingerALE relies on activation likelihood estimation (ALE) which compares foci compiled from multiple articles and estimates the magnitude of overlap, yielding clusters most likely to become active across studies. The most recent algorithm minimizes within-group effects and provides increased power by allowing for inclusion of all possible relevant experiments (Turkeltaub et al., 2012; Eickhoff et al., 2017). Statistical maps were thresholded at $p < 0.05$ using a cluster-level correction for multiple comparisons and a cluster forming threshold at $p < 0.001$ (Eickhoff et al., 2017). To compare results of each meta-analysis representing prediction errors, reversal errors, and reversal switches, we also performed conjunction analyses and contrast analyses. The threshold for group-contrasts was set to $p < 0.01$ uncorrected for multiple comparisons (5000 permutations, 50 mm^3 minimum cluster-size).

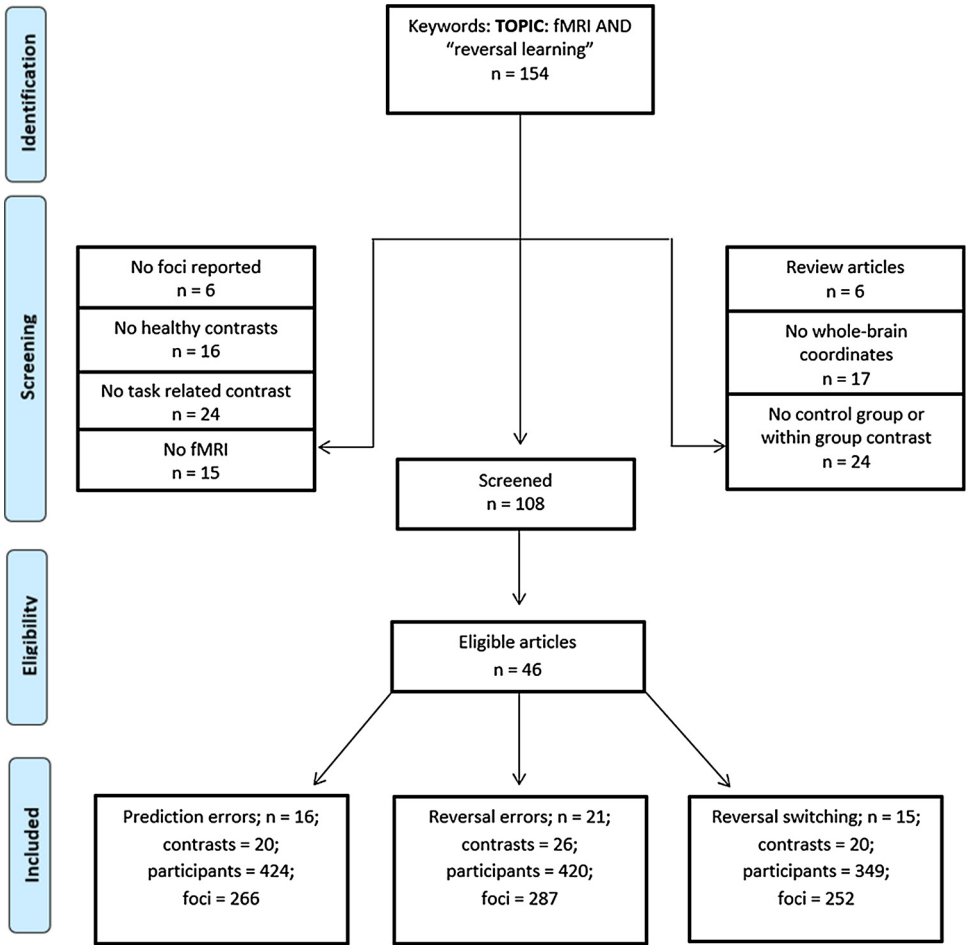

Fig. 2. PRISMA flowchart illustrating exclusion criteria and eligibility for relevant studies.

Table 2
Information on source datasets for reversal errors.

Article	n	Mean age (SD)	Age range	Contrast	Task type	Probabilities[a]	Stimuli	Foci
Cools et al. (2002)	13	25.9 (3.82)	22–37	FRE > CR	2-Choice	Fixed	Shapes	3
Culbreth et al. (2015)	21	36.6 (9.2)	NA	FRE > ER	2-Choice	80/20	Fractals	20
de Ruiter et al. (2009)	19	34.1 (9.3)	NA	RE > BL	2-Choice	80/20	Objects	9
Dodds et al. (2008)	17	22.2	19–33	FRE > CR	2-Choice	Fixed	Shapes	9
Freyer et al. (2009)[a]	10	39.8 (10.03)	NA	FRE > CR	2-Choice	Various	Shapes	5
				FRE > CR	2-Choice	Various	Shapes	6
Ghahremani et al. (2010)	16	23 (4)	18–30	RE > ER	Predict	Fixed	Fractals	13
Greening et al. (2011)	21	24.5 (2.8)	20–32	RE > All[b]	2-Choice	Fixed	Fractals	22
Hampton et al. (2006)	16	NA	NA	FRE > BL	2-Choice	70/30	Fractals	3
Jocham et al. (2009a)	28	26.12	20–32	FRE > RE	2-Choice	75/25	Shapes	19
Jocham et al. (2009b)[a]	21	24.6 (0.76)	21–35	FRE > CR	2-Choice	75/25	Shapes	11
				FRE > CR	2-Choice	75/25	Shapes	6
Kringelbach and Rolls (2003)	21	NA	NA	RE > CR	2-Choice	Fixed	Faces	7
Mitchell et al. (2008)	13	29.15 (6.76)	22.38	RE > CR	2-Choice	Fixed	Stock Market	7
Mullette-Gillman and Huettel (2009)	14	22.4	18–29	RE > BL	2-Choice	Fixed	Shapes	21
Nashiro et al. (2012)	19	25.58	19–35	RE > BL	2-Choice	Fixed	Faces	33
				RE > BL	2-Choice	Fixed	Faces	20
O'Doherty et al. (2001)	9	25.4	22–30	RE > CR	2-Choice	70/30,40/60	Fractals	1
Ohira et al. (2011)	20	32.64 (2.31)	NA	RE > CR	2-Choice	70/30	Shapes	5
Remijnse et al. (2005)	27	32 (7.7)	22–53	FRE > BL	2-Choice	80/20	Objects	12
Remijnse et al. (2006)	27	32 (7.7)	22–53	FRE > ER	2-Choice	80/20	Objects	8
Ruge and Wolfensteller (2016)	27	24.6	21–35	RE > CR	Predict	Fixed	Shapes	18
Waegeman et al. (2014)	40	19.83 (1.45)	18–24	FRE > CR	2-Choice	80/20	Letters	11
Zeuner et al. (2016)	18	47.6 (9.4)	25–68	FRE > RE	2-Choice	80/20	Shapes	7
				FRE > CR	2-Choice	80/20	Shapes	11

Note: *n* = sample size; SD = Standard deviation; NA = not available; [a]Probabilities for reward and punishment during acquisition phase; [b]Contrast reflects overcome avoidance versus all trials;
[c]Article includes more than one contrast; FRE = Final reversal error; RE = Reversal error;
ER = Error during acquisition; CR = Correct response; BL = Baseline trial.

Table 3
Information on source datasets for reversal switching.

Article	*n*	Mean age (SD)	Age range	Contrast[b]	Task type	Probabilities	Stimuli	Foci
Bray et al. (2010)	13	21.7 (3.7)	NA	PRC > RE	2-Choice	80/20	Fractals/money	13
Cohen et al. (2008)	21	25 (3.6)	20–30	Shift > Stay	2-Choice	75/25	Shapes	4
Culbreth et al. (2015)	19	36.6 (9.2)	NA	Shift > Stay	2-Choice	80/20	Fractals	32
Ghahremani et al. (2010)	17	23 (4)	18–30	PRC > AC	Predict	Fixed	Fractals	6
Gläscher et al. (2009)	10	22.3 (4.7)	NA	Shift > Stay	2-Choice	70/30	Fractals	4
Goghari and MacDonald (2008)[a]		26.2 (6.6)	NA	Shift > Stay	Cued	50/50	Shapes	13
				Shift > Stay	Cued	50/50	Shapes	9
Hampshire et al. (2012)	16	29 (6)	19–40	PRC > RE	3-Choice	5/6	Faces	22
Hampton et al. (2012)	21	NA	NA	Shift > Stay	2-Choice	70/30	Fractals	3
Lesage et al. (2017)	16	33.1	NA	Shift > Stay	2-Choice	75/25	Fractals/money	5
Linke et al. (2010)	28	22.64 (2.92)	19–32	Shift > Stay	2-Choice	80/20	Cards	22
Liu et al. (2015)	21	24	19–35	PRC > AC	2-Choice	Fixed	Letters	5
Schlagenhauf et al. (2014)		27.2 (4.9)	20–41	Shift > Stay	2-Choice	80/20	Shapes	18
Xue et al. (2008)[a]	17	22.7	19–28	PRC > AC	2-Choice	Fixed	Shapes	17
				PRC > AC	2-Choice	Fixed	Shapes	28
				PRC > AC	2-Choice	Fixed	Shapes	20
Xue et al. (2013)[a]	47	25.36	19–31	PRC > AC	Predict	Fixed	Fractals	8
				PRC > AC	Predict	Fixed	Fractals	3
				PRC > AC	Predict	Fixed	Fractals	3
Zhang et al. (2015)	14	24.6 (4.9)	19–34	Shift > Stay	2-Choice	2/3	Shapes/money	17

Note: *n* = sample size; SD = Standard deviation; NA = not available; [a]Probabilities for reward and punishment during acquisition phase; [b]Shift > Stay reflects shifting strategy during reversal; [c]Article includes more than one contrast; PRC = Post-reversal correct trials; RE = Reversal error; AC = Acquisition correct trials.

3. Results

3.1. ALE maps

Table 4 shows a list of all regions concordant across studies for prediction errors (2a), reversal errors (2b) and reversal switches (2c). Significant results for each meta-analysis representing these contrasts are displayed in Fig. 3 and conjunction analysis results are displayed in Fig. 4.

3.2. Prediction errors

The meta-analysis associated with prediction errors revealed the largest cluster within the left caudate body, yet the area with the highest likelihood to be concordant across studies was the right insula (BA 13). Other regions included the left claustrum (overlapping with the left insula), left superior frontal gyrus (BA 8) and cingulate gyrus (BA 32). We also compared the meta-analysis on prediction errors with the reversal errors meta-analysis to assess the differences in neural structure associated with error-related processing. Compared to reversal errors, prediction errors produced a large cluster involving activity within the left amygdala, left parahippocampal gyrus (BA 28), left caudate body and left putamen.

3.3. Reversal errors

The meta-analysis on reversal errors produced similar regions as compared to prediction errors. Conjunction analysis revealed that reversal errors, like prediction errors, produced concordant clusters within the bilateral insulae/claustrum (BA 13) and medial frontal/cingulate cortex (BA 6/32). However, the main analysis on reversal errors in addition produced bilateral superior frontal gyri (BA 9) and bilateral inferior parietal gyri (BA 40). Compared to prediction errors and reversal switches, reversal errors produced no additional suprathreshold clusters.

3.4. Reversal switches

The meta-analysis on reversal switches generated a concordant cluster within right inferior frontal gyrus (BA 44), the largest cluster and was most likely to become active. In addition, reversal switches also produced concordance within the left insula gyrus (BA 13) and right medial frontal gyrus (BA 6). Finally, we compared the meta-analyses on reversal switches with reversal errors to disentangle the neural structures associated with learning during the reversal phase of the reversal learning paradigm. The conjunction analysis on reversal switches and reversal errors produced similar regions, namely the left insula gyrus (BA 13). Compared to reversal errors, reversal switches produced more right frontal gyri activity, which overlapped with the right insula gyrus (BA 13).

4. Discussion

Although several brain regions are implicated in reversal learning, the exact mapping between brain regions and functions in reversal learning remains poorly understood. Specifically, the functional significance of the commonly observed brain areas activated in reversal learning studies, such as the striatum and prefrontal cortex, is not clear. Non-human primates with lesions to the prefrontal cortex tend to perseverate on learned stimuli associations despite receiving negative feedback (Iversen and Mishkin, 1970; Jones and Mishkin, 1972; Stern and Passingham, 1995; Rygula et al., 2010). Although lesioned primates and functional MRI studies with healthy humans provide evidence that the ventral part of the frontal cortex corresponds with reversal learning (O'Doherty et al., 2001; Hampton et al., 2006; Shiner et al., 2014; Culbreth et al., 2015; Zhang et al., 2015), some studies have shown no direct evidence (e.g. Cohen et al., 2008; Linke et al., 2010; Hampshire et al., 2012; Lesage et al., 2017).

The meta-analysis on prediction errors produced activity within the striatum, namely the left caudate and lentiform nucleus. Prior meta-analysis on prediction errors among a variety of task paradigms have shown concordant activation within the bilateral striatum (Garrison et al., 2013; Fouragnan et al., 2018); however, in the current study only left striatum activity was concordant across studies. Perhaps unilaterality of the ventral striatum may be explained by the non-overlapping regions of the striatum across studies. For example, although foci from many studies included in the current meta-analysis reported bilateral striatum activity (e.g. Tobler et al., 2006; D'Cruz et al., 2011, 2016; Boehme et al., 2016; Meder et al., 2016), quite a number of studies display only right striatum activity (Li et al., 2011; Boll et al., 2013; Hauser et al., 2015b; Nickchen et al., 2017). In addition, those that reported bilateral striatum activity varied with regards to

Table 4
Concordant brain regions associated with reversal learning paradigm.

Condition	Cluster #	Volume mm^3	ALE value	x	y	z	Label
Prediction errors (PE)	1	2448	0.025	−10	6	8	L Caudate Body
			0.021	−18	2	−10	L Lentiform Nucleus
	2	1184	0.028	30	20	2	R Insula BA 13
	3	1024	0.023	−30	20	−2	L Claustrum
	4	904	0.020	0	18	50	L Superior Frontal Gyrus BA 8
			0.016	2	12	42	R Cingulate Gyrus BA 32
Reversal errors (RE)	1	2136	0.023	28	18	6	R Claustrum
			0.023	28	20	0	R Claustrum
	2	1296	0.028	40	34	30	R Superior Frontal Gyrus BA 9
	3	1184	0.030	−32	18	0	L Insula BA 13
	4	1000	0.025	−42	20	36	L Superior Frontal Gyrus BA 9
	5	960	0.022	36	−46	36	R Inferior Parietal Gyrus BA 40
	6	840	0.020	−2	26	36	L Cingulate Gyrus BA 32
			0.013	0	12	42	L Medial Frontal Gyrus BA 6
	7	784	0.024	−46	−44	40	L Inferior Parietal Gyrus BA 40
Reversal switches (RS)	1	2064	0.030	46	16	2	R Inferior Frontal Gyrus
			0.029	46	16	8	R Precentral Gyrus BA 44
	2	864	0.018	−36	18	4	L Insula BA 13
			0.016	−36	14	−2	L Insula BA 13
			0.014	−30	20	0	L Claustrum
	3	800	0.021	2	12	46	R Medial Frontal Gyrus BA 6
PE & RE	1	1040	0.022	28	20	6	R Claustrum
			0.022	28	20	0	R Claustrum
	2	784	0.023	−30	20	−2	L Claustrum
	3	88	0.013	0	12	42	L Medial Frontal Gyrus BA 6
RE & RS	1	520	0.017	−34	18	4	L Insula BA 13
			0.014	−30	20	0	L Claustrum
PE & RS	1	344	0.015	−34	18	4	L Insula BA 13
			0.014	−30	20	0	L Claustrum
	2	272	0.016	2	16	48	R Superior Frontal BA 8
PE > RE	1	952	3.540	−22	−2	−10	L Amygdala
			3.238	−18	−1	−12	L Parahippocampal Gyrus BA 28
			3.035	−12	6	−8	L Caudate
			2.878	−7	5	7	L Caudate
			2.847	−14	8	−4	L Putamen
PE > RS	1	200	3.061	−22	−2	−8	L Putamen
			2.947	−19	−2	−12	L Amygdala
RS > PE	1	1968	3.431	51.7	19.7	4.7	R Inferior Frontal BA 47
			3.352	48.3	16.7	10.7	R Inferior Frontal BA 44
			3.290	49.8	13.3	−0.7	R Superior Temporal BA 22
			3.194	48	12	6	R Insula BA 13
			3.155	45	16.8	4.8	R Insula BA 13
RS > RE	1	1144	3.238	49	17	2	R Inferior Frontal
			2.988	43	12	3	R Insula BA 13
RE > PE							
RE > RS							No Suprathreshold Clusters
							No Suprathreshold Clusters

Note: L = Left; R = Right; BA = Brodmann area; Coordinates are reported in Talairach and all results are thresholded with cluster-level threshold was set to $p = 0.05$ whereas the cluster-forming threshold was set to $p < 0.001$.

stereotaxic coordinate space. For example, studies included in the meta-analysis containing bilateral activity report putamen (Tobler et al., 2006; Boehme et al., 2016), ventral striatum (D'Cruz et al., 2011, 2016; Friedel et al., 2015; Meder et al., 2016), dorsal striatum (Gläscher et al., 2009), and caudate nucleus (Schiller et al., 2008; D'Cruz et al., 2016). Thus, it is likely that bilateral striatum activity is involved; however, the left caudate nucleus appears to play a more critical role since only the left caudate nucleus survived statistical thresholding. Interestingly, the left caudate nucleus becomes active when stimulus-reward/punishment contingencies are reversed yet not when stimuli dimensions differ from previous trials (Rogers et al., 2000). This may suggest that left caudate nucleus specificity may be explained by prediction errors occurring when participants are expecting to receive reward contingencies yet receive unexpected punishment contingencies instead. The contrast analysis on prediction errors revealed concordant activity within the left amygdala, an area that appeared to be adjacent to the left caudate nucleus. Together with the striatum, the amygdala has been implicated in associative learning (Schiller et al., 2008; Li et al., 2011; Boll et al., 2013). Previous studies in both animals and humans have emphasized an important role for amygdala in encoding expected reward (Hampton et al., 2006; Paton et al., 2006; Schoenbaum et al., 1998, 2003), and learning to predict aversive outcomes (Schiller et al., 2008; Li et al., 2011; Eippert et al., 2012). Moreover, the left amygdala has been shown to be active during "worse than expected" prediction error outcomes (Meder et al., 2016) supporting the notion that the amygdala corresponds with associability of aversive stimuli (Li et al., 2011). However, it is important to acknowledge that studies investigating reversal learning can be methodologically different between humans and other animals. In human studies, reward is almost always secondary, conditioned reinforcers that often entail delayed access rather than primary reinforcers such as food or drugs, that are commonly used in animal research. Sensory modality of learning also differs across species. Learning in some modalities, e.g., involving olfactory sense, is easily acquired in rodents, whereas visual discrimination paradigms are learned more readily in primates. Length of training and probabilistic reinforcement schedules also differ between species (see Hampton et al., 2006; Paton et al., 2006). It remains to be examined whether there are preserved neural substrates of reversal learning across species

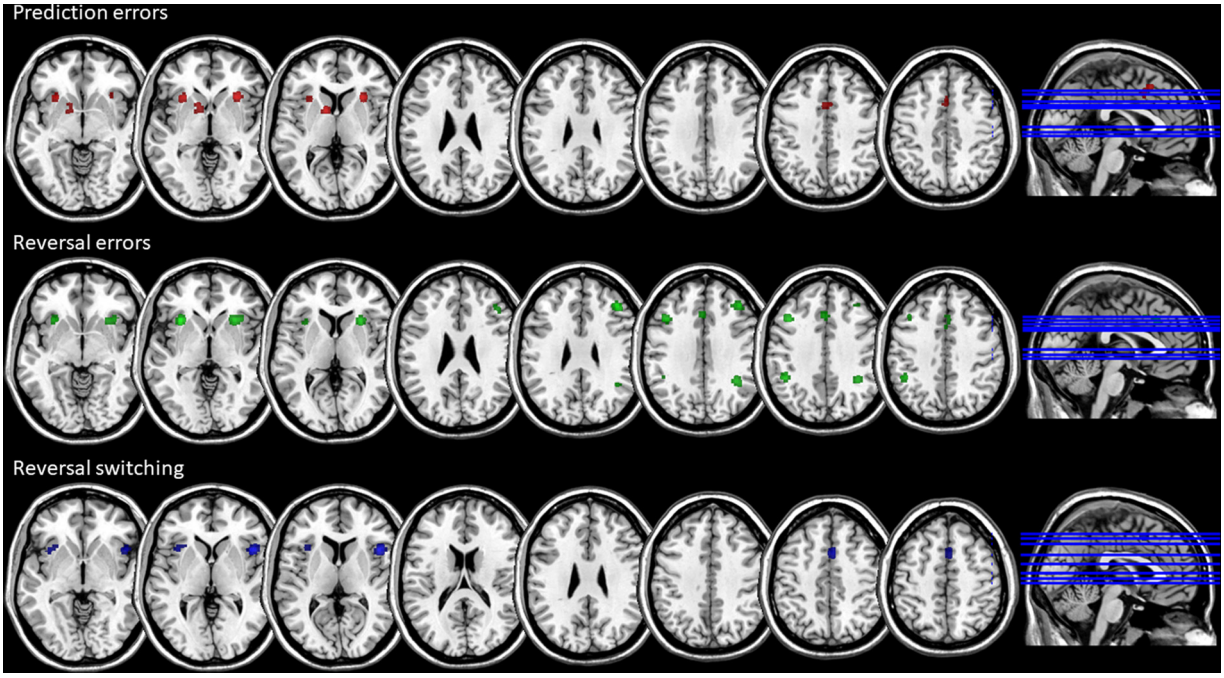

Fig. 3. Concordant activation across studies for reversal learning. From top to bottom: Prediction errors (in red), reversal errors (in green), and reversal switching (in blue). Slices are not consistent across contrasts.

(Izquierdo et al., 2017).

We compared meta-analysis across reversal errors and reversal switches and found activity within the right inferior frontal gyrus during reversal switching. This finding corresponds with the hypothesis that ventral parts of the frontal cortex are recruited for reversal learning, after which participants successfully switch to a new association (O'Doherty et al., 2001; Hampton et al., 2006; Shiner et al., 2014; Culbreth et al., 2015; Hauser et al., 2015a; Zhang et al., 2015). Successfully switching to an alternative choice (Derrfuss et al., 2005; Kim et al., 2012) while successfully suppressing prepotent responses (Zheng et al., 2008; Chevrier et al., 2007; Chikazoe et al., 2007; Simmonds et al., 2008; Swick et al., 2011; Dambacher et al., 2014a, 2014b) are essential functions of the right inferior frontal cortex. Interestingly, the right inferior frontal gyrus is not only necessary for

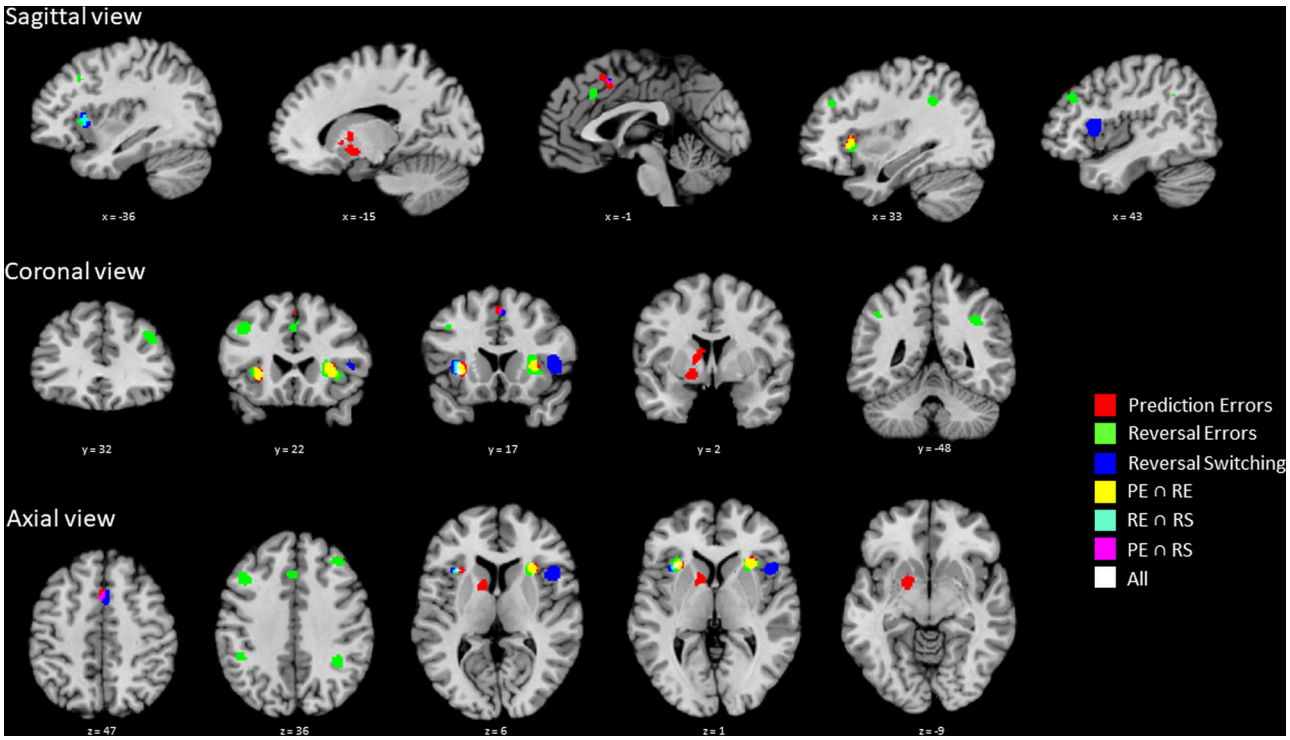

Fig. 4. Overlap of concordant activation across contrasts displayed for sagittal, axial and coronal view for prediction errors (in red), reversal errors (in green), and reversal switching (in blue). Conjunction of these contrasts are represented in yellow (prediction errors and reversal errors), cyan (reversal errors and reversal switching), magnetic (prediction errors and reversal switching), and white (all contrasts).

overcoming previously learned associations in the case of reversal learning but also for response inhibition (Hampshire et al., 2010) and specifically negative priming, a similar cognitive phenomenon marked by a decrease in performance when current target stimuli were employed as distractor stimuli in previous trials (Frings et al., 2015; see 6 for meta-analysis Yaple and Arsalidou, 2016). This may suggest that the right inferior frontal cluster observed in reversal learning paradigms represents the ability to disassociate prior learned associations after learning new associations. Furthermore, we demonstrated concordant bilateral frontal and parietal regions when receiving feedback associated with reversal errors, yet no frontal and parietal regions when switching to new associations. Prefrontal and parietal cortical regions increase in activation in the midst of learning a new rule yet become less active when a rule is learned and automatized (Liu et al., 2015). Taken together, our results may indicate that while reversal errors recruit bilateral prefrontal and parietal cortical regions to explore novel associations, once a new association is learned, the right inferior frontal cortex may inhibit prior associations.

It is important to consider the fact that all three meta-analyses yielded concordant activity within the cingulate and insulae, regions attributed to a salience network (Menon and Uddin, 2010). Dosenbach et al., 2006 had identified that a similar 'cingulo-opercular' network, involving the dorsal anterior cingulate cortex and bilateral anterior insula/frontal operculum, has an important role in implementing task sets and shifting to new sets. Specifically, executive networks such as the fronto-parietal and cingulo-opercular networks may account for multiple executive operations or may operate together during a single cognitive process (Dosenbach et al., 2007, 2008; Velanova et al., 2008; Fair et al., 2009; Gratton et al., 2017). While the fronto-parietal network may be 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). Perhaps these executive networks may account for the current findings; the fronto-parietal network was concordant during the 'trial and error' phase of reversal learning perhaps reflecting an increase in adaptive control as a means to adjust to previous errors between trials. The cingulo-opercular executive network that carries signals associated with stable set-maintenance was found in all aspects of reversal learning, perhaps to maintain cognitive control during error-related processing and during which new associations are established. Since prediction errors are measured from all trials using reinforcement learning algorithms while reversal errors are specific to errors occurring prior to switching, the processes overlapping with these events may correspond to concordant activity of the cingulo-opercular 'salience' network.

4.1. Limitations and future directions

Several limitations to the study are worth mentioning. First, it is important to acknowledge that due to study heterogeneity, the meta-analyses performed in the current study cannot account for differences among task design. These differences include: the type of stimuli (shapes, money, faces), number of consecutive correct responses prior to the switch; task designs that use a mild shock stimuli (e.g. Schiller et al., 2008; Li et al., 2011; Boll et al., 2013), rather than monetary incentives (e.g. Cohen et al., 2008; Dodds et al., 2008; Hauser et al., 2015b); reward selections with varied (e.g. O'Doherty et al., 2001; Nickchen et al., 2017; Fouragnan et al., 2017) vs. fixed probabilities (e.g. Kringelbach and Rolls, 2003; Xue et al., 2008; Ruge and Wolfensteller, 2016); and task designs in which 'incorrect' selections yield a loss (e.g. O'Doherty et al., 2001; Cohen et al., 2008; Gläscher et al., 2009), or no reward (e.g. Fouragnan et al., 2017). We attempted to confront these issues by performing supplementary tests (See Supplementary Materials section). The results were analogous to the main analyses, despite lower sample size. For future directions, we encourage others to perform meta-analyses once new datasets become available.

Secondly, although different types of errors are defined in the literature, these response types/stages in reversal learning are not mutually exclusive and they might overlap. For example, early in a reversal, reversal errors are similar to probabilistic errors which trigger prediction errors and activate prediction error-related regions. Finally, few studies have investigated other stages of error processing, such as first reversal errors vs. final reversal errors. It is unclear whether such distinctions are psychologically meaningful or not and whether different brain regions are engaged in processing these different types of errors.

5. Conclusion

Although reversal learning has been widely used in animal studies and human neuroimaging research to investigate the neural signatures of adaptive learning, the exact mapping between specific cognitive processes during the learning and brain networks remain unclear. Our study showed that the cingulo-opercular network was involved in different stages of reversal learning, whereas other brain networks were only involved in certain processes of the reversal learning: the striatum was uniquely involved in encoding reward prediction errors before reversal, the frontoparietal network encoded reversal errors after reversals occurred, and the inferior frontal network was activated in reversal switching, presumably to suppress prior stimulus-response mappings. This dynamic brain network together supports the successful adaptation to changing reward contingencies. Dysfunctions in any of these networks may contribute to clinical populations that are characterized by characteristic dysfunctions of flexible learning, such as schizophrenia and addiction.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neubiorev.2019.04.006.

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