Decision-making cognition in neurodegenerative diseases

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Abstract | A large proportion of human social neuroscience research has focused on the issue of decision-making. Impaired decision-making is a symptomatic feature of a number of neurodegenerative diseases, but the nature of these decision-making deficits depends on the particular disease. Thus, examining the qualitative differences in decision-making impairments associated with different neurodegenerative diseases could provide valuable information regarding the underlying neural basis of decision-making. Nevertheless, few comparative reports of decision-making across patient groups exist. In this Review, we examine the neuroanatomical substrates of decision-making in relation to the neuropathological changes that occur in Alzheimer disease, frontotemporal dementia, Parkinson disease and Huntington disease. We then examine the main findings from studies of decision-making in these neurodegenerative diseases. Finally, we suggest a number of recommendations that future studies could adopt to aid our understanding of decision-making cognition.

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Introduction

Life demands that we make innumerable decisions on a daily basis. Some of these decisions have to be made quickly and unexpectedly, whereas others can be reflected on over time. Personal experiences can provide us with information relating to possible outcomes associated with a given decision, and decisions taken on the basis of experience typically involve emotional and motivational factors. Decisions must also be made about unfamiliar scenarios, without evaluation of the potential risks or benefits that might occur as a consequence of these decisions. Evidently, 'healthy' decision-making is crucial for everyday living.

Assessment of cognitive deficits in neurodegenerative diseases has focused almost entirely on memory, language, attention, visuospatial perception and executive functioning. In the past decade, however, the study of decision-making in these conditions has increased, prompting the development of new tasks that have enabled this cognitive process to be readily assessed in the laboratory setting. In this Review, we assess the neural basis of decision-making cognition in relation to the neuroanatomical changes associated with neurodegenerative disease, and provide an overview of the various decision-making impairments that are associated with frontotemporal dementia (FTD), Parkinson disease (PD), Huntington disease (HD), and Alzheimer disease (AD). We also propose a number of methodological recommendations that could be adopted in future studies to further our understanding of decision-making.

Competing interests
The authors declare no competing interests.

Neuropathological changes

Alzheimer disease

In the early stages of AD, degeneration occurs in the medial temporal lobes, including the hippocampus and the entorhinal cortex. As the disease progresses, other brain areas, such as the lateral temporal, frontal and parietal cortices, are typically affected.[1,2] Neurodegeneration in the basal forebrain leads to a decrease in acetylcholine levels throughout the brain[3] and, together with atrophy of the aforementioned brain structures, results in a progressive decline of memory functions, as well as language and visuospatial abilities. Other cognitive domains such as executive functions might also be affected.[4]

Frontotemporal dementia

FTD is an umbrella term for a group of degenerative diseases characterized by pathological changes occurring within the temporal and frontal cortices.[5,6] Behavioral variant FTD (bvFTD), primary progressive aphasia—including subsyndromes such as progressive nonfluent aphasia and semantic dementia—and 'extrapyramidal' diseases, such as corticobasal degeneration, progressive supranuclear palsy, and motor neuron disease—especially amyotrophic lateral sclerosis—all have FTD-like pathological features.[7] In this Review, the term 'FTD' refers exclusively to bvFTD, as patients with this disease commonly experience decision-making deficits. Early in the disease process, FTD-associated pathological changes are evident in the superior medial and orbitofrontal brain regions within the prefrontal cortex, whereas anterior regions of the frontal lobes are affected at later time periods.[8] Impaired executive functioning, severe changes in personality and social cognition, deficits in impulse control, loss of insight, compulsiveness and

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Key points

- Decision-making is a complex mental function influenced by multiple cognitive and behavioral processes
- Several tasks have been developed that assess different types of decision-making
- Understanding how different brain areas contribute to successful performance on decision-making tasks can help us to identify which pathological changes associated with specific neurodegenerative diseases contribute to poor decision-making
- Studies that incorporate multiple measures of decision-making in the same patient populations, as well as assessment of other cognitive and behavioral processes, could further our knowledge of decision-making cognition
- Elucidation of the processes underlying decision-making could lead to more-objective diagnostic tests for impairments in this cognitive function, as well as the development of effective rehabilitation strategies and pharmacological treatments

perseverations, and withdrawal and apathy are all clinical symptoms associated with FTD.[9–11] These symptoms and deficits in decision-making seem to be most closely associated with neurodegeneration in the orbitofrontal cortex. Following damage to this part of the cortex, humans can display an array of behavioral changes that closely resemble psychiatric symptoms seen in mania, addiction, obsessive–compulsive disorder, attention-deficit hyperactivity disorder and personality disorders. Patients with damage to the orbitofrontal cortex also tend to make impulsive decisions about relationships or money, without considering the long-term consequences of their actions.

Parkinson disease and Huntington disease

In contrast to AD and FTD, which are both predominantly characterized by degeneration in cortical brain areas, PD and HD are characterized by neurodegeneration of subcortical structures. For example, progressive loss of dopaminergic neurons in the substantia nigra, which is an essential component of the basal ganglia circuitry, is a characteristic feature of PD. Loss of these dopaminergic neurons is considered to be one of the underlying mechanisms that contributes to motor symptoms such as bradykinesia, rigidity and tremor that patients with PD commonly experience.[12] By contrast, patients with HD typically experience uncontrollable choreic movements, which are thought to reflect a dramatic loss of medium spiny neurons in the neostriatum.[13] Nevertheless, because the brain structures affected in both PD and HD are integral components of various neural circuits that can affect brain areas associated with nonmotor functions such as cognition, marked cognitive and behavioral changes are frequently observed in patients with these conditions. In fact, patients who have either of these movement disorders frequently present with impaired executive functioning and marked neuropsychiatric symptoms.[14–19]

Decision-making paradigms

As mentioned above, not all decisions are made under the same circumstances. When making a choice between two or more options, one might not always know the odds of a favorable outcome. Decision-making under ambiguity or explicit risk are examples of decision-making without knowledge of the outcome. Although many other different types of decision-making exist, studies of decision-making in patients with neurodegenerative diseases have used these two decision-making paradigms extensively.[20]

Decision-making under ambiguity

Patients with neurodegenerative diseases are in no way exempt from making everyday choices without prior knowledge of the outcome. For example, especially during the early stages of the disease, decisions must constantly be made regarding financial issues, medical treatments and activities of daily living. These are examples of decisions made under ambiguity. In an attempt to mimic real-life ambiguous decision-making scenarios, Bechara *et al.*[21] developed the Iowa Gambling Task (IGT), the goal of which is to maximize an initial bet of $2000. Participants are asked to choose between four decks of cards, A–D. Each card is associated with either an advantageous outcome (the participant wins money) or a disadvantageous outcome (the participant loses money). At the beginning of the task, participants are unaware that two of the decks are 'advantageous'—cards selected from these decks are associated with either small monetary rewards or, in comparison to the rewards, smaller losses—whereas the other two decks are 'disadvantageous'—cards selected from these decks are associated with either large monetary rewards or even larger losses. Repeated selection of cards from the 'advantageous' decks will result in overall profit, whereas repeated selection of cards from the 'disadvantageous' decks will result in a net loss over time.

The IGT is said to measure decision-making in ambiguous situations, because in order to perform successfully one must use the feedback gained throughout the task to identify strategies that maximize the initial bet. Healthy 'normal' volunteers tend to predominantly choose cards from the advantageous decks after ≈40 card choices, whereas patients with lesions to the ventromedial and orbitofrontal prefrontal cortex tend to consistently choose disadvantageous cards,[21–23] illustrating the important contribution made by these anterior brain areas to decision-making. Further research has shown that patients with a wide variety of neurological and psychiatric disorders also consistently choose disadvantageous cards.[20,24] Performance on the IGT is now known to be affected by neurodegenerative changes in the prefrontal cortex,[23,25–27] and by deficits in working memory[23] and fluid intelligence—the ability to solve problems in novel situations.[28]

The IGT is clearly a very complex task. If an individual performs poorly on the task, one cannot determine whether their poor performance reflects the fact that they failed to learn which decks were advantageous and which were disadvantageous, or whether they determined the differences between the decks perfectly well but simply preferred the disadvantageous option. Furthermore, the task might only be a measure of ambiguous decision-making during the early trials. When participants are able to identify which of the decks are 'safe' and which are 'risky', the IGT becomes a task of decision-making

under explicit risk, which has been associated with activity in different neural structures from those involved in decision-making under ambiguity (see below). As a result, the extent to which later stages of the IGT measure ambiguous decision-making is a controversial topic.[24,29,30] Furthermore, the original assumption that the IGT is a measure of ventromedial prefrontal cortex activity is only valid if other cognitive domains and their underlying neural substrates are spared. Nevertheless, integrity of the prefrontal cortex is, evidently, a requirement for successful performance on the IGT. Furthermore, Hsu *et al.*[31] have highlighted the pivotal role of the limbic loop—which includes the medial orbitofrontal cortex, anterior cingulate gyrus, ventral striatum and nucleus accumbens[32,33]—in the successful performance of the IGT. The limbic loop can be altered at various levels in different neurodegenerative diseases, resulting in impaired decision-making.

Decision-making under risk

Patients with neurodegenerative diseases are frequently faced with real-life decisions for which they have thorough and explicit information regarding the risks and consequences that might result from their choices. For example, patients might be aware of the legal consequences of their actions or the statistically determined survival rates of certain treatment alternatives.[20] Such decisions are said to be made under explicit risk. Most studies investigating decision-making in risky situations have typically used either the Cambridge Gambling Task (CGT),[34,35] or the Game of Dice Task (GDT),[36] although other similar paradigms have been developed, including the Probability-Associated Gambling task,[37,38] the Balloon Analog Risk Task[39] and the Cups Task.[40]

The CGT is a computerized task in which participants are presented with a row of 10 boxes, each of which can be either red or blue. Participants are asked to decide and bet on whether a token has been hidden under a red or a blue box, and the proportion of boxes of each color changes from trial to trial; for example, red:blue ratios of 9:1, 7:3 or 5:5. Healthy 'normal' participants are expected to adjust their bet according to the ratio of red and blue boxes; that is, betting fewer points if the odds of winning are lower. Participants do not need to generate long-term strategies in this task because decisions are made solely on winning probabilities associated with the specific box ratio in each trial. Therefore, learning and working memory are less strongly linked to performance on this task than on tasks such as the IGT. Results from neuroimaging studies, however, indicate that activity in the ventromedial prefrontal cortex is required for successful performance on the CGT.[27]

Researchers should also be able to assess a patient's capacity to make decisions under risk on the basis of explicit rules for reinforcement and punishment that are maintained throughout the length of the task. This approach provides a means of assessing strategic decision-making based on calculations of risk and processing of feedback from previous trials.[20] These criteria are fulfilled by the GDT, during which participants are asked to guess which number (or combination of numbers) will finish face upwards after rolling a dice. If participants choose a specific number, they have a one in six chance of winning $1,000, and a five in six chance of losing the same amount. If the participant decides to bet on two numbers, they have a one in three chance of winning $500 and a two in three chance of losing the same amount. Participants are also allowed to bet on three numbers for a 50% chance of winning or losing $200, or they can bet on four numbers with a two in three chance of winning $100 or a one in three chance of losing the same amount. Betting on a combination of three or four numbers is safe and advantageous in the long run because the probability of winning is higher than chance. Studies have shown that successful performance on this task requires functioning of the ventromedial prefrontal and dorsolateral prefrontal cortices.[27]

Executive functions in decision-making

Executive functions such as forward planning, anticipation, judgment, reasoning, long-term memory and working memory are all mental processes that are essential for normal daily living. Given that decision-making is a complex mental process that requires the coordination of several simultaneous cognitive processes, executive functions are, perhaps not surprisingly, important in healthy decision-making. In fact, different executive functions are thought to be differentially linked to risky and ambiguous decision-making. The exact involvement of executive functions in decision-making is a controversial topic,[20,24] which probably reflects the lack of convergent data regarding this issue. In general, however, executive functioning is more strongly correlated with performance on tasks of risky decision-making[20,36,41] than with successful performance on the IGT,[20,42] indicating that dorsolateral prefrontal circuitry probably has a more central role in decisions based on explicit rules than in decisions made under ambiguous conditions. When tasks such as the GDT require participants to categorize stimuli and generate and/or evaluate strategies, task performance is strongly linked to executive test scores. Higher scores on tests of executive functioning are associated with more-advantageous performance on decision-making tasks under risk.[43] Nevertheless, positive correlations between executive functioning and successful performance on the IGT have been reported,[44–47] indicating that activity in the dorsolateral prefrontal cortex might also be required for successful decision-making under ambiguity. These findings might also reflect the fact that the last part of the IGT assesses decision-making under explicit risk.[20]

Neuroanatomy of decision-making

Human social interactions are extremely complex, and decisions can be influenced by factors such as adaptive strategies, personal preferences, reward evaluation, reinforcement learning, social cooperation, competition and control, as well as other parameters, including uncertainty, ambiguity and probability.[20,48–50] Given the complexity of decision-making, the fact that no single convergent model has yet been proposed is, perhaps,

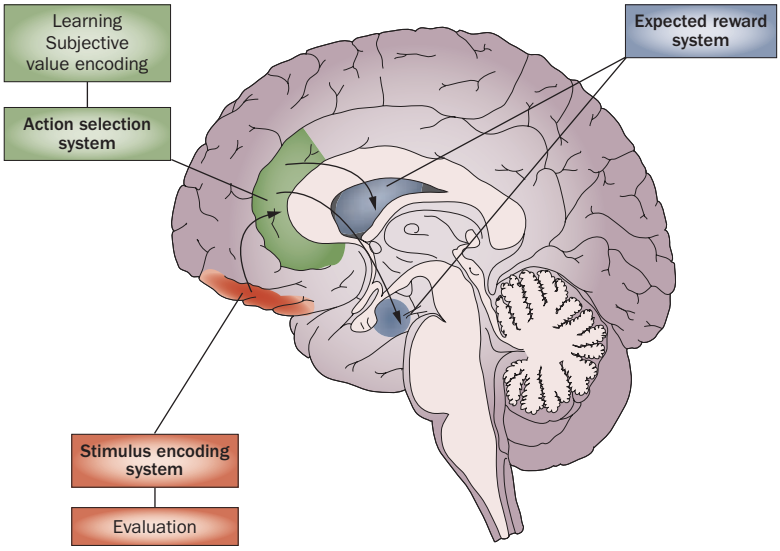

Figure 1 | A neuroanatomical model of decision-making. Three main systems are thought to be involved in decision-making: a stimulus encoding system (orbitofrontal cortex shown in red), an action selection system (anterior cingulate cortex shown in green) and an expected reward system (basal ganglia and amygdala shown in blue). Other brain areas that are involved in decision-making include the ventromedial prefrontal cortex (stimulus encoding), the lateral prefrontal and parietal cortices (action selection), and the insula (expected reward).

not surprising. Nevertheless, a consensus has been reached concerning a number of fundamental aspects of decision-making. For example, normal decision-making is thought to require an extended neural network, mainly comprising the frontostriatal and limbic loops including serotonergic and dopaminergic pathways, the lateral, medial and orbitofrontal cortex, the striatum, amygdala, basal ganglia, and anterior cingulate cortex.[20,48,49,51] Furthermore, the prefrontal cortex seems to have a critical role in reinforcement-guided decision-making.[52–54]

Three main systems have been suggested to be involved in decision-making: a 'stimulus encoding system', an 'action selection system' and an 'expected reward system' (Figure 1). The stimulus encoding system is important during the evaluation stages of decision-making, and this initial stage seems to be strongly associated with activity in the ventromedial prefrontal cortex, striatum[49] and orbitofrontal cortex,[54,55] and in dopaminergic pathways involving the ventral tegmental area, nucleus accumbens, striatum, and frontal cortex.[49]

The action selection system is involved in learning and subjective value encoding. Actions that follow a decision seem to be processed predominantly in the anterior cingulate cortex.[55,56] Related processes, such as error perception, as well as exploratory actions and voluntary choices, are also processed in the anterior cingulate cortex.[55] The lateral prefrontal cortex and lateral and medial intraparietal cotices are also activated during this stage of the decision-making process.[49]

The expected reward system is associated with activity in the amygdala, insula cortex, basal ganglia—including the caudate nucleus, putamen and globus pallidus—and the orbitofrontal cortex.[48,57] Reward-based decision-making can be affected by the brain reward system, which consists of the ventral tegmental area, ventral striatum, prefrontal cortex and amygdala.[57] The amygdala also seems to have an important role in emotional learning, which can affect decision-making.[51] The dopaminergic system is thought to modulate the expected reward system, as activity of this system relates to reward learning and prediction of errors.[48,56] In fact, learning the subjective value of objects is critically dependent on midbrain dopamine levels.[49,53]

In addition to these three components, other brain areas are thought to influence decision-making. For example, 'social' paradigms of decision-making—tasks that test an individual's ability to consider the preferences or choices of others—seem to require functioning of brain areas that are associated with theory of mind (ToM), such as the paracingulate cortex, in addition to the striatum, insula cortex, and orbitofrontal cortex.[48,49] Moreover, 'special' forms of decision-making, such as moral decision-making, seem to be associated with activity in the orbitofrontal and dorsolateral prefrontal cortex, cingulate cortex, precuneus and temporoparietal junction.[58] Furthermore, when complex decisions are being made, activity in the insula and posterior cingulate cortex is known to modulate the activity of the prefrontal cortex,[54] and simple tasks involving human volition can engage presupplementary and parietal areas during decision-making.[59] Notably, the numerous brain areas mentioned above interact during different processes. For example, the orbitofrontal cortex is involved not only in evaluation of stimuli but also in prediction of rewards.[57] Similarly, brain areas not classically related to decision-making under ambiguity—the cingulate and parietal cortices—seem to be required for successful performance on the IGT.[23,60] For instance, some patients with lesions in the anterior cingulate cortex might perform normally in the Stroop and Go/No-go tasks,[26] which require action selection—participants must choose between competing stimuli—yet show impaired performance on tasks of decision-making. In summary, decision-making requires coordinated activity within a wide variety of brain areas and neural networks.

Neuroimaging studies

Neuroimaging and lesion studies that have used the IGT, CGT or GDT are in agreement with the extended neuroanatomical model of decision-making introduced above.

Iowa Gambling Task

Impairments on the IGT are often interpreted as reflecting orbitofrontal and/or ventromedial prefrontal cortex dysfunction, as well as caused by altered processing in limbic structures, especially the amygdala.[20] PET studies have shown that decreased activity in the orbitofrontal prefrontal cortex is associated with impaired performance on the IGT.[61–63] Functional MRI (fMRI) studies have consistently documented activation in the dorsolateral prefrontal cortex, dorsal anterior cingulated cortex, insula cortex and parietal areas during performance on the IGT.[64] Moreover, a report has linked activity in specific brain areas to particular subprocesses during performance on

Table 1 | Summary of main studies of decision-making cognition in FTD

Study	Participants	Decision-making paradigm	Correlation with EF	Other multivariate comparison?	Brain and/or peripheral biomarker?	Main results
Rahman *et al.* (1999)[66]	8 FTD, 8 controls	CGT	No	No	No	Deficit in risk adjustment and risk-taking behavior, and increased deliberation times in patient group
Rahman *et al.* (2005)[67]	8 FTD	CGT	No	No	Yes: cardiovascular	Attenuation of risk-taking behavior following single dose (40 mg) of methylphenidate
Torralva *et al.* (2007)[68]	20 FTD, 10 controls	IGT	No	Yes: no correlations	No	Poor performance on IGT independent of ToM deficits
Torralva *et al.* (2009)[72]	35 FTD, 14 controls	IGT	Yes: impaired mental flexibility on WCST	Yes: no correlations	No	Poor performance on IGT
Manes *et al.* (2010)[74]	FTD (1)	IGT	No	No	No	Genuine risk-taking behavior

Abbreviations: CGT, Cambridge Gambling Task; EF, executive functions; FTD, frontotemporal dementia; IGT, Iowa Gambling Task; ToM, Theory of Mind; WCST, Wisconsin Card Sorting Test.

the IGT. The dorsolateral prefrontal cortex was associated with working memory, whereas the insula and posterior cingulated cortex were associated with emotional states. Orbitofrontal and ventromedial cortices were associated with the coupling of working memory and emotional states and the ventral striatum, anterior cingulate cortex and motor supplementary areas were associated with implementing behavioral decisions.[65]

Cambridge Gambling and Game Of Dice Tasks

Activity in the ventromedial prefrontal cortex has frequently been associated with successful performance on the CGT.[20] Only a few studies have used neuroimaging to identify brain regions associated with successful performance on the GDT. On the basis of the executive demand posed by this task, activity in the dorsolateral prefrontal area is thought to be required for its successful performance.[20,41] A meta-analysis of fMRI studies suggests that the orbitofrontal cortex, medial prefrontal cortex, caudate and rostral anterior cingulate cortex are also required for decision-making under risk.[64]

Disease and decision-making

Frontotemporal dementia

Using the CGT to study decision-making in a group of eight patients with mild FTD and eight age-matched and IQ-matched controls, Rahman *et al.*[66] demonstrated that patients with FTD took longer to place bets than did control participants. The researchers also found that the patients with FTD placed larger bets than healthy controls. Furthermore, patients with FTD performed similarly on the CGT to those with focal lesions of the orbitofrontal cortex.[35] The researchers concluded that the behavior of patients with FTD on the CGT was genuinely risk-seeking, rather than cognitively impulsive.

In another group of patients with mild FTD, administration of a single dose (40 mg) of methylphenidate—a psychostimulant typically prescribed for patients with attention-deficit hyperactivity disorder—attenuated the patients' risky decision-making on the CGT in the absence of autonomic changes (Table 1).[67] Strikingly, this normalization of risky decision-making was not accompanied by increased scores on other tasks that are known to require frontal lobe activity. Whether methylphenidate's beneficial effect reflects its action on dopamine transporters in the striatum and the ventromedial prefrontal cortex or its actions on ascending catecholamine systems that project to the orbitofrontal cortex is unknown. Nevertheless, these seminal studies indicate that impaired decision-making in patients with FTD is probably associated with deficits in ventromedial areas of the frontal lobe.

Two major questions arise from these findings. First, were decision-making deficits in these patients specific to situations under risk (both studies only used the CGT)? Second, were these deficits accompanied by impairments in other cognitive functions that rely strongly on the prefrontal cortex? To address these questions, Torralva *et al.*[68] compared the performance of patients with FTD with that of controls on the IGT and ToM tasks. ToM is defined as the ability to infer other people's thoughts or feelings and has been extensively linked to activity in the frontal lobes.[69–71] When participating in the IGT, patients with FTD exhibited genuine decision-making impairments under ambiguity, as indicated by their increased and consistent decisions to choose cards from the disadvantageous decks, especially towards the second half of the test. Compared with controls, these patients also showed impaired ToM performance, but their scores on ToM tasks were not associated with performance on the IGT. Therefore, although both normal decision-making and ToM depend on the integrity of the prefrontal cortex, these two cognitive functions seem to be mediated by independently functioning neural circuits, and impaired decision-making can apparently occur in the absence of ToM deficits.

Table 2 | Summary of main studies on decision-making in AD

Study	Participants	Decision-making paradigm	Correlation with EF	Other multivariate comparison?	Brain and/or peripheral biomarker?	Main results
Torralva *et al.* (2000)[75]	25 AD, 20 controls	IGT	Yes: impaired memory	Yes: no correlations	No	Patients with AD had impaired performance on IGT
Delazer *et al.* (2007)[43]	19 AD, 25 controls	GDT	Yes: impaired set-shifting within the patient group	No	No	Patient group displayed no risky behavior or any evidence of strategic thinking
Sinz *et al.* (2008)[37]	22 AD, 22 controls	IGT and PAG	Yes: deficient inhibitory control, deficits in motor programming in the patient group	No	No	Decision-making under ambiguity and decision-making under risk were impaired in patients with mild AD, characterized by a lack of advantageous strategies

Abbreviations: AD, Alzheimer disease; EF, executive functions; GDT, Game of Dice Task; IGT, Iowa Gambling Task; PAG, Probability-Associated Gambling.

As mentioned above, the last half of the IGT is thought to test both ambiguous and risky decision-making, so successful performance on this task is thought to require integrity of both the ventromedial and dorsolateral prefrontal brain areas. Early FTD has been shown to be associated with neurodegeneration in the superior medial and orbitofrontal brain regions, whereas subsequent progression is associated with neurodegeneration in the prefrontal cortex.[8] These observations could explain why this patient population has severe decision-making deficits under ambiguous and/or risky conditions. The IGT could be used to provide complementary information to a frontal test battery, especially in the early stages of the disease before severe dementia develops.

In everyday clinical practice, a subset of patients with early FTD show normal neuropsychological performance on standard assessment batteries. Compared with routine neuropsychological tests, therefore, the IGT might be a superior means of identifying patients with this condition. We have recently demonstrated that patients with FTD who demonstrate normal performance on general cognitive screening tests and classic tests of executive function demonstrate impaired decision-making on the IGT.[72–74] Furthermore, patients with FTD who perform normally on classic executive tests have also been shown to have deficits on other tasks that closely mimic real-life scenarios. The fact that patients with FTD can perform normally on standard neuropsychological assessment batteries but show dysfunctional decision-making should be highlighted.

Alzheimer disease

Patients with AD typically perform less well on the IGT than do healthy controls.[75] Furthermore, in these patients, scores on the IGT correlate significantly with performance on verbal and visual anterograde memory tests (Table 2), but not with scores on a wide variety of psychiatric scales, indicating that poor decision-making in patients with AD could be more closely associated with neuropsychological disturbances than psychiatric symptoms that can develop after disease onset. Delazer *et al.*[43] administered the GDT to a group of patients with mild AD (mean Mini Mental State Examination score 25.2, SD = 2.8) and age-matched controls, and found no significant difference in the total numbers of safe choices—combinations of three or four numbers—between the two groups.[76] The proportion of safe to risky choices, however, was significantly higher in the control group than in the patient group, and patients with AD alternated more frequently between safe and risky choices. The latter observation might indicate that patients with AD make decisions randomly and are unable to develop advantageous strategies. Remarkably, no differences in reaction time were evident between the groups, and patients with AD did not exhibit changes in their choices throughout the task. On the basis of positive correlations between decision-making performance on the GDT and performance on Parts A and B of the Trail Making Test, which measures sustained attention and set-shifting, deficits in attention and executive functions have been suggested to prevent patients with AD from remembering the outcomes of previous trials, which could negatively influence the development of advantageous strategies.[77] The fact that attention and executive functioning are known to depend strongly on the activity of dorsolateral neural circuits—which are known to be involved in decision-making under risk—supports this hypothesis.[31]

In a follow-up study, patients with AD were assessed on the IGT.[37] On this task of ambiguous decision-making, the patients selected cards from advantageous decks significantly less frequently than did controls and, like the patients with AD who were tested on the GDT, they alternated between advantageous and disadvantageous choices more often than controls. The frequency with which the patients with AD alternated between advantageous and disadvantageous choices was found to correlate positively with scores on an inhibitory control test, namely the Go/No-go subtest of the Frontal Assessment Battery. When performing this test, patients are asked to either execute or inhibit a motor response depending on the cue they receive. Poor performance on the IGT was associated with poor performance on the Go/No-go test, suggesting that altered functioning of the prefrontal cortex might be causing the seemingly random choices

made by the patients with AD. Furthermore, considering the circuits proposed by Hsu *et al.*[31] for decision-making under uncertainty and the neural basis for decision-making processes introduced above, patients with AD whose pathology involves neurodegeneration in the amygdala[78,79] and dysfunction in the connections to the ventromedial frontal cortex[4,80,81] are expected to be unable to generate advantageous strategies.

Parkinson disease

Patients with idiopathic PD can experience cognitive deficits, even in the early stages of the disease.[82] Many of these deficits are similar to those seen in patients with injury to the prefrontal cortex, such as impairments in working memory, planning, learning, and set-shifting—the ability to alter ongoing behavior in response to environmental cues or changing goals.[83] In view of the underlying neuropathological changes that characterize PD, and since specific neurotransmitter systems—including dopaminergic pathways—have been shown to be involved in cognitive functions such as value representation, weighing gains and losses, and choosing between alternatives,[84] PD has become a popular model for studying decision-making.

The mesocorticolimbic dopaminergic system is typically affected in patients with PD,[85,86] and changes in this signaling system could substantially alter the activity of orbitofrontal pathways and, hence, affect decision-making. Establishing a link between the loss of central dopamine pathways and deficits in cognitive functions, however, has not proved to be straightforward. The involvement of dopamine signaling in real-life decision-making has remained a controversial topic since the earliest studies that compared decision-making performance in patients with PD 'on' and 'off' medication (Table 3).[87,88] For instance, Czernecki *et al.* found that levodopa administration did not alter the decision-making abilities of patients with PD—in the IGT, patients who were 'on' or 'off' medication did not identify that two decks were 'advantageous' and the other two were 'disadvantageous'.[87] Cools *et al.*[88] showed that compared with controls, patients with PD who were 'on' medication showed abnormal betting behavior, which was characterized by impulsive betting and delay aversion on the CGT. The Czernecki *et al.* and Cools *et al.* studies employed two different decision-making tasks—the IGT and CGT—and successful completion of these distinct tasks requires activity in different regions of the brain (the orbitofrontal and dorsolateral brain areas, respectively). On the GDT, which requires activity in the dorsolateral prefrontal cortex for successful completion, patients with PD were shown to have severe decision-making deficits compared with controls.[41] Moreover, these deficits were found to correlate positively with deficits in executive functioning and emotional feedback processing, indicating that impaired decision-making in patients with PD might result from dysfunctional dorsolateral prefrontal–striatal loop and limbic–orbitofrontal–striatal loop functioning. An ^{18}F-2-fluoro-2-deoxy-D-glucose PET study that assessed the performance of patients with early-stage PD on the IGT found that deficits in the limbic–orbitofrontal–striatal loop were associated with poor task performance. The dorsolateral prefrontal–striatal loop, however, was shown to be relatively unimpaired in the study participants.[61] Deficits in the limbic–orbitofrontal–striatal loop probably also account for the impaired performance of patients with late-stage PD on the IGT.[89]

Patients with PD who perform poorly on the IGT are typically impaired on ToM tasks, such as the reading the mind in the eyes (RMIE) task.[90] As mentioned above, deficits in decision-making and ToM have been found to be dissociated in patients with bvFTD.[68] The apparent association between decision-making dysfunction and ToM deficits in patients with PD probably reflects the fact that the RMIE task selectively measures the 'affective' component of ToM, which is strongly linked to ventromedial prefrontal cortex activity.[91–94] Some have argued that decision-making impairments in patients with PD with otherwise preserved cognitive performance—for example normal executive functioning—occurs because dysfunction of the limbic loop increases when other limbic–prefrontal circuits are spared.[95] Patients with PD have lower skin conductance responses than controls during IGT performance.[96] This difference might reflect abnormal activity in the amygdala in the patient group, as this brain structure, which is connected to the orbitofrontal cortex via a neural pathway, is necessary to trigger emotional responses.[97] A study conducted in 24 patients with early PD showed that poor performance on the IGT was accompanied by degeneration of the amygdala and the orbitofrontal cortex, and seemed to be particularly associated with lateral degeneration of the latter structure in the left hemisphere.[98]

Despite the apparent agreement between the findings discussed above, the extent to which deficits in the orbitofrontal prefrontal cortex and the dorsolateral prefrontal cortex affect decision-making in PD is a controversial topic. Indeed, several studies have shown that the dorsolateral prefrontal–striatal loop is affected first in PD, and the limbic–orbitofrontal–striatal loop seems to be spared in the early stages of the disease.[83] Euteneuer *et al.* have assessed PD patients without dementia and healthy controls on the IGT and the GDT while recording electrodermal responses.[99] The researchers found that the patients with PD were significantly impaired on the GDT but not on the IGT, and that impairments in executive functions correlated positively with impaired performance on the former task only. In light of these results, dorsolateral prefrontal cortex dysfunction seems to occur even in PD patients without dementia, and affects decision-making under explicit rules, but not necessarily ambiguous decision-making. The researchers also found that patients with PD had lower electrodermal responses to losses, but not to gains, on both tasks compared with healthy controls, revealing that these patients were insensitive to negative feedback, which is associated with activity in the limbic loop. The limbic loop might be relatively spared in PD patients without dementia compared with those who develop dementia.

Table 3 | Summary of main studies of decision-making in PD

Study	Participants	Decision-making paradigm	Correlation with EF	Other multivariate comparison?	Brain and/or peripheral biomarker?	Main results
Czernecki *et al.* (2002)[87]	23 PD, 28 controls	IGT	Yes: decreased "frontal score" in patient group	Yes: demographic variables	No	No benefit of levodopa administration on decision-making
Cools *et al.* (2003)[88]	12 PD, 20 controls	CGT	No	No	No	Patients 'on' medication exhibited abnormal decision-making strategies
Thiel *et al.* (2003)[61]	5 PD, 5 controls	IGT	No	No	Yes: decreased activity in fronto-subcortical loops	No deficit on the IGT
Brand *et al.* (2004)[41]	20 PD, 20 controls	GDT	Yes: impaired mental flexibility and set-shifting on MCST in patient group	Yes: emotional feedback processing	No	Patients with PD preferred selecting cards from the disadvantageous decks
Perreta *et al.* (2005)[89]	16 early PD, 16 late PD, 19 controls	IGT	No	Yes: BDI total score in early PD	No	Both PD groups presented with learning impairments
Mimura *et al.* (2006)[90]	18 PD, 40 controls	IGT	No	Yes: affective component of ToM	No	Patients with PD had deficits in decision-making, which correlated with affective ToM
Pagonabarraga *et al.* (2007)[95]	35 PD, 31 controls	IGT	No	Yes: memory and GCP	No	More-severe deficits on the IGT associated with better general cognitive performance
Kobayakawa *et al.* (2007)[96]	34 PD, 22 controls	IGT	No	Yes: emotional responses and SCR	Yes: decreased SCRs	Patients with PD selected more disadvantageous decks on the IGT and their SCR was lower than controls
Ibarretxe-Bilbao *et al.* (2009)[98]	24 early PD, 24 controls	IGT	No	Yes: Ekman total score and RDS	Yes: gray matter loss in the right amygdala and in the OFC	Patients with PD had impaired decision-making on the IGT; volume in left lateral orbitofrontal cortex showed a slight correlation with IGT scores in the patient group
Euteneuer *et al.* (2009)[99]	21 PD, 23 controls	IGT, GDT	Yes: impaired EFs with GDT but not IGT	No	Yes: impaired EDRs	Patients with PD were significantly impaired on the GDT, but not on the IGT
Delazer *et al.* (2009)[100]	20 PD, 19 PDD, 20 controls	IGT, PAG	Yes: deficits in several EFs in the PD group	No	No	Both PD and PPD groups demonstrated impaired decision-making under ambiguity; but only the PDD group was impaired on the PAG
Poletti *et al.* (2010)[101]	30 PD, 25 controls	IGT	No	No	No	Patients with PD were unimpaired on the IGT

Abbreviations: BDI, Beck Depression Inventory; CGT, Cambridge Gambling Task; EDRs, electrodermal responses; EF, executive functions; GCP, global cognitive performance; GDT, Game of Dice Task; IGT, Iowa Gambling Task; MCST, Modified Card Sorting Test; OFC, orbitofrontal cortex; PAG, Probability-Associated Gambling; PD, Parkinson disease; PDD, Parkinson disease with dementia; RDS, reverse digit span; SCR, skin conductance response; ToM, Theory of Mind.

In an attempt to clarify the contribution of the limbic–orbitofrontal–striatal loop and the dorsolateral prefrontal–striatal loop to impaired decision-making, Delazer *et al.*[100] assessed the performance of patients with PD with dementia (PDD) and without dementia on the IGT and a task of decision-making under explicit risk. Both groups of patients exhibited impaired decision-making under ambiguity (IGT), but only the PDD group performed poorly on the risky decision-making task. This observation might indicate that pathological changes evident in patients with PDD could severely affect both the limbic and dorsolateral systems, which are both involved in successful decision-making under risk, but not for decision-making under ambiguity. By contrast, PD patients without dementia might have pathological changes that affect only the limbic–orbitofrontal–striatal loop. Although activity in this neural pathway is important for healthy performance on the IGT—especially during the earlier trials—pathological changes in this circuitry might not necessarily disrupt performance on decision-making under explicit risk. In light of the heterogeneous patterns of decision-making deficits with which patients with PD can present, Poletti *et al.* assessed the performance of *de novo* PD patients without dementia—none of whom had yet received dopaminergic medication—and matched controls on the IGT. The researchers found no significant differences between the groups. Since dopamine levels in these patients had not been altered by medication, the researchers concluded that decision-making deficits in PD are most probably associated with dopaminergic overstimulation of the orbital frontostriatal circuits caused by dopaminergic drugs.[101]

Huntington disease

At early time points in the disease process, HD is associated with loss of medium spiny neurons in the neostriatum.[13]

Table 4 | Summary of main studies of decision-making in HD

Study	Participants	Decision-making paradigm	Correlation with EF reported?	Other multivariate comparison?	Brain and/or peripheral biomarker?	Main results
Watkins *et al.* (2000)[103]	20 HD, 25 controls	CGT	Yes: impaired visuospatial planning	Yes: activities of daily living scores	No	Unimpaired decision-making in patients with HD
Stout *et al.* (2001)[106]	14 HD, 20 PD, 31 controls	IGT	No	Yes: MDRS	No	Decision-making deficits in HD group owing to learning and memory deficits
Busemeyer & Stout (2002)[107]	14 HD, 20 PD, 31 controls	IGT	No	No	No	Altered decision-making in HD group owing to deficits in working memory
Campbell *et al.* (2004)[108]	15 HD, 16 controls	IGT	No	No	Yes: decreased skin conductance response in patients with HD	Altered decision-making in patients with HD owing to learning and memory deficits

Abbreviations: CGT, Cambridge Gambling Task; EF, executive functions; HD, Huntington disease; IGT, Iowa Gambling Task; MDRS, Mattis Dementia Rating Scale; PD, Parkinson disease.

As the disease progresses, neurodegeneration advances in a stereotypical manner—dorsal to ventral, anterior to posterior, and medial to lateral—meaning that the dorsal striatum is affected at early stages of the disease. The dorsolateral prefrontal cortex loop, which includes the dorsal caudate, is also affected early in the disease process. By contrast, the ventral striatum, which is part of the orbitofrontal cortex loop[32,33] is typically affected at later stages of the disease process,[102] and is usually relatively spared in comparison to the dorsolateral prefrontal cortex loop.

In a seminal study by Watkins *et al.*,[103] 20 patients with early HD and 25 age-matched controls were assessed on the one-touch Tower of London Task (TOLT)[104] and the CGT. The former task is a visuospatial planning task that is generally considered to rely on activity in the dorsolateral prefrontal cortex,[104,105] which seems to be unnecessary for successful performance on the CGT. As expected, patients with early HD demonstrated impaired planning on the TOLT but had similar scores to controls on the CGT (Table 4). Thus, the results from this study indicate that patients with early HD do not have impairments in decision-making. However, findings from a later study that compared the performance of patients with HD with age-matched healthy controls on the IGT, a general cognitive battery—which included assessment of attention, perseveration, construction, conceptualization and memory—and a frontal lobe personality scale revealed that patients with HD made substantially fewer advantageous choices on the IGT than controls.[106] Intriguingly, the differences between the two groups were more evident towards the second half of the task, at which point successful performance is thought to require dorsolateral prefrontal cortex activity. In fact, performance on the IGT correlated positively with measures of learning and memory, two cognitive functions that are strongly associated with activity in the dorsolateral prefrontal cortex. By contrast, performance on the IGT did not correlate with symptomatic measures of apathy or disinhibition, which have been linked to activity in anterior cingulate and ventromedial areas, respectively. Poor performances on the IGT by patients with HD might, therefore, reflect impaired learning during the later stages of the test, and could potentially highlight the contribution of the dorsolateral prefrontal cortex to successful performance towards the end of this task.[23,26,27]

In the same study, no significant difference in performance on the IGT between controls and a group of patients with PD was evident, even though the latter had similar cognitive impairments to the patients with HD in terms of memory, attention and language domains.[106] The difference between the two patient groups probably stems from the fact that performance on the IGT by patients with PD was not associated with deficits in learning and memory, indicating that the dorsolateral prefrontal cortex contribution to this decision-making task was probably spared in the PD population. Furthermore, Busemeyer and Stout have demonstrated that poor performance on this task by patients with HD can be linked to deficits in working memory and increased recklessness and/or impulsivity.[107]

In another group of patients with HD, skin conductance responses were measured during participation in the IGT.[108] No differences in autonomic function were observed when the patients won or lost. This result indicates that losing might be less important and, therefore, less readily processed by patients with HD compared with healthy controls. Alterations in the projections between the caudate nucleus and the lateral orbitofrontal cortex are thought to be associated with indifference to losing.[108]

Limitations and future directions

Studies of decision-making in neurodegenerative diseases have increased our understanding of this complex

cognitive function. Both cortical and subcortical structures have been shown to contribute to normal decision-making, and frontotemporal cortices seem to be crucial for decision-making under both ambiguity and explicit risk. As mentioned above, however, impaired decision-making can also result from deficits in other cognitive functions such as memory, and standard tests of decision-making, such as the IGT, cannot reliably discriminate between decision-making deficits that are caused by dysfunctional activity in different brain structures. As a result, additional decision-making tasks must be developed that can detect subtle differences in decision-making deficits so that the underlying functional and structural deficits can be accurately identified.

As mentioned previously, the IGT is generally considered to be a test of decision-making under ambiguity, but probably becomes a test of decision-making under risk during the later stages of the task. Furthermore, the extent to which data derived from the IGT is purely a measure of decision-making is still a matter of controversy, as personality and mood are known to influence an individual's performance on this test.[29] Nevertheless, substantial evidence exists that indicates that successful performance on the IGT is strongly associated with activity in the ventromedial and orbitofrontal prefrontal cortices and the amygdala during the early stages of the task,[31] and with activity in the dorsolateral prefrontal cortex when study participants can predict which of the decks of cards are advantageous and disadvantageous in the later stages.[23] Successful performance on the CGT is associated with activity in the ventromedial prefrontal cortex,[23,27] whereas successful performance on the GDT has been linked to activity in both the ventromedial and dorsolateral prefrontal cortices.[20]

Unfortunately, most studies of decision-making in patients with neurodegenerative diseases have used only one measure of decision-making at a time. The few studies that have employed two tests of decision-making within the same patient population have provided valuable information regarding the involvement of distinct brain areas in impaired decision-making. Advancements in the field have also been limited by a lack of multivariate comparisons, which could have aided our understanding of how demographic, clinical and neuropsychological variables associated with neurodegenerative diseases affect decision-making.

To further our understanding of decision-making cognition in neurodegenerative diseases, we feel that future studies in this field should incorporate one or more of the following suggestions. First, studies should include at least the three most popular measures of decision-making—IGT, CGT and GDT—as each task assesses different aspects of decision-making, and each measure might be biased by important factors such as personality traits, mood at time of assessment, comprehension of task, and working memory and other executive functions. For example, the IGT has been criticized for the fact that performance on this test can be influenced by personal beliefs and that performance patterns by healthy people on the test can vary considerably.[24,29] Use of multiple measures of decision-making in the same study could improve the accuracy of the results. Second, executive functions and cognitive–behavioral processes such as apathy, impulsivity and disinhibition that can affect decision-making must be measured as part of a thorough assessment battery. Several cognitive processes such as emotional shortcuts—personal biases, inclinations, hunches and intuition—regret, cognitive heuristics, working memory, inhibition, risk-taking and motivation[20,24,26,109,110] can affect everyday decision-making. Deficits in some of these cognitive processes can negatively affect decision-making and, consequently, assessing these cognitive processes will be important in future studies. In addition, incorporation of multivariate analyses into future studies could aid our understanding of decision-making impairments in neurodegenerative disorders. Third, peripheral measures (skin conductance, heart rate, blood pressure) and central measures (cortical activity as measured by fMRI or event-related potentials) of impaired decision-making have not been employed routinely in neurodegenerative disease research. Since decision-making undoubtedly affects various peripheral and neural processes, we think that future studies should include both peripheral and central measures of decision-making. Consequently, adapted versions of the IGT have been designed so that PET[111] or fMRI[112] can be conducted during performance of the task. Similarly, new decision-making tasks have been developed to enable other neuroimaging procedures[113] or assessment with event-related potentials to be undertaken during decision-making tasks.[114]

Conclusions

This Review represents the first comprehensive appraisal of decision-making in neurodegenerative diseases, assessing how the pathological changes that characterize these conditions might negatively affect decision-making.

Understanding the requirement of different cognitive processes for successful performance on decision-making tasks can help us to identify which pathological changes associated with specific neurodegenerative diseases contribute to poor decision-making. In FTD, for example, neurodegeneration in prefrontal brain areas—particularly the orbitofrontal cortex—seems to have a central role in the development of genuine risk-taking behavior that is observed in both ambiguous and risky scenarios (as assessed by early IGT and CGD, respectively). Furthermore, study of this neurodegenerative disease has provided insight into the role of the ventromedial prefrontal cortex in decision-making.

In AD, decision-making is not 'risky' *per se,* but can be problematic owing to randomness. The inability to develop value-based strategies is generally attributed to deficits in learning and memory in patients with AD, and altered connectivity between the amygdala and the prefrontal cortex could be the underlying cause of these cognitive impairments. Later in the disease process, neurodegeneration in multiple areas of the brain, including the frontal and parietal cortices, might further impair decision-making in patients with AD.

In PD, dysfunction in limbic and cognitive loops that results from neurodegeneration in the basal ganglia might contribute to decision-making deficits. Whether the decision-making profile of patients with PD can be influenced by changing dopamine levels is unknown. However, patients with PD who are 'off' dopaminergic medication typically perform as well as controls on decision-making tasks, indicating that decision-making-deficits in patients with PD might be influenced by dopaminergic stimulation of orbitofrontal striatal circuits following drug administration. Neurodegeneration in the basal ganglia also seems to be associated with decision-making impairments in patients with HD. In earlier stages of the disease, impairment in the dorsolateral loop is considered to affect the functioning of the dorsolateral prefrontal cortex, which seems to cause poor performance on IGT. As the disease progresses, the putamen and adjacent brain regions are also typically affected, which can lead to disruption of other frontostriatal connections and to general decision-making deficits on multiple tasks.

The study of decision-making in neurodegenerative diseases has important clinical implications. A better understanding of the complex biological processes that affect decision-making could lead to more-objective diagnostic tests for impairments in this cognitive function, as well as development of effective rehabilitation strategies, and rational pharmacological treatments for the many patients who exhibit impaired decision-making.

Future research in this area should include multiple measures of decision-making, as well as measures of other cognitive and behavioral processes, and potential peripheral and/or central decision-making biomarkers. By implementing the above, we will gain a more profound understanding of how neurodegeneration can affect the way we make choices every day.

Review criteria

PubMed and MEDLINE were searched for articles published up until May 2010 using combinations of the following terms: "frontotemporal dementia", "FTD", "Alzheimer disease", "AD", "Parkinson disease", "PD", "Huntington disease", "HD", "decision-making", "decision", "choice making", "choices" and "risk". We limited searches to studies reported in English and further references were found manually by reviewing the bibliographies of identified publications.

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Author contributions

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