Decision making and neuropsychiatry

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Abnormal decision making is a central feature of neuropsychiatric disorders. Recent investigations of the neural substrates underlying decision making have involved qualitative assessment of the cognition of decision making in clinical lesion studies (in patients with frontal lobe dementia) and neuropsychiatric disorders such as mania, substance abuse and personality disorders. A neural network involving the orbitofrontal cortex, ventral striatum and modulatory ascending neurotransmitter systems has been identified as having a fundamental role in decision making and in the neural basis of neuropsychiatric diseases. This network accounts for the dissociations among decision-making deficits in different clinical populations. Ultimately, a more refined and sophisticated characterization of such deficits might guide the early diagnosis and cognitive and therapeutic rehabilitation of these patients.

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Abnormal decision making has been demonstrated to lie at the core of several common neuropsychiatric disorders ranging from substance abuse to mania. Crucially, these deficits can all be explained within a unified theoretical framework.

Reports of the detrimental effects of brain lesions upon decision making have existed since the classic neurological case of Phineas Gage, arguably the earliest recorded case of 'acquired sociopathy'[1,2]. Patients with injury to the prefrontal cortex (PFC) engage in decisions and behaviours that have repeated negative consequences for their wellbeing[3–5]. They act as though they have lost the ability to ponder different courses of action and to select the one that promises the best balance of short- and long-term benefit. They also have difficulty in planning and organizing their own lives and tend to make poor decisions about friends, business associates and day-to-day activities. Specifically, patients with lesions of the orbitofrontal region of the prefrontal cortex (OFC) exhibit profound personality changes, problems with self-conduct, difficulties with emotional reactions to sensory stimuli, difficulties with social interactions, and problems making decisions within the context of their everyday lives. All this is in the conspicuous absence of the marked cognitive deficits more frequently shown by patients with damage to dorsal areas of PFC (Refs 6–8).

Recent research has been advanced significantly by the demonstration that patients exhibiting 'acquired sociopathy' following orbitofrontal damage also show consistent deficits on a laboratory 'gambling task' involving choices between actions that differ in terms of the size and probabilities of their associated punishments and rewards[9,10]. It has, however, only recently been realized that an understanding of the neural substrates can be applied to clinical disorders, and attempts are now being made to compare the nature of the decision making in these disorders.

The complexity of decision-making processes means that deficits in decision-making cognition can be manifested in several ways. An individual might take a protracted time to make a decision, allocate an inappropriate amount of resources to a given decision or tend to make decisions that are unlikely to produce the desired outcome. For example, one deficit demonstrated by patients with orbitofrontal lesions is a very large increase in deliberation times associated with their decisions[11]. These data reflect the clinical observation that such patients take protracted times to make decisions in their day-to-day lives, and confirm that damage to the OFC is especially associated with decision-making deficits when there is limited contextual information to assist the identification of the optimal response. The slow, ineffective deliberation between choices suggests that the OFC does not mediate a simple inhibitory mechanism. Significantly, in a decision-making task that we have developed, in which subjects place bets with different odds of success (Box 1), OFC-lesioned patients risk significantly less of their accumulated reward than controls at the more favourable odds. Damage to the OFC can thus lead to a pattern of conservative behaviour rather than a pattern of gambling and risk-taking decisions; these patterns are therefore dissociable. A key point regarding this result is that patients with lesions to more dorsal areas of PFC appear to be unaffected in such decision making. Instead, the dorsolateral PFC has repeatedly been shown to mediate important aspects of the executive control of behaviour, such as working memory, planning and attention[12–14]. These findings emphasize functional as well as structural differences between different areas of PFC.

The decision-making task shown in Box 1 has been applied successfully to several different neuropsychiatric disorders and has the particular advantage of having been validated through functional neuroimaging, as well as lesion studies. A recent PET study of decision-making cognition required subjects to 'gamble' accumulated reward on predictions about which of two mutually exclusive outcomes would occur[15]. Critically, the largest reward was always associated with the least likely of the two outcomes, ensuring an element of conflict inherent in risk-taking. Resolving these decisions was associated with three distinct foci of activation

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Box 1. Neurocognitive assessment of decision making

To assess decision making in the laboratory, we have developed a computerized decision-making task[a] (Fig. I). Subjects are told that the computer has hidden a yellow token at random inside one box of a configuration of red and blue boxes. The subjects first have to decide in what colour box the token has been hidden, before attempting to increase their points by betting on whether or not they believe their choice to be correct. There are two betting conditions: (1) the bet on offer either ascends or descends, and (2) the subjects touch the screen when they are happy with the bet on offer. One of the boxes at the top of the display then opens to reveal the actual location of the yellow token and the chosen bet is added to or subtracted from the total points score, according to whether the initial colour decision was correct. Subjects are given 100 points at the beginning of each block of trials and, although no real monetary significance is attached to the points accumulated by the end of the task, subjects are encouraged to treat the points as valuable and to accumulate as many as possible. If a subject's score falls to just 1 point, the current block terminates and the next begins.

This computerized task provides explicit information about the relative attractiveness of two mutually exclusive response options. It has a lighter load on 'working memory' than other decision-making tasks because it is less dependent on the outcome of previous trials. By using information presented in a readily comprehensible visual format, this task allows subjects to choose what they perceive to be the most likely outcome and, importantly, to state how much they are prepared to bet that they are correct. In real life, this relates to the need to weigh-up available opportunities, judge the relative probabilities of a successful outcome and then choose how much current resources or reward should be committed to the chosen strategy.

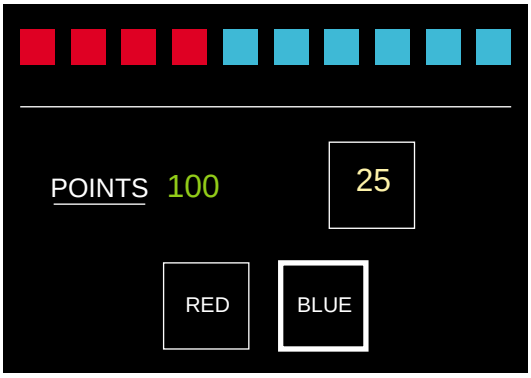

Fig. I. View of the screen in a task used to assess decision-making cognition in healthy volunteers and patient groups. (See text for details.)

Reference

a Rogers, R.D. *et al.* (1999) Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. *Neuropsychopharmacology* 20, 322–339

within the right inferior and orbital PFC (Fig. 1): (1) laterally in the anterior part of the middle frontal gyrus, (2) medially in the orbital gyrus and (3) posteriorly in the anterior portion of the inferior frontal gyrus.

By contrast, increases in the degree of conflict associated with these decisions were associated with increased activity within the anterior cingulate cortex, together with only limited, mainly left-sided, changes in orbital PFC activity. Choices in this study were not associated with any significant changes in neural activity within dorsolateral prefrontal areas, consistent with the findings from brain-damaged patients[11]. Elucidation of the neural substrates underlying decision making using these different neuroscientific techniques is clearly essential to understand decision-making abnormalities in neuropsychiatric disorders.

Somatic markers

To explain the dissociation between personal decision-making ability and other aspects of cognition, markers or biasing factors in humans have been postulated to act in normal cognition to enhance decision making[10]. For the brain to compute expected utilities accurately (as a computer might) would take a finite time; it is better to make an imperfect decision quickly than eventually to make what would have been the perfect decision. Damasio has argued that 'somatic markers' provide a way of speeding up decision making[7]. Somatic markers are signals relating to body states (in other words, representations of the body itself) that are acquired early in the sampling of novel action–outcome contingencies. Once retrieved, these markers influence the processes of responding to stimuli in several ways; some markers act consciously ('in mind') and others covertly, in a 'non-minded' manner. The markers 'pre-bias' cognitive systems, preventing them from considering particularly bad courses of action. Somatic markers, therefore, constitute a rapidly retrieved signal that improves performance by removing options from the consideration of a computationally intensive cognitive process.

One example of a somatic marker is the skin conductance response (SCR) induced by sympathetic nervous system activity (and thus is an index of autonomic arousal). This marker is probably to be

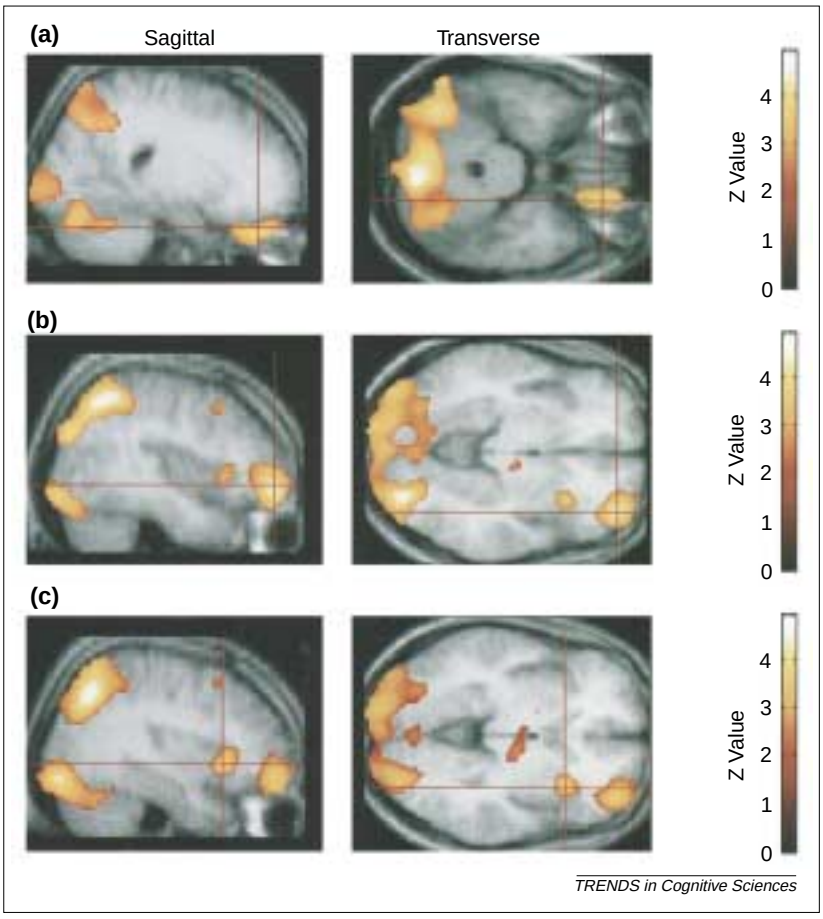

Fig. 1. Neuroimaging of the decision-making task. Peaks of activity-associated performance in the decision-making task illustrated in Box 1 (compared with a visuomotor control task) rendered onto the averaged MRI scans of eight volunteer subjects used in the study[15] (threshold, $P < 0.01$). (a) Peak activation in orbitomedial PFC (BA 11). (b) Peak activation within orbitolateral PFC (BA 10). (c) activation within the inferior convexity (BA 47). (Reproduced by kind permission of the Society for Neuroscience.)

both sensed and generated by the PFC. There is fMRI evidence that neural activity involving both medial prefrontal cortex and the right OFC accompanies the generation and afferent representation of discrete SCRs (Ref. 16). The marker can reach the OFC directly, through the somatosensory cortex, or indirectly, through the interactions of the ascending somatic sensory system and the ascending, chemically defined neurotransmitter systems of the isodendritic core. Learned versions of somatic responses might also be 'reproduced' within the somatosensory cortex and relayed to the OFC in a manner that is sometimes described as an 'as if' loop (the somatosensory information originates in the cortex but 'as if' it had been produced in the body itself). By contrast, the medial network of the PFC appears to be the primary source of visceromotor outputs to the hypothalamus and brainstem. Central autonomic effectors, including the amygdala, are capable of activating somatic responses in the viscera and endocrine systems[17]. Like subjects with damage to the OFC, subjects with somatosensory cortical damage or damage to the amygdala are impaired in the gambling task of Bechara *et al.*[18,19], suggesting a role for these structures (and the peripheral nervous system) in decision making. This is in keeping with the somatic marker hypothesis outlined above. Current lesion and neuroimaging studies therefore identify the OFC (Refs 20,21), and its functional interactions with related structures such as the amygdala and somatosensory cortices, as being critical to many aspects of decision making and social/emotive cognition (see Fig. 2).

Clinical disorders disrupting these systems include substance abuse, ruptured anterior communicating artery aneurysms, frontal-variant frontotemporal dementia, bipolar and unipolar depression and personality disorders. As deficits in decision making are now both qualifiable and quantifiable, it is essential to define, clinically and neuropsychologically, the meaning of commonly used terms such as 'impulsivity', 'risk-taking' and 'disinhibition'.

Decision making in substance abusers

Examining the decision-making behaviour of substance abusers provides a useful starting point, because drug abuse could reflect a breakdown of the ability to evaluate potential reward against harm from drug self-administration. Activity in the OFC and its connections have now been found to play a role in several components of the maladaptive behaviour of substance abuse, including expectancy, craving and impaired decision making[22].

The importance of the ventral striatum and the amygdala in humans is being further highlighted in novel functional neuroimaging studies by Breiter and Rosen[23]. These structures are part of an extended neural network involved in processing the features of rewards and assigning value to the goals of behaviour in the context of motivational states. Recent findings indicate that chronic amphetamine abusers show a pattern of decision-making deficit closely resembling those shown by OFC-lesioned patients. This suggests that decision-making

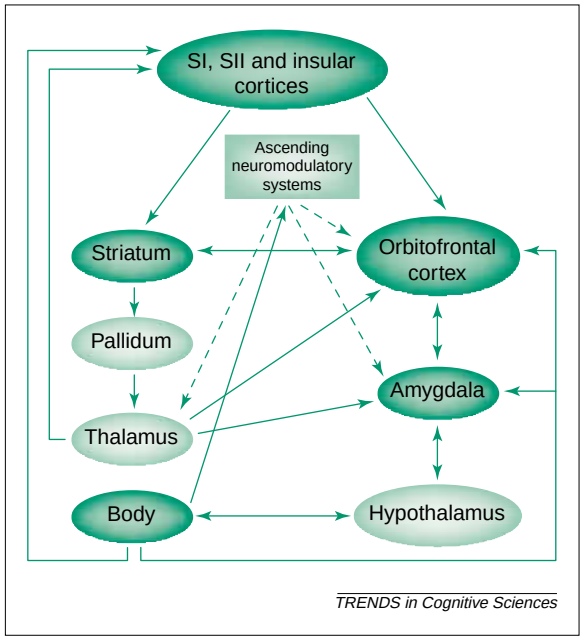

Fig. 2. The neural substrates of decision making. Postulated key structures involved in decision making, and their inter-relationships.

cognition might be susceptible to altered neuromodulation affecting OFC function. Such deficits can be induced in normal humans by acute plasma tryptophan depletion, which leads to reduced 5-HT function. Young, healthy, tryptophan-depleted subjects exhibit an increased tendency to choose the least probable of two outcomes and a trend to increased deliberation times[11]. It seems likely, therefore, that a reduction in central 5-HT, strongly associated with disorganized, impulsive and aggressive behaviour in humans[24], is also associated with altered decision making in laboratory settings.

It should be appreciated that substance abusers might have premorbid personality characteristics (e.g. sensation-seeking behaviour) that make them potentially vulnerable to substance abuse in the first instance. This could reflect a complex interplay of currently ill-defined genetic factors. Further research is needed to explore these possibilities, incorporating independent measures of the contribution of such personality factors to performance on decision-making tasks and their association with abuse of different substances, including alcohol. Bechara and colleagues[25] studied subjects meeting DSM-IV criteria for dependence on either alcohol or stimulants (methamphetamine). They found that performance (categorized as 'good as controls', 'impaired' or 'severely impaired') was independent of age, sex, level of education, intelligence or the type of abused substance. Deficits were, however, related to the length of time for which the subject had been abstinent and to the number of prior relapses. These results are particularly significant because they suggest that at least a subgroup of substance abusers – those who relapse repeatedly and cannot remain abstinent for a long period – suffer from a decision-making deficit reminiscent of that seen in patients with OFC lesions.

'Risk-taking' behaviour

Frontotemporal dementia

In a rather different clinical condition – frontal-variant frontotemporal dementia (fvFTD) – PFC neurodegeneration is the principal cause for a circumscribed behavioural syndrome in which the majority of patients are brought to the clinic unaware of major pervasive changes in their personality, behaviour and social conduct, as observed by informants[26]. Patients can appear apathetic or withdrawn, or alternatively they can become socially disinhibited with facetiousness and inappropriate jocularity. Their ability to plan and organize complex activities (for example, work and social engagements) is almost invariably impaired. There is often indifference to domestic and occupational responsibilities, a lack of empathy for family and friends, and a gradual withdrawal from all social interactions.

In our decision-making task, such patients are willing to bet a much higher proportion of their accumulated reward (at all odds ratios) than their age- and IQ-matched controls[27]. However, they show no significant difference from controls in their tendency to choose the most likely outcome. Therefore, although they are able to make accurate probability judgements, they do not adjust the levels of their bets like control subjects. In addition, they did not simply choose their bet early and impulsively; regardless of whether the offered bets ascended or descended, they bet more. They therefore appear to be true risk takers.

There are broad similarities in the performance of fvFTD patients and patients with orbitofrontal lesions studied by Bechara, Damasio and colleagues[9,28] and ourselves. Both groups of patients make abnormal decisions that are no longer personally advantageous and both groups have difficulty planning their future[29]. There is little evidence that defective simple inhibitory control is the primary reason for the poor performance of the fvFTD patients on the decision-making task illustrated in Box 1. Patients exhibit much longer deliberation times, are not consistent in choosing early bets in both the ascending and descending sequences, and generally appear able to adjust their bet as a function of the likelihood that their choice will be correct, albeit betting at an inflated level. Qualitatively, neither the patients with orbitofrontal lesions nor fvFTD patients are able successfully to adjust their behaviour to the opportunities offered by the task. It is possible that patients with fvFTD act in a riskier way because of diminished insight into their own behaviour. Their performance might also be related to their more pronounced 'sociopathic' tendencies, compared with controls with orbitofrontal lesions, and possibly also when compared with a broader pattern of neuropathology.

Ruptured aneurysms of the anterior communicating artery

Risk taking is also shown by patients with subarachnoid haemorrhage caused by ruptured aneurysms of the anterior communicating artery (ACoA). Historically, these patients have been observed to suffer a poor neuropsychological outcome[30,31]. Accounts of such patients outline aspects of a triad of symptoms – memory loss, confabulation and altered personality. The personality changes include impulsivity, disinhibited behaviour, apathy, emotional lability, depression and poor judgments in social situations[32,33]. Although a study of ACoA patients has found frontal lobe function to be unaffected[34], it is probable that the tasks used primarily tapped dorsolateral PFC function. As the anterior communicating artery and its branches supply the orbital aspect of the PFC, it is this part that is most likely to be affected by ischaemic damage subsequent to aneurysmal rupture. A recent study has shown that patients

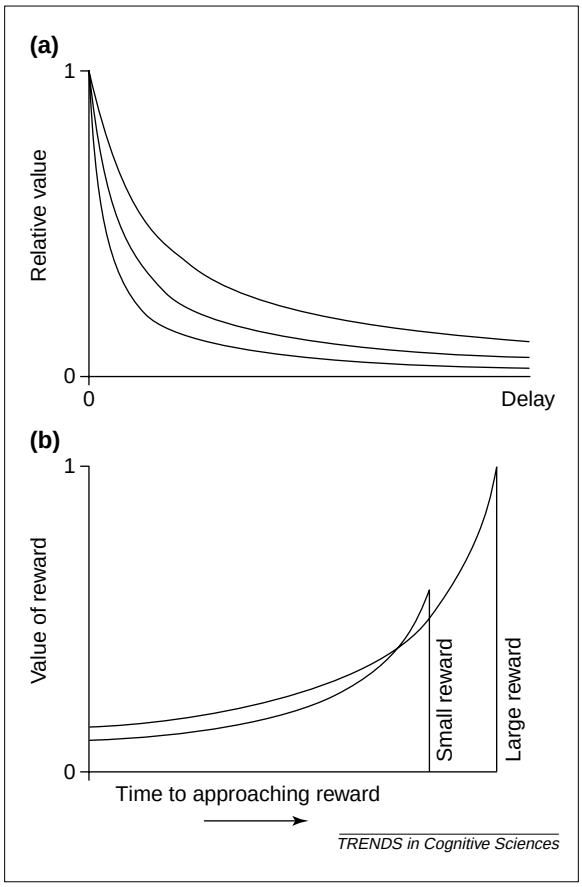

Fig. 3. Hyperbolic temporal discounting of reward value. (a) Hyperbolic discounting, governed by the equation $V = \text{magnitude}/1+K$. delay. Large values of K give the steepest curve. (b) Preference reversal. Given a choice between an early reward value of 0.6 and a later reward value of 1.0, hyperbolic discounting predicts that the larger reward will be chosen if the choice is made far in advance (towards the left of the graph). However, as time goes on, there comes a time just before delivery of the small reward when preference reverses and the small reward is chosen. Adapted from Ref. 48.

achieving a favourable neurological recovery following open surgery for a ruptured ACoA aneurysm also have specific deficits in their decision making[35]. They exhibited risk-taking behaviour, placing higher bets in the decision-making task described in Box 1. This deficit could be the result of direct damage to the OFC itself, as a result of microischaemia or infarction, or caused by a disconnection of orbitofrontal circuits, as a result of distant or generalized brain damage.

Decision making and the regulation of impulsive behaviour

Tasks such as ours can help to clarify the relationship between impulsive responding and risk taking. Impulsivity is multifaceted[36] but includes aspects of sensation seeking, inappropriately short decision times and lack of persistence. In our task, early bets would suggest consistent impulsive, or disinhibited, responding but large bets would indicate risk seeking. As described earlier, using this measure it appears that patients with fvFTD are not consistently impulsive. However, the poor ability of the same patients to switch response in a reversal learning paradigm suggests that inhibitory processes are compromised, leading to some degree of 'cognitive' or 'choice' impulsivity that could represent a complex form of disinhibited behaviour[37]. Some patients might fail to inhibit an action to seek immediate reward when a far better but delayed alternative is available. This could itself be related to impairments in functioning of somatic markers[38]. However, motoric impulsivity and choice impulsivity have been doubly dissociated[38] and so these poor choices are not best characterized as simple failures of inhibition.

Clinically, impulsivity is a central feature of some personality disorder syndromes and, in so far as such patients show consistent deficits in laboratory tests of decision making, we can hypothesize that the neural dysfunctions mediating their behavioural disturbance include altered functioning of the orbitofrontal PFC. It will be a challenge for future research to examine to what extent decision-making cognition in patients with borderline personality disorder is similar to that in patients whose behaviour becomes aberrant because of acquired damage to the prefrontal cortex later in life[39]. However, such altered decision making in patients with certain personality disorder syndromes is also likely to be accompanied by impairments in other impulse control mechanisms that would normally influence other aspects of behaviour and could involve dysfunction of other neural and neuromodulatory systems. Consistent with this, recent results obtained with the decision-making task described in Box 1 (see Ref. 40) indicate that patients with a history of violent behaviour (including self-harm) in the context of a diagnosis of DSM-III R borderline personality disorder exhibit the delayed, maladaptive choices seen in patients with focal lesions of the orbitofrontal cortex, as well as a marked tendency to place early bets in all conditions of the task – behaviour more consistent with the notion of general behavioural disinhibition.

Elucidating neurochemical influences on impulsivity is currently a fundamental clinical issue. For example, the significance of the serotonergic neurotransmitter system in decision making is highlighted by the observations that serotonergic depletion can result in a failure of delayed rewards to motivate behaviour[41]. The temporal discounting function relating the value of a reinforcer to the delay of its occurrence is one of the best studied utility functions. Empirically, it is a hyperbolic function[42–44], which explains features of normal choice such as changes in preference depending on the time of the decision (Fig. 3). Abnormalities of this particular function by which reward utility is calculated have been suggested to occur after neurochemical manipulations. For example, forebrain serotonin depletion, which leads to 'impulsive choice' in a variety of paradigms[44–46], has been suggested to reflect a modification of the temporal discounting function[46,47]. Current evidence suggests that 5-HT depletion steepens this function, such that delayed rewards lose their capacity to motivate or reinforce behaviour. As delayed rewards have unusually low utility, the agent consistently chooses small, immediate rewards over large, delayed rewards – a characteristic of impulsivity[48].

Questions for future research

- What are the relative contributions of the amygdala and the OFC to decision making?
- How can methodologies such as 'efferent connectivity' be used to determine how structures within the decision-making neural system interact?[56]
- To what extent are somatic markers absent or abnormal in neuropsychiatric disorders such as anxiety and depression?
- To what extent are the neural mechanisms governing decision making lateralized in the brain?

Unipolar and bipolar depression

The relevance of examining decision making in unipolar and bipolar ('manic') depression is clear from the DSM-IV classification, which states that individuals currently experiencing major depressive episodes often have difficulty making decisions. Likewise, manic individuals tend to display excessive involvement in pleasurable activities carrying a high potential for painful consequences. Despite markedly different clinical presentations, few studies have reported differences between neuropsychological functioning in mania and depression. However, it has recently been shown that the nature and extent of cognitive impairment differs between these two groups: a recent study has revealed that both manic and depressed patient groups are impaired on our decision-making task (Box 1), as evidenced by slower deliberation times, a failure to accumulate as many points as controls and suboptimal betting strategies[49,50]. In contrast, manic (but not depressed) patients made irrational decisions – an impairment that correlated with the severity of their illness. These results must be considered in the context of PET studies demonstrating that individuals suffering from unipolar depression or bipolar disorder (BD) have abnormal patterns of activity in a circuit including the PFC, amygdala, mediodorsal thalamus and ventromedial striatum[51,52]. In particular, an area of abnormal activity has also been found in BD and familial cases of manic depressive disorder, centred in the posterior medial PFC in the region of the genu of the corpus callosum[52]. Changes in blood flow in this region have also been associated with changes in limbic areas, emphasizing the importance of a distributed neuronal network underlying certain mood states[53].

Clinically, the responses of manic and depressed patients appear more consistent with impulsive rather than risk-taking behaviour. Impulsivity, as measured using clinician and self-administered rating scales, has been shown to be an important dimension of clinical depression in relation to suicide attempts. Additionally, although manic patients do not show true 'risk taking' in the same way as fvFTD patients, they do make 'risky' decisions in the sense that they are more likely to choose less favourable outcomes (a behaviour also seen in patients with neurosurgical lesions of the OFC). Strikingly, manic bipolar patients and patients with frontal dementia share many clinical symptoms. For example, patients with mania are diagnosed on the basis of many symptoms found in frontal dementia (for example, mood changes, overactivity, distractibility, socially inappropriate behaviour, increased appetite, increased libido, delusions and hallucinations, impaired insight). Frontal-variant frontotemporal dementia can sometimes be misdiagnosed as mania[54]. The similarity in symptoms might not be coincidental and could provide important clues to commonalities in the brain areas affected in these disorders. The term 'disinhibition' might also be used to describe the behaviour of patients with mania and frontal dementia and the relationship of various disinhibitory syndromes to dysfunction of the orbitofrontal and basotemporal cortices (particularly of the right hemisphere) is noteworthy[55]. However, the decision-making profiles of these patients are qualitatively different – patients with unipolar or bipolar disorder are not risk takers and patients with mania (unlike patients with fvFTD or unipolar depression) make maladaptive choices.

Conclusion

This review has examined our understanding of the neuroscientific basis of decision making and its relevance to several pertinent neuropsychiatric conditions. Results from studies using several different approaches, including lesion studies, functional neuroimaging and neurophysiology, converge upon the notion that the neural substrates underlying decision making include the OFC, striatum, amygdala, somatosensory cortices and the chemically defined neuromodulatory projections of the isodendritic core, such as the dopamine and 5-HT systems. The work has clear links to the clinic, where hypotheses about the underlying cause of a deficit can be tested, the results perhaps leading to clear applications in a more objective diagnostic system and in effective rehabilitation of patients. A wide range of neuropsychiatric disorders are characterized by subtle deficits in decision-making cognition, which might also show some qualitative differences, and our hypotheses could apply to other conditions that we have not had space to discuss in this review, such as obsessive–compulsive disorder. An understanding of the basis of deficits in decision making can be used constructively to inform our empirical neuropsychological investigation of this most complex cognitive domain. In the clinic, the mere specification of these deficits will help to define more precisely such widely used terms as 'impulsivity', 'disinhibition' and 'risk taking'. Ultimately, once these concepts have been given an adequate definition within the rapidly increasing body of knowledge of the neurochemistry of decision-making, there are real possibilities for rational pharmacotherapy for the many patients exhibiting these clinical symptoms.

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References

1 Harlow, J.M. (1848) Passage of an iron bar through the head. *Boston Med. Surg. J.* 39, 389–393
2 Harlow, J.M. (1868) Recovery from the passage of an iron bar through the head. *Publ. Mass. Med. Soc.* 2, 327–347
3 Tranel, D. (1994) 'Acquired sociopathy': the development of sociopathic behavior following focal brain damage. In *Progress in Experimental Personality and Psychopathology Research* (Vol. 17) (Fowles, D.C. *et al.*, eds), pp. 285–311, Springer-Verlag
4 Damasio, A.R. *et al.* (1990) Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. *Behav. Brain Res.* 41, 81–94
5 Damasio, A.R. *et al.* (1991) Somatic markers and the guidance of behavior: theory and preliminary testing. In: *Frontal Lobe Function and Dysfunction* (Levin, H.S. *et al.*, eds), pp. 217–229, Oxford University Press
6 Stuss, D.T. and Benson, D.F. (1986) *The Frontal Lobes*, Raven
7 Damasio, A.R. (1994) *Descartes' Error: Emotion, Reason and the Human Brain*, Grosset/Putnam
8 Rolls, E.T. *et al.* (1994) Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *J. Neurol. Neurosurg. Psychiatry* 57, 1518–1524
9 Bechara, A. *et al.* (1994) Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50, 7–15
10 Bechara, A. *et al.* (1996) Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. *Cereb. Cortex* 6, 215–225
11 Rogers, R.D. *et al.* (1999) Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. *Neuropsychopharmacology* 20, 322–339
12 Owen, A.M. (1999) The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. *Eur. J. Neurosci.* 9, 1329–1339
13 Dagher, A. *et al.* (1999) Mapping the network for planning: a correlational PET activation study with the Tower of London task. *Brain* 122, 1973–1987
14 Knight, R.T. *et al.* (1995) Role of human prefrontal cortex in attentional control. *Adv. Neurol.* 66, 21–34
15 Rogers, R.D. *et al.* (1999) Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. *J. Neurosci.* 20, 9029–9038
16 Critchley, H.D. *et al.* (2000) Neural activity relating to generation and representation of galvanic skin conductance responses: a functional magnetic resonance imaging study. *J. Neurosci.* 20, 3033–3040
17 Price, J.L. (1999) Networks within the orbital and medial prefrontal cortex. *Neurocase* 5, 231–242
18 Bechara, A. *et al.* (1997) An anatomical system subserving decision-making. *Soc. Neurosci. Abstr.* 23, 495
19 Bechara, A. *et al.* (1998) The use of psychophysiology to predict structural change in anoxic encephalopathy. *Int. J. Psychophysiol.* 30, 147
20 Eslinger, P.J. and Damasio, A.R. (1985) Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. *Neurology* 35, 1731–1741
21 Saver, J.L. and Damasio, A.R. (1991) Preserved access and processing of social knowledge in a patient with acquired sociopathy due to ventromedial frontal damage. *Neuropsychologia* 29, 1241–1249
22 London, E.D. *et al.* (2000) Orbitofrontal cortex and human drug abuse: functional imaging. *Cereb. Cortex* 10, 334–342
23 Breiter, H.C. and Rosen, B.R. (1999) Functional magnetic resonance imaging of brain reward circuitry in the human. *Ann. New York Acad. Sci.* 877, 523–547
24 Linnoila, M. *et al.* (1983) Low cerebrospinal fluid 5-hydroxyindoleacetic acid differentiates impulsive from nonimpulsive violent behavior. *Life Sci.* 33, 2609–2614
25 Bechara, A. *et al.* (2001) Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia* 39, 376–389
26 Rahman, S. *et al.* (1999) Comparative cognitive neuropsychological studies of frontal lobe function: implications for therapeutic strategies in frontal variant frontotemporal dementia. *Dementia Geriatr. Cognit. Disord.* 10 (Suppl. 1), 15–28
27 Rahman, S. *et al.* (1999) Specific cognitive deficits in mild frontal variant frontotemporal dementia. *Brain* 122, 1469–1493
28 Bechara, A. *et al.* (1998) Dissociation of working memory from decision making within the human prefrontal cortex. *J. Neurosci.* 18, 428–437
29 Plaisted, K.C. and Sahakian, B.J. (1997) Dementia of frontal type: living in the here and now. *Aging Ment. Health* 1, 293–295
30 Walton, J. (1956) *Subarachnoid Haemorrhage*, Churchill Livingstone
31 Logue, V. *et al.* (1968) The quality of survival after rupture of an anterior cerebral aneurysm. *Br. J. Psychiatry* 114, 137–160
32 Alexander, M. and Freedman, M. (1984) Amnesia after anterior communicating artery aneurysm. *Neurology* 34, 752–757
33 Ogden, J.A. *et al.* (1997) Neurological and psychosocial outcome four to seven years after subarachnoid haemorrhage. *Neurosurgery* 41, 25–34
34 Ahola, K. (1996) Frontal tests do not detect frontal infarctions after ruptured intracranial aneurysm. *Brain Cognit.* 31, 1–16
35 Mavaddat, N. *et al.* (2000) Deficits in decision-making in patients with aneurysms of the anterior communicating artery. *Brain* 123, 101–109
36 Evenden, J.L. (1999) Varieties of impulsivity. *Psychopharmacology* 146, 348–361
37 Bechara, A. *et al.* (2000) Emotion, decision-making and the orbitofrontal cortex. *Cereb. Cortex* 10, 293–307
38 Bechara, A. *et al.* The somatic marker hypothesis and decision-making. In *The Handbook of Neuropsychology, The Frontal Lobes* (Boller, F. and Grafman, J., eds), Elsevier Science (in press)
39 Blair, R.J. and Cipolotti, L. (2000) Impaired social response reversal: a case of acquired 'sociopathy'. *Brain* 123, 1121–1241
40 Bazanis, E. *et al.* (1999) Impaired decision-making and other cognitive deficits in patients with borderline personality disorder. In *Managing Complexity: Mind, Brain, Body and Abnormal Personalities*, p. 13, International Society for the Study of Personality Disorders
41 Mobini, S. *et al.* (2000) Effects of central 5-hydroxytryptamine depletion on sensitivity to delayed and probabilistic reinforcement. *Psychopharmacology* 152, 390–397
42 Kacelnik, A. (1997) Normative and descriptive models of decision making: time discounting and risk sensitivity. In *Characterizing Human Psychological Adaptations*, pp. 51–70, Ciba Foundation Symposium 208
43 Mazur, J.E. *et al.* (1987) Self-control choice with electrical-stimulation of the brain as a reinforcer. *Behav. Processes* 15, 143–153
44 Richards, J.B. *et al.* (1997) Determination of discount functions in rats with an adjusting-amount procedure. *J. Exp. Anal. Behav.* 67, 353–366
45 Bizot, J. *et al.* (1999) Serotonin and tolerance to delay of reward in rats. *Psychopharmacology* 146, 400–412
46 Wogar, M.A. *et al.* (1993) Effects of lesions of the ascending 5-hydroxytryptaminergic pathways on choice between delayed reinforcers. *Psychopharmacology* 111, 239–243
47 Ho, M. *et al.* (1999) Theory and method in the quantitative analysis of 'impulsive choice' behaviour: implications for psychopharmacology. *Psychopharmacology* 146, 362–372
48 Ainslie, G. (1975) Specious reward: a behavioral theory of impulsiveness and impulse control. *Psychol. Bull.* 82, 463–496
49 Murphy, F.C. *et al.* (2001) Decision-making cognition in mania and depression. *Psychol. Med.* 31, 679–693
50 Sahakian, B.J. *et al.* (2000) Neuropsychology and neuroimaging in depression and mania. *Int. J. Neuropsychopharmacol.* 3 (Suppl. 1), S63–64
51 Drevets, W.C. *et al.* (1992) A functional neuroanatomical study of unipolar depression. *J. Neurosci.* 12, 3628–3641
52 Drevets, W.C. *et al.* (1997) Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386, 824–827
53 Mayberg, H.S. *et al.* (1999) Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am. J. Psychiatry* 156, 675–682
54 Gustafson, L. *et al.* (1992) Frontal lobe degeneration of non-Alzheimer type. *Bailliere's Clin. Neurol.* 1, 559–582
55 Starkstein, S.E. and Robinson, R.G. (1997) Mechanism of disinhibition after brain lesions. *J. Nerv. Ment. Dis.* 185, 108–114
56 Friston, K.J. *et al.* (1997) Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage* 6, 218–229