

## Neural correlates of response reversal: Considering acquisition

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Previous work on response reversal has typically used a single pair of stimuli that serially reverse. This conflation of acquisition and reversal processes has prevented an examination of the functional role of neural systems implicated in response reversal during acquisition despite the relevance of such data in evaluating accounts of response reversal. In the current study, participants encountered 16 independent reversing stimulus pairs in the context of a probabilistic response reversal paradigm. Functional regions of interest identified as involved in response reversal through a contrast used in the previous literature (punished errors made in the reversal phase versus rewarded correct responses), were interrogated across conditions. Consistent with suggestions that middle frontal cortex codes reward, this region showed significantly greater responses to rewarded rather than punished trials irrespective of accuracy or learning phase (acquisition or reversal). Consistent with the suggestion that this coding of the expectation of reinforcement is acquired via input from the amygdala, we observed significant positive connectivity between activity within the amygdala and a region of rostral anterior cingulate cortex highly proximal to this region of middle frontal/mesial prefrontal cortex. In contrast, inferior frontal cortex, anterior cingulate cortex and caudate showed greater responses to punished errors than to the rewarded correct responses. These three regions also showed significant activation to rewarded errors during acquisition, in contrast to positions suggesting that inferior frontal cortex represents punishment or suppresses previously rewarded responses. Moreover, a connectivity analysis with an anterior cingulate cortex seed revealed highly significant positive connectivity among them. The implications of these data for recent accounts of response reversal and of response reversal impairments in specific neuropsychiatric populations are discussed.

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### Introduction

Reversal learning is the alteration of a behavioral response to a previously rewarded stimulus following altered reinforcement contingencies (Rolls, 2004). Impairments in reversal learning are observed in several psychiatric conditions that are associated with a heightened risk of irritability or reactive aggression, such as psychopathy (Blair et al., 2001; Mitchell et al., 2002), intermittent explosive disorder (Best et al., 2002) and pediatric bipolar disorder (Gorrindo et al., 2005). Lesion studies with non-human primates have demonstrated reversal learning impairments following surgical ablation of the orbitofrontal cortex (OFC) (Dias et al., 1996; Iversen and Mishkin, 1970; Izquierdo et al., 2004) and striatum (Divac et al., 1967). Similarly, neuropsychological and neuroimaging work with humans has emphasized the importance of OFC/middle frontal cortex, inferior frontal cortex, anterior cingulate and striatum (Cools et al., 2002; Fellows and Farah, 2003; Hornak et al., 2004; Kringelbach and Rolls, 2003; Nagahama et al., 2001; O'Doherty et al., 2003a,b; Rahman et al., 1999; Remijne et al., 2005; Rogers et al., 2000; Rolls et al., 1994; Swainson et al., 2000). Despite these studies, however, the functional roles of these regions during reversal learning remain unclear.

To summarize, there have been two major claims with respect to response reversal and lateral OFC/inferior frontal cortex, here defined as lateral regions of Brodmann's area (BA) 11 (lateral OFC) and BAs 47 and 45 (inferior frontal cortex). The first is that lateral OFC/inferior frontal cortex has an inhibitory function, suppressing previously rewarded responses (Cools et al., 2002; Elliott et al., 2000; Monchi et al., 2001). Such a position has not only been suggested by work with the response reversal paradigm but also by work with response control paradigms such as Stop and Go/No-Go (see, for a review, Aron et al., 2004).

The second position is that lateral OFC/inferior frontal cortex is involved in the representation of punishment information (Kringelbach and Rolls, 2004; Kringelbach, 2005; O'Doherty et al., 2001b). Under this position, middle frontal cortex (for the current arguments here defined as BA 10), is thought to be involved with the representation of reward (Knutson et al., 2003; Kringelbach and Rolls, 2004; Kringelbach, 2005; O'Doherty et al., 2001b).

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Moreover, it has been suggested that OFC codes the expectation of reinforcement, which is acquired via input from amygdala, and is used to guide behavior (Schoenbaum et al., 2003). In line with this, neuroimaging studies have implicated amygdala, medial OFC/middle frontal cortex and ventral striatum in reward prediction (Gottfried et al., 2003; Knutson and Cooper, 2005; Knutson et al., 2001; Kosson et al., 2006; O'Doherty, 2004). Extending this, Schoenbaum et al.'s (2003) position might predict positive connectivity between the amygdala and those regions of OFC representing reinforcement.

A third possibility notes that several previous studies of response reversal have observed activation of anterior cingulate cortex in addition to lateral OFC/inferior frontal cortex (Cools et al., 2002; Kringelbach and Rolls, 2003; Remijne et al., 2005). While there has been relatively little consideration of its role in response reversal, it is worth noting that dorsal anterior cingulate is implicated in monitoring response conflict (Botvinick et al., 2004; Bush et al., 2000; Carter et al., 1998; Kerns et al., 2004) and error detection (Brown and Braver, 2005; Holroyd et al., 2004), functions likely to be important in response reversal. If anterior cingulate does play a role in response reversal, it is likely to do so through interaction with lateral OFC/inferior frontal cortex. In short, this third position would predict significant positive connectivity between activity within anterior cingulate cortex and lateral OFC/inferior frontal cortex.

Typically neuroimaging investigations of reversal learning have employed paradigms where the reinforcement contingencies of a single pair of stimuli reverse serially throughout (Cools et al., 2002; Kringelbach and Rolls, 2003; O'Doherty et al., 2003a,b; Remijne et al., 2005). There are two potential shortcomings inherent in this design. Firstly, it is possible that alternative strategies might be employed (e.g., rule-based strategies such as "reverse after three incorrect responses"). Indeed, animal lesion studies using this type of paradigm often report impairment only on the first reversal (Dias et al., 1997; Iversen and Mishkin, 1970). Secondly, and more importantly, it is difficult to disentangle acquisition and reversal trials. The participant only experiences acquisition of novel stimuli once. But acquisition data are necessary to test specific predictions that have been generated by the positions on response reversal.

Suggestions that lateral OFC/inferior frontal cortex are involved in inhibition, i.e., that they suppress previously rewarded responses (Cools et al., 2002; Elliott et al., 2000; Monchi et al., 2001) should predict significantly less activity in lateral OFC/inferior frontal cortex during incorrect acquisition relative to incorrect reversal trials. There should be less representation of the previous response and therefore less necessity for suppression. Previous studies, lacking an adequate number of acquisition trials, have been unable to test this prediction. In contrast, suggestions that lateral OFC/inferior frontal cortex codes punishment information (O'Doherty et al., 2001b; Remijne et al., 2005), should predict significantly greater activity in lateral OFC/inferior frontal cortex to punished relative to rewarded trials whether they occur during acquisition or reversal.

We adopted a probabilistic response reversal paradigm whereby participants encountered 24 different stimulus pairs (16 of which reversed after a predetermined number of trials). Following previous investigations (Kringelbach and Rolls, 2003; O'Doherty et al., 2001b), punished errors made in the reversal phase were contrasted with rewarded correct responses. Functionally defined regions of interest were then interrogated with respect to other

events (in particular, rewarded and punished acquisition errors and punished correct responses). Our goal was to test the contrasting predictions of the positions described above.

## Methods

### Subjects

Twenty-eight right-handed adults participated in the study, which was approved by the National Institute of Mental Health Institutional Review Board. Due to a technical error, data from one subject were unusable. A further 6 subjects were excluded from analysis due to poor performance on the reversal learning task (see Results section for further details). Consequently data from twenty-one subjects (11 women and 10 men, mean age=24.71, SD=2.72; range=22–34 years) were analyzed. All subjects were in good health with no past history of psychiatric or neurological disease and gave informed written consent.

### Probabilistic reversal learning task and experimental procedure

On each trial a pair of stimuli (line drawings of common, neutrally valenced, items) were displayed on a white background. Stimuli were positioned in one of four possible left- or right-sided screen locations. Subjects had to choose a stimulus and received either positive ('you win 100 points') or negative ('you lose 100 points') reinforcement subject to their accuracy and the reinforcement contingency of that pair. Each trial lasted 2300 ms and involved the presentation of: the test stimuli for 1100 ms, feedback display for 900 ms and finally a fixation cross for 300 ms (for a timeline see Fig. 1). There was no 'jittering' of trial elements. Subjects were able to respond by left or right thumb button press (corresponding to selection of the left- or right-positioned stimulus respectively) only during the 1100-ms stimuli presentation window. If subjects failed to make a selection they received the feedback: "please respond faster next time" and their points total remained the same. Subjects began the task with 0 points. A running total of points was visible at the bottom of the screen only during the 900-ms feedback display window.

Subjects received eight 6-min-long runs. Each run involved three stimulus pairs. This led to total of 24 distinct pairs, each of which used different line drawings. Each stimulus pair was presented for 40 trials. Following the presentation of one stimulus pair, the subject began their experience with the next stimulus pair. There were thus 120 test trials in any given run. In addition, 24 fixation trials (of 2300-ms duration) were presented per run to serve as a baseline.

The reinforcement contingencies of two of the pairs in each run reversed after 20 trials. The reinforcement contingency of the third pair remained constant throughout (for a total of 16 reversing and 8 non-reversing stimulus pairs in the entire task).

Pairs in half of the runs had a 90–10 probabilistic reinforcement contingency (i.e., the subject was rewarded for selecting the correct stimulus on 90% of trials and rewarded for selecting the incorrect stimulus on 10% of trials [the inverse was true for punishment contingencies]), and the other half had a 70–30 probabilistic reinforcement contingency. The order of runs and stimulus pairs within runs was randomized for each subject.

The following instructions, taken from Swanson et al. (2000), were presented to the subject: 'pairs of objects will appear on the screen. On each go you have to choose one of these objects and the

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