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The neuropsychology of ventral prefrontal cortex: Decision-making and reversal learning

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Abstract

Converging evidence from human lesion, animal lesion, and human functional neuroimaging studies implicates overlapping neural circuitry in ventral prefrontal cortex in decision-making and reversal learning. The ascending 5-HT and dopamine neurotransmitter systems have a modulatory role in both processes. There is accumulating evidence that measures of decision-making and reversal learning may be useful as functional markers of ventral prefrontal cortex integrity in psychiatric and neurological disorders. Whilst existing measures of decision-making may have superior sensitivity, reversal learning may offer superior selectivity, particularly within prefrontal cortex. Effective decision-making on existing measures requires the ability to adapt behaviour on the basis of changes in emotional significance, and this may underlie the shared neural circuitry with reversal learning.

Keywords: Orbitofrontal; Basal ganglia; Parkinson's disease; Addiction; Psychopathy; Risk taking

1. Introduction

Following brain injury to the orbitofrontal and ventromedial prefrontal cortex (PFC), human patients display gross alterations in social and emotional behaviour with largely preserved perception, language, memory, and even executive function (Bechara, Tranel, & Damasio, 2000; Damasio, 1994; Malloy, Bihrle, Duffy, & Cimino, 1993; Rolls, 1999). Characterisation of this profile using cognitive testing has been the target of considerable research, not least because the behaviour of patients with ventral prefrontal lesions resembles aspects of symptomatology seen in psychiatric conditions including psychopathy (Lapierre, Braun, & Hodgins, 1995) and substance abuse (Bechara & Damasio, 2002). Two cognitive domains have received particular attention in recent years: decision-making and reversal learning. The development of several measures of decision-making has stemmed largely from observations by Damasio, Bechara and colleagues, that patients with ventromedial prefrontal cortex damage are impaired in their ability to make successful everyday decisions regarding employment, relationships, and personal finances. Specifically, it has been proposed that these patients are unable to use past experiences to guide their ongoing decision-making ('myopia for the future') (Bechara et al., 2000; Damasio, 1994). Recent interest in reversal learning, in contrast, has developed from pre-clinical research over more than three decades demonstrating that rodents and non-human primates with lesions to the orbitofrontal cortex are unable to adapt their responding following changes in stimulus–reward contingencies (Butter, 1969; Jones & Mishkin, 1972).

The purpose of this article is to review converging evidence for the involvement of ventral prefrontal cortex in decision-making and reversal learning, from (1) human lesion studies, (2) animal lesion studies, and (3) human functional neuroimaging studies. Evidence for the contribution of the ascending 5-HT and dopamine neurotransmitter systems to these domains will also be described. Recent cognitive research in a number of clinical groups has begun to investigate the sensitivity and selectivity of decision-making and reversal learning deficits as indices of ventral prefrontal dysfunction.

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2. The cognitive neuroscience of decision-making

Decision-making requires the evaluation of multiple response options, followed by the selection of the response considered optimal. Each response option may be characterised in terms of the reward and punishment outcomes with which it is associated. Response options may vary in terms of (1) the magnitude of reward and punishment, (2) the probability of receiving reward or punishment, and (3) the delay to reward or punishment. This framework provides scope for a range of decision-making abnormalities in clinical groups. Deficits may become apparent in terms of increased sensitivity to reward or reduced sensitivity to punishment, or at a more complex level under situations of conflict; for example, a failure to avoid rewards with long-term negative consequences, or the preference for a small immediate reward over a larger but delayed reward. This latter phenomenon is known as temporal (or delay) discounting, and exemplifies the relationship between decision-making and impulsivity, given that an operational definition of impulsive behaviour is the tendency to choose a small or inferior immediate reward over a larger delayed reward (Evenden, 1999; Logue, 1988).

2.1. Human lesion studies

Neuropsychological studies of decision-making in humans have utilised two paradigms in recent years: the Iowa Gambling Task (Bechara, Damasio, Damasio, & Anderson, 1994) and the Cambridge Gamble Task (Rogers, Everitt, et al., 1999). The Iowa Gambling Task is described in detail elsewhere in this issue (Bechara, this issue). The task emphasises the *learning* of reward and punishment associations in order to guide ongoing decision-making. Healthy subjects performing the Iowa Gambling Task learn to avoid 'risky' card decks that offer high immediate rewards with a concomitant risk of occasional very high punishment. They develop a preference instead for 'safe' card decks where the immediate rewards are smaller but there is a low risk of punishment. Patients with bilateral damage to the ventromedial PFC do not acquire a preference for the safe decks on the Iowa Gambling Task, but instead prefer the risky decks for the duration of the task (Bechara et al., 1994, 2000). On the basis of these findings, ventromedial PFC has been posited to mediate the learning and retrieval of the affective information that guides decision-making (Damasio, 1994).

The Cambridge Gamble Task was developed to quantify decision-making outside of a learning context. The information needed to make each decision is presented to the subject on each trial, and hence the learning demand across trials is minimised. On each trial the subject first makes a relatively simple probabilistic judgment on whether a token is hidden under a red or a blue box. Ten boxes are presented in total on each trial, and the ratio of red to blue boxes varies across trials (9:1, 8:2, 7:3, and 6:4). Second, the subject is required to bet a proportion of their points total, reflecting their confidence in that judgment (see Fig. 1). The betting stage of the Cambridge Gamble Task provides a direct measure of high-risk behaviour, uncontaminated by learning. Fixed bets are offered to the subject in an ascending or descending sequence, and the subject must delay their response until the amount displayed is the amount they would like to bet. For example, in the ascending sequence, the first bet offered is very small and the amount increments every few seconds. The discrepancy between bets placed in the ascending and descending conditions provides an index of impulsivity: the impulsive subject may be less able to delay responding to place an appropriate bet, and therefore would be expected to place high bets in the descending condition, and low bets in the ascending condition. A non-impulsive subject, in contrast, would show similar betting in the ascending and descending conditions.

Four studies to date have examined performance on the Cambridge Gamble Task in patients with frontal lobe pathology affecting the ventral PFC. Increased betting relative to matched controls has been shown in patients with (1) subarachnoid haemorrhage of the anterior communicating artery, the blood vessel that supplies ventral PFC (Mavaddat, Kirkpatrick, Rogers, & Sahakian, 2000), (2) frontal variant fronto-temporal dementia (Rahman, Sahakian, Hodges, Rogers, & Robbins, 1999; described in more detail below), and (3) large prefrontal lesions including orbitofrontal cortex,

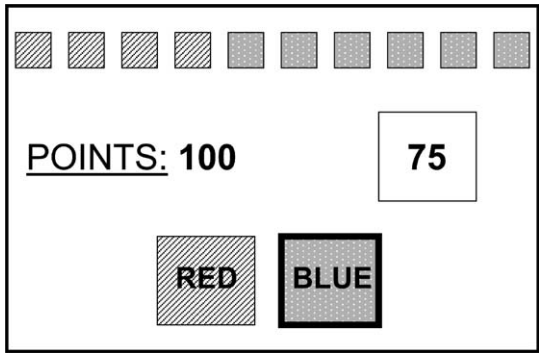

Fig. 1. A schematic representation of the computer screen display from the Cambridge Gamble Task. Subjects are presented on each trial with 10 red and blue boxes (in this example 4 are red and 6 are blue), where one box hides a token. They must first make a probabilistic judgment of whether they think the token is under a red or blue box (on the trial depicted they have selected BLUE). Latencies to make these judgments are recorded. Second, they must place a bet on their confidence in their red/blue decision. Bets are generated automatically by the computer in the box on the right side of the screen (reading 75 in the example). Bets are presented in an ascending or descending sequence, incrementing or decrementing in percentages of the points total every 5 s.

caused by haemorrhage or tumour resection (Manes et al., 2002). Whilst probabilistic judgment was at the level of healthy controls in these three studies, the latencies to make those judgments were increased in every study, plausibly reflecting an incipient deficit. In a fourth study, patients with prefrontal lesions including the orbital region showed poorer probabilistic judgment than brain-damaged controls without orbitofrontal damage, and placed lower bets (Rogers, Everitt, et al., 1999). Probabilistic judgment and betting on the task therefore appear to be closely linked, and this relationship is consistently disrupted by damage to ventral prefrontal cortex.

2.2. Functional neuroimaging studies

Functional neuroimaging provides a valuable convergent methodology for investigating the neural mechanisms of decision-making, because lesions in patient studies are rarely discrete, and the degree of functional reorganisation post-lesion cannot be quantified. Ventral prefrontal cortex involvement in the Cambridge Gamble Task is supported by two PET studies that used an adapted version of the task emphasising the conflict between probability and reward (Rogers, Owen, et al., 1999; Rubinsztein et al., 2001). On each trial, the subject was required to make a probabilistic judgment where the less likely option was always associated with a higher bet. Contrasts of the decision-making condition with a visuo-motor control task revealed significant activations in ventral prefrontal cortex including the orbitofrontal gyrus (Rogers, Owen, et al., 1999).

In a PET study using the Iowa Gambling Task (Ernst et al., 2002), a subtraction analysis of decision-making minus control task revealed more widespread frontal activations in orbitofrontal, anterior cingulate, and dorsolateral PFC. However, the control condition in this study entailed the selection of cards in a specified order (i.e., A B C D A B C D), from four decks matched in terms of gains and losses. The decision-making minus control comparison therefore included the processing of magnitudes, probabilities, and delays to both rewards and punishments, but also more generic processing including learning and behavioural adaptation. It is hardly surprising that this contrast activated a large frontal network. In the same study, task performance (the number of non-risky decisions) correlated with the neural response in a more discrete network comprising ventrolateral PFC and caudate nucleus (Ernst et al., 2002). The study therefore provides further evidence for ventral PFC involvement in decision-making, but also highlights the potential non-selectivity of the Iowa Gambling Task in a neuropsychological setting, given the widespread frontal recruitment demonstrated in the subtraction analysis.

2.3. Animal lesion studies

Decision-making in rodents is assessed using the delayed reward paradigm, where the animal discriminates between a small reward (e.g., a single food pellet) available immediately and a larger reward (e.g., two food pellets) available after a delay. Impulsive responding can be quantified in rodents by their preference for the small immediate reward. In a variation of the task, the larger reward may be available at a reduced probability rather than a delay. The delay to, or probability of, the larger reinforcer can be varied over blocks to ascertain the point at which preference switches from the large to the small reinforcer, or varied over trials using an adjusting procedure to calculate an indifference point (Mazur, 1987). Whilst this paradigm is far simpler than tasks used to assess decision-making in humans, it nonetheless requires the animal to use recent experience of reward to guide the ongoing selection between options varying in terms of either delay or probability.

Orbitofrontal cortex lesions in rodents increased the preference for small immediate rewards over delayed rewards, and increased preference for a small, certain reinforcer over a larger uncertain reinforcer (Mobini et al., 2002). In these experiments, quinolinic acid lesions to orbitofrontal cortex were administered prior to training on the task, and hence the findings resemble Bechara's data in emphasising the role of learning in decision-making. Lesions of the nucleus accumbens (part of the ventral striatum) also increased responding to the small immediate reward, contrasting with unchanged performance following lesions of the medial PFC or anterior cingulate cortex (Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001). The nucleus accumbens is reciprocally connected with the orbitofrontal cortex, which may indicate that rather than functioning in isolation, fronto-striatal interactions of orbitofrontal cortex and nucleus accumbens may contribute to effective decision-making.

2.4. Psychopharmacological studies

The delayed reward paradigm has been used to investigate the role of 5-HT neurotransmission in decision-making, given the association between impulsivity and reduced 5-HT function (Soubrie, 1986). Selective lesions of the ascending 5-HT projection using the neurotoxin 5,7-dihydroxytryptamine were reported to increase impulsive responding by reducing the indifference delay (Mobini, Chiang, Ho, Bradshaw, & Szabadi, 2000). Conversely, responding to the small, immediate reward was decreased in rodents by administration of 5-HT reuptake inhibitors (Bizot, Thiebot, Le Bihan, Soubrie, & Simon, 1988) and the 5-HT releasing agent fenfluramine (Poulos, Parker, & Le, 1996; Soubrie, 1986). Administration of fenfluramine to human

subjects with conduct disorder also reduced impulsive responding on a delayed reward task based on the animal paradigm (Cherek & Lane, 2000). The specificity of 5-HT effects to delay-related decision-making remains unclear. 5-HT neurotoxic lesions in the rat did not affect discrimination between probabilistic reinforcers (Mobini et al., 2000), but in human volunteers, acute dietary depletion of tryptophan, the precursor of 5-HT, reduced betting, and impaired probabilistic judgment on the Cambridge Gamble Task, with a profile resembling the effect in orbitofrontal patients (Rogers, Everitt, et al., 1999).

There is a smaller corpus of research investigating dopamine modulation of decision-making. Using the adjusting procedure in rodents, Wade, de Wit, and Richards (2000) showed increases in the indifference delay following administration of amphetamine, and decreases with dopamine D_2 antagonists flupenthixol and raclopride. Reduced preference for the small, immediate reward following amphetamine was replicated recently in humans by de Wit, Enggasser, and Richards (2002). Our own data show that the effects of D-amphetamine on delayed choice in rats can be complex, depending on how well the delayed reinforcer is signalled to the rat by conditioned reinforcement (Cardinal, Robbins, & Everitt, 2000). Thus, under conditions of weak stimulus control by a conditioned reinforcer, D-amphetamine enhanced choice of the small, immediate reward, but under strong stimulus control, choice of the delayed reward was enhanced. These combined data indicate that the choice between delayed rewards is clearly modulated by dopamine, and as discussed in more detail below, we have recently found that L-DOPA medication in Parkinson's disease increases impulsive responding on the Cambridge Gamble Task, whilst improving performance on a measure of task switching sensitive to dorsolateral PFC function.

2.5. Specificity of decision-making effects to ventral prefrontal cortex

Accumulating evidence from functional imaging and animal lesion studies indicates that ventral prefrontal cortex is part of an extended neural circuit mediating decision-making, rather than operating in isolation. In view of recent models of fronto-striatal connectivity, the role of the basal ganglia in human decision-making has been investigated in a number of studies. In Parkinson's disease, where neurodegeneration in the early stages primarily affects the dorsal striatum, Iowa Gambling Task performance was reported in the normal range (Czernecki et al., 2002; Stout, Rodawalt, & Siemers, 2001), although Czernecki et al. (2002) found that patients with Parkinson's disease failed to show a practice effect in a second test session, unlike controls. The profile in Huntington's disease is less clear, as one study using the Iowa Gambling Task showed deficits relative to controls (Stout et al., 2001) whereas a study using the Cambridge Gamble Task showed intact performance (Watkins et al., 2000). As discussed below, the medication status of patients and the stage of the illness may be critical determinants of the neuropsychological profile in these disorders.

The amygdala is a further structure implicated in decision-making circuitry. Iowa Gambling Task deficits are pronounced in patients with amygdala damage, although these patients show a dissociable autonomic profile. Whereas control subjects performing the Iowa Gambling Task developed an 'anticipatory' skin conductance response (SCR) prior to selection from the risky decks (Bechara, Tranel, Damasio, & Damasio, 1996), patients with amygdala lesions did not acquire anticipatory SCRs and showed blunted SCRs to punishing feedback (Bechara, Damasio, Damasio, & Lee, 1999). Patients with ventromedial PFC lesions also failed to acquire anticipatory SCRs to the risky decks, but show comparable SCRs to controls in response to punishing feedback (Bechara et al., 1996). This suggests that at a cognitive level, ventromedial PFC patients experience reward and punishment normally, but are unable to use the experiences to guide future behaviour, whereas following amygdala damage, patients show decision-making deficits due to blunted emotional responses in the initial processing.

The specificity of decision-making deficits within prefrontal cortex is a critical issue in clinical studies. Performance on the Iowa Gambling Task and Cambridge Gamble Task was intact in two studies in patients with lesions restricted to dorsolateral and dorsomedial PFC (Bechara, Damasio, Tranel, & Anderson, 1998; Rogers, Blackshaw, et al., 1999). However, in a subsequent study, Iowa Gambling Task deficits were demonstrated in patients with discrete dorsolateral PFC lesions, discrete dorsomedial PFC lesions, and large prefrontal lesions including both dorsal and ventral aspects (Manes et al., 2002). Cambridge Gamble Task performance was unimpaired in the dorsolateral and dorsomedial groups (Manes et al., 2002). At least two factors may have contributed to the discrepancies between these reports. First, preliminary evidence indicates that right-sided lesions may impair decision-making to a greater extent than left-sided lesions (Clark, Manes, Antoun, Sahakian, & Robbins, 2003; Tranel, Bechara, & Denburg, 2002), and there was a relatively high proportion of right-sided patients in the impaired groups in the Manes et al. (2002) report. The second factor is the level of background neuropsychological functioning: patients in the Manes et al. report had deficits in planning, set-shifting, and working memory, which may all contribute to Iowa Gambling Task deficits. In the study by Bechara et al. (1998) only a subgroup of the dorsal patients had working memory problems, and

other aspects of executive function were not reported. Executive problems may be less likely to disrupt performance on the Cambridge Gamble Task because of the independent-trial structure, and this may be consistent with the findings of Manes et al. (2002) that discrete dorsolateral and dorsomedial groups are impaired on the Iowa Gambling Task but intact on the Cambridge Gamble Task.

In summary, there is converging evidence from human lesion, animal lesion, and human functional imaging studies that decision-making measures are sensitive to damage in ventral prefrontal cortex, and that ventral prefrontal cortex is activated during healthy decision-making and correlates with task performance. However, there are remaining concerns about the neuropsychological selectivity of the existing decision-making measures, given the complex structure of decision-making as well as the involvement of extraneous cognitive processes such as learning and behavioural adaptation. It is necessary to demonstrate that levels of background neuropsychological functioning are intact in order to infer ventral PFC, rather than dorsal PFC, mediation of decision-making deficits. Ventral prefrontal cortex may mediate decision-making through its connectivity with the amygdala and nucleus accumbens, and there is accumulating evidence for the contribution of the 5-HT and dopamine neurotransmitter systems.

3. The cognitive neuroscience of reversal learning

Reversal learning involves the adaptation of behaviour according to changes in stimulus–reward contingencies, a capacity relevant to social and emotional behaviour (Rolls, 1999). It is exemplified by visual discrimination tasks where subjects must learn to respond according to the opposite, previously irrelevant, stimulus–reward pairing. Impaired reversal learning has been attributed to the loss of inhibitory control of affective responding (Dias, Robbins, & Roberts, 1996). As such, deficits in reversal learning may be related to the impairments described above on decision-making tasks, measuring risk-taking and impulsive responding. Below we review converging evidence from studies in rodents, primates and human subjects, for the involvement of ventral prefrontal cortex and ventral striatum in reversal learning, and in addition, we highlight parallels between findings in humans using measures of decision-making and reversal learning.

3.1. Animal lesion studies

Reversal learning is disrupted by lesions of the orbitofrontal cortex in rodents and non-human primates (Butter, 1969; Dias et al., 1996; Iversen & Mishkin, 1970; Jones & Mishkin, 1972). This deficit has been characterised in part as a perseverative response tendency to the previously relevant stimulus, reflecting persistent interference from a prepotent response, as well as impaired new stimulus–reward learning. It is accompanied by disinhibitory impairments on Go/NoGo discrimination (Iversen & Mishkin, 1970; Jones & Mishkin, 1972; Meunier, Bachevalier, & Mishkin, 1997) and deficits in extinction, where the animal continues to respond to a stimulus that is no longer rewarded (Butter, 1969). Single-cell recording studies have confirmed that the firing of orbitofrontal neurons changes with alterations in the reward contingencies. Thus, the response of a neuron in the macaque orbitofrontal cortex was shown to reverse from firing to a previously rewarded stimulus to a newly rewarded stimulus (Rolls, Critchley, Mason, & Wakeman, 1996; Thorpe, Rolls, & Maddison, 1983).

A perseverative response tendency following ventral prefrontal damage contrasts with an impairment in stimulus–reward learning observed following temporal lobe lesions, including the amygdala (Jones & Mishkin, 1972), and spatial working memory deficits observed following lesions to dorsolateral parts of the prefrontal cortex (Goldman Rakic, 1987). A double dissociation between reversal learning and higher-level attentional set shifting has been shown in marmosets using the Intra-dimensional/Extra-dimensional (ID/ED) shift test (Dias et al., 1996), a task designed to decompose the Wisconsin Card Sorting Test into its constituent elements (Downes et al., 1989). The deficit in reversal learning following orbitofrontal damage was accompanied by intact performance on attentional set shifting (extra-dimensional (ED) shifting). Conversely, lesions of the marmoset lateral prefrontal cortex impaired ED set shifting whilst leaving reversal learning intact (Dias et al., 1996). These findings have led to the development of several models of segregated prefrontal cortex function (O'Reilly, Noelle, Braver, & Cohen, 2002), and are supported by recent evidence for a pharmacological double dissociation in patients with Parkinson's disease, using a reversal learning task and a high-level attentional shifting task, discussed below (Cools, Barker, Sahakian, & Robbins, 2001).

Neuroanatomical evidence indicates that strong topographical connections exist between the ventral parts of the prefrontal cortex and ventral parts of the striatum (including the ventral caudate nucleus and the nucleus accumbens), in relatively segregated 'fronto-striatal loops' (Alexander, DeLong, & Strick, 1986). In keeping with this evidence, lesions to the ventral striatum also disrupt reversal learning, leading to a perseverative response tendency (Annett, McGregor, & Robbins, 1989; Divac, Rosvold, & Szwarcbart, 1967; Stern & Passingham, 1995; Taghzouti, Louilot, Herman, Le Moal, & Simon, 1985). Like the orbitofrontal impairment, this deficit contrasts with a visual discrimination learning

impairment following lesions to the tail of the caudate nucleus (which is connected to the medial temporal lobe) (Divac et al., 1967). Moreover, single-cell studies have shown that neuronal responses in the ventral striatum reflect the output of orbitofrontal neurons (Rolls, Thorpe, & Maddison, 1983). It is hypothesised that the ventral striatum, integrating motivational information from the limbic system to the motor system (Mogenson, 1987), may mediate the effects of stimulus–reward associations and their changes in goal-directed behaviour (Robbins, Cador, Taylor, & Everitt, 1989; Rolls, 1999).

3.2. Human lesion studies

Reversal learning is disrupted in humans with frontal lobe lesions, who performed as well as control subjects on the initial acquisition of a visual discrimination (Daum, Schugens, Channon, Polkey, & Gray, 1991). Patients with temporal lobe lesions, in contrast, were impaired on the initial acquisition of a visual discrimination, whilst their performance on reversal learning was intact (Daum et al., 1991). The reversal deficit was further associated with ventral prefrontal cortex in a study by Rolls, Hornak, Wade, and McGrath (1994), who showed severe impairments on both reversal learning and extinction in patients with frontal damage including ventral prefrontal cortex, compared to a group of patients with frontal damage that did not include the ventral prefrontal cortex. The patients with ventral PFC damage exhibited a perseverative response tendency, paralleling the impairment of monkeys with orbitofrontal lesions (Jones & Mishkin, 1972), and the reversal deficit correlated with scores on a questionnaire assessing socially inappropriate behaviour (Rolls et al., 1994). The non-selectivity of the ventral lesions must be considered a limitation, and this study was also confounded by lesion laterality: 10 of 12 patients in the ventral group had right-sided or bilateral lesions, suggesting a laterality effect in the same direction as decision-making deficits. However, a recent report by Farah and Fellows (2003) confirmed reversal deficits in patients with focal ventral prefrontal lesions, and showed intact reversal performance in patients with focal dorsolateral PFC lesions. In a further study, a group of patients with frontal variant fronto-temporal dementia, who typically display disinhibited symptomatology, showed impairments in reversal learning (and decision-making) whilst showing intact performance on executive functions associated with the dorsolateral prefrontal cortex (Rahman et al., 1999).

3.3. Functional neuroimaging studies

The human lesion studies described above are limited by the non-selectivity of patients' lesions to ventral prefrontal cortex. Functional neuroimaging studies provide stronger evidence for the selective involvement of the ventral PFC in reversal learning, and concur with the evidence from animal studies that reversal learning implicates ventral fronto-striatal circuitry. Neuroimaging studies in healthy volunteers have previously associated the ventral prefrontal cortex and the ventral striatum with a variety of functions related indirectly to reversal learning, including unconditioned (Zald & Pardo, 1997) and conditioned reward processing (Berns, McClure, Pagnoni, & Montague, 2001; Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Knutson, Adams, Fong, & Hommer, 2001) and low-level inhibitory control (Garavan, Ross, & Stein, 1999; Konishi et al., 1999). To date, four neuroimaging studies have investigated neural responses during reversal learning tasks. Using fMRI, Nagahama et al. (2001) reported signal changes in posteroventral prefrontal cortex during reversal learning, which were accompanied by responses in the dorsolateral PFC during high-level set shifting, in an analogue of the Wisconsin Card Sorting Test. These authors did not scan the lower part of the brain (below the AC–PC axis), which precludes conclusions about the orbitofrontal cortex and the ventral striatum. O'Doherty, Kringelbach, Rolls, Hornak, and Andrews (2001) employed a reversal task to assess reward- and punishment-related responses using event-related fMRI, and reported effects in dissociable parts of the orbitofrontal cortex during reception of reward versus punishment. It was not possible to exclude the contribution of reversal learning to the punishment-related signal changes. A PET study by Rogers, Andrews, Grasby, Brooks, and Robbins (2000) scanned subjects on an analogue of the ID/ED shift task, with separate blocks of reversal learning and attentional set-shifting. Significant changes were observed in the dorsolateral prefrontal cortex during attentional set shifting, and in the ventral caudate nucleus during reversal learning. No blood flow changes were detected in prefrontal cortex during reversal blocks, but it is possible that the use of a blocked design, which necessitates the averaging of activity over an extended period of time, may have overlooked a transient reversal response in prefrontal cortex.

Given these limitations of existing imaging studies, we recently performed an event-related functional MRI study, in which 13 healthy volunteers were scanned on a serial reversal learning task (Cools, Clark, Owen, & Robbins, 2002) to test directly the hypothesis that reversal learning in humans implicates ventral fronto-striatal circuitry. A difficult probabilistic task was employed, where subjects received negative feedback to correct responses on a minority of trials. Following contingency reversal, subjects made on average approximately three perseverative errors before reversing. The use of an event-related design enabled the separate investigation of distinct error trial types that loaded differentially on reversal shifting and simple negative feedback. Significant signal changes were shown in the

ventrolateral prefrontal cortex and the ventral striatum. The ventrolateral PFC response was stronger in the right hemisphere but also clearly present in the corresponding region of the left hemisphere (see also Nagahama et al., 2001). Region of interest analyses showed that these signal changes were significantly greater during the final reversal errors, which directly preceded a shift of responding to the newly relevant stimulus. Negative feedback without reversal was not associated with significant signal changes in this circuitry. These results suggest that the response in ventral fronto-striatal circuitry is primarily attributable to reversal learning and cannot be explained by an effect of negative feedback or punishment.

3.4. Psychopharmacological studies

There is accumulating preclinical evidence for the modulation of reversal learning by both dopamine and 5-HT neurotransmission. Dopaminergic lesions of the nucleus accumbens using the neurotoxin 6-OHDA impaired reversal learning in rodents (Taghzouti et al., 1985), but in marmosets, stimulation of the dopamine system with amphetamine induced perseverative responding on a reversal task, and this effect was prevented by pre-treatment with the D_2 antagonist haloperidol (Ridley, Haystead, & Baker, 1981). Administration of the dopamine D_3 receptor agonist 7-OH-DPAT also disrupted reversal learning in marmosets, which was reversed by the D_2/D_3 antagonist raclopride (Smith, Neill, & Costall, 1999). Initial acquisition of the visual discrimination was unimpaired by 7-OH-DPAT (Smith et al., 1999). These data are consistent with recent theorising that the mesocorticolimbic dopamine system is critical for reward-related learning and behavioural adaptation (Robbins et al., 1989; Schultz, 2002; Schultz, Apicella, Scarnati, & Ljungberg, 1992).

Recent data from an L-DOPA withdrawal study in patients with Parkinson's disease indicate that functional overactivity of the dopamine system also impairs reversal learning in humans (Cools et al., 2001; Swainson et al., 2000). Parkinson's patients suffer from dopamine depletion mainly in the dorsal parts of the striatum, leading to severe motor disturbance and subtle cognitive deficits. Although L-DOPA consistently remediates the motor symptoms and indeed some cognitive deficits (Lange et al., 1992), it may have *detrimental* effects on other cognitive functions. The data showed that withdrawal of L-DOPA medication was associated with significantly impaired performance on a task of attentional shifting, but ameliorated deficits on a task of probabilistic reversal learning (Cools et al., 2001). Thus, L-DOPA had a detrimental effect on reversal learning, whilst ameliorating a high-level task-shifting deficit. This detrimental effect of L-DOPA was hypothesised to be a result of 'overdosing' ventral fronto-striatal circuitry, given neuropathological evidence that, at least in the early stages of the disease, dopamine depletion is restricted to the dorsal parts of the striatum and its connections to the dorsolateral PFC, whilst the ventral striatum and its connections to the ventral PFC are relatively intact (Kish, Shannak, & Hornykiewicz, 1988). The data are consistent with a further study by Mehta, Swainson, Ogilvie, Sahakian, and Robbins (2001) who showed that administration of the dopamine D_2 agonist bromocriptine in healthy volunteers impairs performance on the probabilistic reversal learning task, whilst improving performance on a spatial memory task. Together, these data concur with the animal studies, indicating that both insufficient as well as excessive levels of dopamine may impair cognitive function, including reversal learning (Arnsten, 1998; Ridley et al., 1981; Zahrt, Taylor, Mathew, & Arnsten, 1997).

In keeping with the mutual antagonism between the mesocorticolimbic dopamine and 5-HT systems (Millan, Dekeyne, & Gobert, 1998), reversal learning is also significantly modulated by 5-HT manipulations in animals (Barnes et al., 1990; Domeney et al., 1991; King, Martin, & Melville, 1974; Nomura, 1992). Thus, a reversal learning impairment was found in serotonin-depleted rats (Nomura, 1992) and administration of high doses of the 5-HT_3 receptor antagonist, ondansetron, impaired reversal learning in marmosets, whilst low doses of the same drug improved performance (Domeney et al., 1991). However, these effects were not specific to reversal learning, but extended to learning the initial discrimination. In aged monkeys, ondansetron enhanced the acquisition of a visual discrimination but did not affect reversal learning (Arnsten, Lin, Van Dyck, & Stanhope, 1997).

Consistent with animal studies, two studies in healthy human volunteers showed that 5-HT suppression by acute tryptophan depletion impairs reversal learning on the ID/ED shift task (Park et al., 1994; Rogers, Blackshaw, et al., 1999). In both studies, performance on tasks associated with the dorsolateral prefrontal cortex was relatively intact; for example, ED shifting in the Rogers, Blackshaw, et al. (1999) study. Response latencies on the probabilistic reversal learning task were also significantly increased following tryptophan depletion in healthy volunteers (Murphy, Smith, Cowen, Robbins, & Sahakian, 2002). However, consistent with animal studies using 5-HT manipulations, the effect generalised to the initial visual discrimination acquisition stage.

To summarise, a wealth of data support the involvement of ventral prefrontal cortex, through interaction with the ventral striatum, in reversal learning. As with the evidence reviewed above for decision-making, dopamine and 5-HT manipulations have been shown to modulate reversal learning, although the effects for 5-HT may be generalised effects on learning, rather than

reversal learning per se. The effect of ventral prefrontal lesions on reversal learning has been dissociated from the effects of lateral prefrontal lesions on higher-level attentional set shifting (Dias et al., 1996), and from the effects of medial temporal lesions on the initial acquisition of the visual discrimination (Daum et al., 1991; Jones & Mishkin, 1972). Dopamine modulation has also been demonstrated to have contrasting effects on reversal learning, and attentional shifting and working memory (Cools et al., 2001; Mehta et al., 2001). Reversal learning tasks may therefore exhibit a higher degree of neuropsychological selectivity relative to measures of decision-making that have been discussed above, and this may prove pertinent in neuropsychological studies attempting to characterise prefrontal cortex function in psychiatric disorders.

4. The development of decision-making and reversal learning

The current interest in the neural mechanisms of decision-making and reversal learning has been based largely upon adult neuropsychological cases, and lesion studies in non-human primates, respectively. The development of these cognitive domains has only recently begun to be investigated. One issue (see also Bechara, this issue; Machado & Bachevalier, 2003) is whether the degree of cognitive dysfunction following developmental damage to orbitofrontal cortex is more, or less, severe than that following lesions in adulthood. The high degree of plasticity known to exist in, for example, the language system may not generalise to the neural circuitry controlling social cognition; indeed developmental damage may lead to qualitatively more severe impairment than damage in adulthood (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999). The same theoretical issues surround the long-term effects of pharmacological manipulations on the developing brain. This applies both to the recreational use of substances of abuse during adolescence, and also to the effects of daily treatment with drugs such as methylphenidate, prescribed increasingly for Attention Deficit Hyperactivity Disorder (ADHD) to young children. Controversial links have been made between methylphenidate treatment and substance abuse later in life (cf. Robbins, 2002), and the persistence of ADHD symptoms into adulthood (DeGrandpre, 2000). Cognitive assays of ventral prefrontal function—both in humans and non-human species—will be critical for the successful dissection of the many causative factors in this field.

In human neuropsychological research, a fundamental issue is whether the same tasks can be used to assess decision-making and reversal learning in children and adolescents as in adults. Ernst et al. (2003) administered the Iowa Gambling Task to healthy 12–14 year old adolescents and healthy adults aged 21–44. Both groups developed a preference for the safe decks over the course of the task, and there were no significant differences between the two groups. However, the adolescents selected more risky cards on average, and in a study by Blair, Colledge, and Mitchell (2001) using a wider age range (9 to 17 years), the number of risky choices was negatively correlated with age. In these two studies, Iowa Gambling Task deficits were shown in boys with psychopathic tendencies (Blair et al., 2001), but not in adolescents with behavior disorders at assumed high-risk for substance abuse (Ernst et al., 2003). Researchers should consider using age as a covariate in future studies of decision-making in young groups.

The simpler tasks used to measure reversal learning should be more amenable to administration in child and adolescent groups. Whilst no studies to date have validated any reversal measures in children against an adult population, reversal learning on the ID/ED task is in the range of healthy adults and does not correlate with age (Blair et al., 2001). Kodituwakku, May, Clericuzio, and Weers (2001) reported no association between age and reversal errors in children and adolescents aged 7–19, on the task used by Rolls et al. (1994) with modified instructions. Reversal learning (and extinction) deficits were shown on the same task in children with Attention Deficit Hyperactivity Disorder (Itami & Uno, 2002), and using a discriminant function analysis, this study showed that reversal and extinction errors correctly classified 79% of ADHD children and 100% of controls. Whilst there is no direct evidence that ventral prefrontal cortex is recruited during reversal learning and decision-making in adolescents, it would appear that the measures used in adult research can be employed in adolescent groups with similar sensitivity.

5. Synthesis

The ability to update and correct behaviour on the basis of changes in emotional significance is critical to performance on both reversal learning and decision-making tasks (see also Rolls, 1999). Reversal learning by definition involves a shift of responding from a stimulus that is no longer rewarded, to a previously unrewarded stimulus. In the context of the decision-making measures discussed above, the need for behavioural adaptation is more subtle and has previously been overlooked. Yet successful performance on the Iowa Gambling Task typically involves a shift in responding away from the risky desks that initially seem rewarding, but are gradually associated with high punishment, to the safe decks. As subjects begin to experience the contingencies of the different decks, responding to the risky decks may become prepotent, and thus inhibitory

control will be required to shift away from these stimuli. This process is directly comparable to the process implicated in the initial phase of reversal learning to suppress prepotent responding. In the Cambridge Gamble Task, both the probabilistic judgment and the betting decision involve the adaptation of behaviour, on a trial by trial basis, according to changes in emotional significance of the stimuli. A failure to adapt over trials may be associated with a reduced ability to moderate the bet according to the ratio of boxes ('risk adjustment'), or in more extreme cases, a perseverative tendency to select the same colour regardless of the ratio of red and blue boxes.

Multiple parallels exist between the effects on reversal learning and decision-making, which support the hypothesis that these paradigms measure closely related constructs. A small number of studies in neurological and psychiatric groups have demonstrated parallel effects on tests of reversal learning and decision-making in the same patients. As mentioned previously, Rahman et al. (1999) showed that frontal variant Fronto-Temporal Dementia is characterised by increased betting on the Cambridge Gamble Task, and impaired reversal on the ID/ED shift task, in the presence of intact performance on ED shifting and other dorsolateral PFC measures. Symptomatology in frontal variant Fronto-Temporal Dementia resembles the disinhibition syndrome seen after lesions to orbitofrontal cortex (Gregory & Hodges, 1996), and preliminary structural imaging evidence indicates that neurodegeneration preferentially affects the ventral aspects of prefrontal cortex in this condition (Gregory, Serra-Mestres, & Hodges, 1999; Lough & Hodges, 2002).

A combined impairment in decision-making and reversal learning was also observed in a recent study on psychopathic individuals (Mitchell, Colledge, Leonard, & Blair, 2002), who selected more cards from the risky decks on the Iowa Gambling Task, and made more reversal errors on the ID/ED task. Thus, psychopathic individuals did not adjust their behaviour to avoid making risky decisions and they did not shift their responding when the previously rewarded stimulus was no longer rewarded. ED shifting performance was at the level of controls in this study. Iowa Gambling Task deficits have also been reported in subclinical psychopathy (van Honk, Hermans, Putman, Montagne, & Schutter, 2002) and Intermittent Explosive Disorder (Best, Williams, & Coccaro, 2002). Whilst there are numerous case reports of acquired psychopathy secondary to orbitofrontal damage (Damasio, Tranel, & Damasio, 1990), there is limited evidence at present for prefrontal structural abnormalities in subjects with non-organic psychopathy (Laakso et al., 2002; Raine, Lencz, Bihrle, LaCasse, & Colletti, 2000).

Decision-making deficits have been reported in a number of recent studies in substance abusers, and this may pertain to why chronic drug users persistently select an immediately rewarding option (i.e., drug administration) despite the large long-term negative implications for their health and finances. Iowa Gambling Task deficits have been reported in several groups of substance abusers, and these deficits are, to a large extent, irrespective of the substance abused (Bechara & Damasio, 2002, reviewed by Clark & Robbins, 2002). Whilst widespread cognitive impairment has been shown in severe, chronic abusers (Mintzer & Stitzer, 2002; Ornstein et al., 2000), one of the best-controlled studies to date in abstinent polydrug users has shown decision-making impairment in combination with normal performance on the Wisconsin Card Sort Test and measures of background intellectual functioning (Bechara & Damasio, 2002). Moreover, a study in cocaine addicts (Monterosso, Ehrman, Napier, O'Brien, & Childress, 2001) has provided important validatory evidence that the Iowa Gambling Task, the Cambridge Gamble Task, and the delayed reward procedure are inter-correlated and therefore may be measuring the same construct.

Reversal learning, in contrast, has been largely overlooked in research on substance abuse in humans and constitutes a target for future research. Jentsch, Olausson, De La Garza, and Taylor (2002) have shown that the repeated administration of cocaine to monkeys results in reversal learning deficits that persist even after 30 days withdrawal. Whilst drugs of abuse have complex pharmacological actions that differ widely between drugs, one shared action of drugs of abuse is to increase dopamine levels in the nucleus accumbens (Di Chiara et al., 1999; Wise, 1993). Long-term neuroadaptations to drug use may be associated with persisting deficits in cognitive functions dependent upon this area and affiliated circuitry. Functional alterations in ventral striatum, orbitofrontal cortex, and amygdala have been shown in substance abusers both at rest and after cue-induced craving (Goldstein & Volkow, 2002). Chronic stimulant abuse has also been associated with orbitofrontal degeneration at postmortem (Wilson et al., 1996). It is possible that in addition to the neurotoxic effects of drug abuse, there may be a pre-existing orbitofrontal disruption that conveys vulnerability to abuse of a range of substances. Cognitive markers of orbitofrontal function provide a direct method of testing these hypotheses in high-risk populations.

Comparable effects on decision-making and reversal learning have been demonstrated at the psychopharmacological level. As discussed above, acute dietary tryptophan depletion, decreasing 5-HT neurotransmission, selectively impaired reversal learning on the ID/ED shift task (Park et al., 1994; Rogers, Blackshaw, et al., 1999), and decreased betting and impaired probabilistic choice on the Cambridge Gamble Task (Rogers, Everitt, et al., 1999). We have also recently demonstrated

comparable effects of a dopaminergic manipulation on reversal learning and decision-making, using the L-DOPA withdrawal technique in patients with mild Parkinson's disease. In the study described above (Cools et al., 2001), we showed that patients on L-DOPA medication exhibit impaired probabilistic reversal learning, but improved task switching compared with patients off medication. In a follow-up study (Cools, Barker, Sahakian, & Robbins, 2003) using a within-subjects design, we showed that L-DOPA medication induced impulsive responding on the Cambridge Gamble Task: patients on medication placed their bets more quickly following their red/blue decision than both patients off medication and control subjects. This increased impulsivity was accompanied by improved task switching, as in the previous study. L-DOPA-induced impairments in reversal learning may therefore generalise to abnormal behaviour on a decision-making paradigm also associated with ventral prefrontal cortex.

To our knowledge, dissociable effects of reversal learning and decision-making have been reported in only two studies to date. In an independent study assessing the effects of L-DOPA medication in patients with Parkinson's disease, Czernecki et al. (2002) reported that L-DOPA treatment increased perseverative responding on a task of extinction, improved reversal performance, and did not affect the Iowa Gambling Task. Nonetheless, reversal learning was shown to correlate with Iowa Gambling Task performance. The use of a within-subjects design with tasks placing such a high demand on learning may account for these discrepant findings, and the longer disease duration in this sample (mean 14.9 years, presumably associated with depletion of more ventral brain areas) compared with the patients in our studies (Cools et al., 2001, 2003) may explain the discrepancy with our own data.

A second recent report in boys with psychopathic tendencies identified a further dissociation, with these subjects making more risky selections on the Iowa Gambling Task but showing intact reversal learning on the ID/ED task (Blair et al., 2001). A study in adult psychopaths from the same research laboratory (Mitchell et al., 2002) reported a dual impairment on the same two tasks. The authors hypothesise that this distinct result between boys and adults may be a consequence of developmental differences in the degree of orbitofrontal cortex impairment, and implies reduced sensitivity of reversal learning relative to the Iowa Gambling Task (see also Blair, this issue). This difference in sensitivity may be due to the probabilistic nature of the Iowa Gambling Task. On the ID/ED reversal stages, responses to the previously rewarded stimulus are punished on 100% of trials following contingency reversal, making the need for behavioural adaptation very salient. On the Iowa Gambling Task, in contrast, choices of disadvantageous decks are punished on only a proportion of trials, and therefore the cues to adapt are more subtle (Blair et al., 2001). This hypothesis would predict that a probabilistic reversal learning task, such as that used by Swainson et al. (2000), Cools et al. (2001), Rogers, Blackshaw, et al. (1999), and Murphy et al. (2002) may be more sensitive to orbitofrontal disruption and may provide more comparable data to the decision-making measures (Blair et al., 2001).

In conclusion, lesions of the ventral prefrontal cortex, including orbitofrontal cortex, impair reversal learning and decision-making performance in both humans and animals. Functional neuroimaging studies provide convergent evidence, demonstrating ventral prefrontal cortex responses during performance of decision-making and reversal learning tasks in healthy human subjects. The ascending dopamine and 5-HT systems contribute to both reversal learning and decision-making, and these cognitive functions of ventral prefrontal cortex are likely to be mediated through interaction with the amygdala and ventral striatum. Measures of decision-making and reversal learning may therefore represent neuropsychological 'assays' for investigating the integrity of this neural circuitry in psychiatric and neurological disorders. There is preliminary evidence that measures of decision-making may provide a higher degree of sensitivity in clinical populations compared to measures of simple reversal learning such as the ID/ED shift task (Blair et al., 2001; Mitchell et al., 2002). However, this consideration may trade off against the improved selectivity of reversal learning tasks, particularly within prefrontal cortex, given the complex executive contributions to existing measures of decision-making. The introduction of a probabilistic component to reversal learning tasks may reduce the saliency of the serial reversal shifts, and thus increase sensitivity without affecting selectivity.

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