Comparative Cognitive Neuropsychological Studies of Frontal Lobe Function: Implications for Therapeutic Strategies in Frontal Variant Frontotemporal Dementia

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Abstract
Patients with mild frontal variant frontotemporal dementia (fvFTD) who attend the clinic are usually unaware of the pervasive changes in their personality and behaviour, despite the fact it is these changes which have prompted the referral from the patient’s spouse or carer. Comparative studies across various species offer unique insights into the heterogeneous structure and functions of the prefrontal cortex, and can allow a novel approach to the precise identification of the neuropsychological deficits present in these patients. We have found that they may show marked deficits on tests sensitive to ventromedial prefrontal or orbitofrontal function, in the relative absence of impairments on tests sensitive to dorsolateral prefrontal function. We highlight important differences in the neurocognitive profile of these patients with that of patients with other neurodegenerative conditions, including basal ganglia diseases and dementia of the Alzheimer type. The specific nature of these neuropsychological deficits, together with converging evidence from clinical and neuropathological studies, may provide useful clues about the predominant locus of dysfunction in the early stages of fvFTD and possible underlying neurotransmitter abnormalities. This is important for the successful development of therapeutic intervention strategies for both cognitive and behavioural symptoms in fvFTD. Finally, we evaluate critically the rationales for therapeutic modulation of noradrenergic, serotonergic and dopaminergic neurotransmitter systems at various stages of disease.

Key Words
Comparative studies · Dopamine · Dorsolateral · Frontotemporal dementia · Idazoxan · Noradrenaline · Orbitofrontal · Prefrontal · Serotonin · Therapeutic strategies

Introduction
Two key issues concerning frontal variant frontotemporal dementia (fvFTD) include the potential contribution of cognitive neuropsychology to the diagnosis of this clinical disorder, and its differential diagnosis from other neurodegenerative diseases (in particular, dementia of the Alzheimer type, DAT). Another major consideration has been the need to identify any neurotransmitter systems that might be compromised early in disease, and the implications of this for the successful development of rational strategies for the treatment of behavioural and
cognitive symptoms. This particular issue shall be the focus of the latter part of this article.

To address the general question of differential diagnosis, and in particular the discrimination from DAT, it is useful to note that fvFTD affects younger patients, with its peak onset in the presenium [1]. Patients with fvFTD present clinically with early changes in personality and loss of social awareness [2]. Clinically, the majority of patients with fvFTD who attend the clinic are usually unaware of the pervasive changes in their personality and behaviour, despite the fact it is these changes which have prompted the referral from the patient’s spouse or carer. Patients may appear apathetic or withdrawn, or alternatively may become socially disinhibited with facetiousness and inappropriate jocularity. Mental rigidity and an inability to appreciate the subtler aspects of language such as irony are common. Stereotyped or ritualistic behaviour are also common. 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.

Many of these behavioural symptoms (such as the loss of personal awareness, hyperorality, stereotyped and perseverative behaviour, a progressive reduction of speech and preserved spatial orientation) may all be useful in differentiating patients with fvFTD from those with DAT [3]. This observation is particularly useful in the context of a previous study which had revealed that whilst personality change, unconcern and socially inappropriate behaviour in frontotemporal dementia were prominent in fvFTD, disturbance in memory and topographical orientation tended to be prominent in patients with DAT [4]. As in other dementias, neuroimaging may, in addition, contribute significantly to the diagnosis. In one HMPAO-SPECT study [5], blood flow was found to be significantly lower in the frontal lobes, anterior temporal cortex, and the basal ganglia, in patients with frontal lobe dementia, compared to patients with DAT. Within the frontal lobe dementia group, blood flow was significantly lower in the orbital than in the dorsal frontal cortex, and in the anterior or temporal than in the dorsal temporal cortex.

In considering specifically the potential role of cognitive neuropsychology to the diagnosis of fvFTD, it is important to recognize that fundamental to our understanding of the prefrontal cortex have been exquisite neuroanatomical studies which have revealed that there appears to be an overall correspondence among all constituent areas in the brains of humans and monkeys [6]. Also important has been the recognition that the prefrontal cortex has developed substantially in primates through evolution [7], and this may have, as a consequence, resulted in the prefrontal cortex in both monkeys and in man being heterogeneous in its functions and its distinct patterns of cortical and subcortical structural connectivity. On the basis of anatomical and neurophysiological evidence, the concept of parallel and segregated cortico-striato-pallidal-thalamocortical circuit loops has evolved which emphasizes the functional interrelationships between the neocortex and striatum [8, 9]. In humans, the functional roles of various frontal-subcortical loops have been successfully identified, on the basis of clinical syndromes and neuroimaging studies. Sophisticated methods for neuropsychological assessment, as well as a comprehensive understanding of functional neuroanatomy, may therefore allow considered appraisal of the nature of cognitive deficits in frontotemporal dementia. Whilst there are clear methodological considerations (for example, the decrementing process may extend beyond a particular focus and hence cognitive deficits may relate to dysfunction of an extended neural network), it is still important that attempts should be made to isolate the anatomical region involved to direct the selection of further cognitive and behavioural investigations [10].

The importance of the consequences of lesions of the frontal lobe in terms of changes in behaviour and personality in animals was described elegantly by Ferrier [11] in 1876. Animals with bilateral frontal lobe ablations were described as hyperactive, impulsive, and lacking affection and socialization; apathy and inattention were also emphasized by Ferrier. Parallels in the human literature have been subsequently found, with Blumer and Benson [12] in 1975 describing patients with frontal lobe lesions as ‘pseudodepressed’ (patients appearing slow and lacking in initiative or concern), or ‘pseudopathic’ (patients demonstrating restlessness and impulsivity). Our understanding of the effects of lesions of distinct areas of the frontal cortex may also be clarified further within the context of the concept of the frontal-subcortical loops described earlier. Two circuits which may be hypothesized to be affected by the pathological process include the dorsolateral prefrontal circuit (which includes the dorsolateral convexities of the prefrontal cortex and the dorsolateral portion of the caudate), and also the lateral orbitofrontal circuit (which includes the orbitofrontal cortex and the ventromedial portion of the caudate nucleus).

To identify the major domains of neuropsychological deficit in patients with mild fvFTD and the putative underlying locus of pathology, it is useful to note that the patients in the early stages of fvFTD clinically are somewhat similar to those with defined neurosurgical lesions of
the ventromedial prefrontal cortex. Damasio and co-workers [13] have described how, in general, patients with ventromedial frontal lobe lesions exhibit an inability to initiate, organize, and carry out normal activities, and also demonstrate poor decision-making, financial mistakes, breakup of relationships, perseverative activities, and decreased spontaneity. Patients in the early stages of FvFTD also bear some resemblance to other patient groups with dysfunction principally of the orbitofrontal-subcortical circuit, for example those with ruptured anterior communicating aneurysms, orbitofrontal tumours, and inferior frontal lobe infarction [14–16]. In contrast, patients with dorsolateral prefrontal-subcortical dysfunction are predominantly characterized by impairments in executive function [17].

Major insights into the functions of the orbitofrontal cortex have been provided by the studies of Bechara et al. [18]. They have found that patients with damage to the orbitofrontal cortex are very prone to make bad decisions in gambling games because, hypothetically, they do not develop a ‘gut feeling’ indexed for example by changes in GSR. Recently, Bechara et al. [18] have made a significant contribution to advancing our understanding of dissociations of prefrontal cortical function. In their study, all subjects with ventromedial lesions were impaired on their gambling task, whereas only a subset of these subjects with the most anteriorly placed lesions were normal on the working memory tasks; however, subjects with right dorsolateral/high mesial lesions were impaired on the working memory tasks but not on the gambling task. Recent results from the primate literature also detail other cognitive deficits consequent upon orbitofrontal damage. Dias et al. [19, 20] have reported a double dissociation in the prefrontal cortex of affective and attentional shifts in the marmoset following excitotoxic lesions to the lateral and orbitofrontal cortex. Whereas damage to the lateral prefrontal cortex in monkeys causes a loss of inhibitory control in attentional selection (an extradimensional shift), damage to the orbitofrontal cortex in monkeys causes a loss of inhibitory control in ‘affective’ processing (a reversal), thereby impairing the ability to alter behaviour in response to fluctuations in the emotional significance of stimuli. Neither lesion affected learning at the intradimensional stage.

In this paper, we shall describe the neurocognitive deficits in patients with mild FvFTD that we have found, and outline differences with other neurodegenerative conditions (such as DAT and basal ganglia disorders) and patients with focal neurosurgical lesions (in particular, frontal and temporal lobe excisions). In the neuropsychological assessment of frontal lobe function in FvFTD, various tests may be applied to demonstrate that these patients show distinct deficits in comparison to other neurodegenerative conditions. Therefore, we shall describe the performance of these patients and other patient groups on computerized neuropsychological assessment, which includes tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB): (a) pattern recognition; (b) spatial recognition; (c) a planning task (the ‘one-touch Tower of London’); (d) a spatial working memory task; (e) an attentional set-shifting task, and (f) a decision-making task. These tests allow detailed automatic recording of response accuracy and speed via a touch-screen apparatus, and have been designed to reflect theoretical developments in the cognitive neuroscience of memory, attention, and executive functions [21]. This particular type of neuropsychological assessment also has the further advantages of facilitating cross-species comparisons between rats, primates, and humans, being also sensitive to a variety of brain pathologies and defined pharmacological challenges.

Neuropsychological Assessment

Pattern and Spatial Recognition

The CANTAB contains a test of visual pattern recognition memory using a serial recognition task analogous to other paradigms to test visual memory for sets of objects in nonhuman primates [22, 23], and a complementary test of visuospatial recognition memory. These tests have now been used in a variety of neurodegenerative diseases, and in patients with selective neurosurgical lesions. Performance on the pattern recognition test has been shown to be impaired in patients with temporal lobe excisions and amygdalo-hippocampectomy, whilst the spatial recognition test is sensitive to frontal lobe lesions [24]. The use of visual, nonverbal material enables comparisons to be made with the extensive nonhuman literature defining the neural and neurochemical substrates of visual learning and memory.

The recognition tests appear extremely sensitive to the cognitive deficits in probable dementia of the Alzheimer type (pDAT), patients with both mild and moderate pDAT being impaired on pattern and visuospatial recognition [25–27], presumably reflecting early temporal lobe pathology seen in DAT [28]. In a cross-sectional study of patients with Parkinson’s disease (PD) classified as either nonmedicated, medicated with mild disability, or medicated with severe disability [29], it was found that no
Fig. 1. Two tests of cognition to assess fronto-subcortical function. 
a ‘One-touch Tower of London’ – the subject is asked to work out the minimum number of moves that would be required to achieve the goal arrangement presented in the upper half of the screen from the arrangement in the lower half, and to make their response by pressing one of several choices offered on the screen. 
b Spatial working memory – a token can be revealed by touching the boxes: it will not be in the same box twice (see text for details).

patient group was impaired on the test of pattern recognition memory, and only the group with severe clinical disability were impaired on spatial recognition. In a study of patients with mild-moderate pDAT and patients with Huntington’s disease (HD) matched for severity of dementia [30], both groups were impaired on pattern and spatial recognition, with the HD group performing significantly worse on both tests. In contrast to other patients with neurodegenerative conditions, patients with fvFTD appear unimpaired on the pattern and spatial recognition task.

Tower of London
The ‘Tower of London’ task was modified by Shallice [31] from the earlier Tower of Hanoi task to stress the capacity for mental planning with only a single goal outcome specified. In one form of the task, after considering

the starting and goal configurations of a set of coloured balls on the screen, the subject manoeuvres these balls between the locations simply by touching them and their desired destinations. However, this nature of the task does not avoid completely the ‘on-line editing problems’ noted by Goel and Grafman [32], as subjects may have to stop to think during performance of the sequence. In a variant of this task (the ‘one-touch Tower of London’), the subject is asked to consider an arrangement of coloured balls hanging in ‘socks’ or ‘pockets’ to match a goal arrangement presented in the top half of the screen. Subjects are then simply asked to work out the minimum number of moves that would be required to achieve the goal arrangement, and to make their response by pressing one of several choices offered on the screen. This task provides a purer measure of the look ahead function in planning and its important memory component. A typical appearance of the computer screen during this task is shown in figure 1a.

Using the ‘one-touch Tower of London’, patients with fvFTD are found to be unimpaired compared to controls in the accuracy of their solutions. A possible explanation for this may be derived from what is known about the precise neural substrates underlying successful performance in this task. In a recent positron emission tomography (PET) neuroimaging study [33] using the ‘one-touch Tower of London’, regional increases in regional cerebral blood flow (rCBF) were produced in a distributed cortical network that included the superior occipito-parietal cortex and three main zones in the frontal cortex: the premotor area, a band of activation including the dorsolateral prefrontal cortex bilaterally and the frontopolar cortex on the right. Patients with mild fvFTD may therefore be relatively unimpaired in the ‘one-touch Tower of London task’ because, at that stage of disease, the site of pathology does not predominantly involve the dorsolateral prefrontal cortex.

Spatial Working Memory
Primates and humans have developed the capacity to process information ‘on line’, a capacity that is considered to underlie comprehension, thinking, and executive functions [34]. The spatial working memory task is essentially a modification of one used to examine the effects of dorsolateral prefrontal cortex lesions in primates [35], and is conceptually similar to the ‘radial arm maze’ which has been successfully used to assess the role of the hippocampus in working memory in rats [36]. The test is open-ended in the sense that the subject is free to produce his or her own ‘self-ordered’ sequences of responses.
In our version of the task, adapted for humans, subjects are required to ‘search through’ a number of red boxes presented on the computer screen (by touching each one) in order to find blue ‘tokens’ that were hidden inside. Figure 1b shows the typical appearance of a screen from this task. The object of the task is to avoid those boxes in which a token had already been found. Importantly, the subjects are able to search through the boxes in any order that they wish, although the number of boxes visited before a token was found was determined by the computer.

As can be seen in figure 2, neurosurgical patients with frontal lobe damage are significantly impaired on this task, making more returns to boxes (‘between search’ errors) in which a token had previously been found, at all levels of task difficulty as determined by the number of boxes employed (2, 3, 4, 6, or 8). This task may also be sensitive to deficits in patients with temporal lobe damage, although only at the most extreme level of task difficulty (i.e. 8 boxes); the task has also proved sensitive to deficits in medicated PD patients with both mild and severe clinical symptoms [37], HD patients [31], and also in patients with multiple system atrophy and Steele-Richardson-Olszewski syndrome [38].

Interestingly, we found that patients with fvFTD, even with their presumed frontal lobe pathology, are also relatively unimpaired on the test of spatial working memory. Again, a possible reason for this may be derived from what is known about the precise neural substrates underlying successful performance in the task. In recent PET studies, components of working memory have been investigated using a close analogue of the spatial working memory task [39]. These studies indicated two major areas of activation in the dorsolateral and ventrolateral prefrontal cortex. Further data suggest that the ventrolateral area may play a role in the ‘passive’ receipt of items for memory (as in spatial span performance), whereas the dorsolateral prefrontal cortex is important for the ‘monitoring’ role by which candidate sequences are compared with the goal sequence. A recent meta-analysis of functional neu-
Fig. 3. Stages of the attentional set-shifting task. Subjects have to choose between the two stimuli to receive positive feedback according to a learned rule. When they reach a criterion of six consecutively correct answers at each stage, they move onto the next stage unless 50 trials have occurred in which case the test is terminated. Reversal refers to a reversal of the contingencies, such that the correct and incorrect stimuli are unpredictably swapped. The stimuli are presented randomly with respect to spatial location. 1: Simple discrimination between shapes; 2 and 3: compound discrimination, in which the white lines are introduced as distractors; 4 and 5: dimensional shifts are implemented with unexpected changes to novel exemplars of both shape and line; with intradimensional shift, shape remains relevant (one of the new shapes is correct, regardless of its pairing with line); with extradimensional shift, line becomes relevant (one of the lines is correct, regardless of its pairing with shape).

Neuroimaging studies indeed suggests that the specific regions of the lateral prefrontal cortex (dorsolateral or ventrolateral) prefrontal cortex make identical contributions to both spatial and nonspatial working memory [40].

The observation that these patients with fvFTD are unimpaired on the spatial working memory task is useful since, arguably, successful planning in the Tower of London task places a significant load on spatial working memory not only in terms of the storage of a correct sequence but also in the search processes required in any analytical problem of this type by which possible solutions are considered and either rejected or accepted [41]. Furthermore, the lack of impairment in the spatial working memory task, in addition to the relative lack of impairment in the ‘one-touch Tower of London’ task, lends further support to the hypothesis that the dorsolateral prefrontal cortex is not predominantly affected in the mild stages of fvFTD. We now examine the evidence for the hypothesis that a major locus of dysfunction relatively early in the course of fvFTD is, rather, the ventromedial prefrontal (or orbitofrontal) cortex.

**Attentional Set-Shifting**

The Wisconsin Card Sorting Test (WCST) is the classical test of cognitive set-shifting. However, it is a deceptively complex task which may be solved using a number of different approaches. We have devised a computerized test of attentional set-shifting ability which deconstructs the WCST into its constituent elements. A detailed account of this attentional set-shifting paradigm has been described elsewhere [42, 43], but, in brief, the paradigm is based on studies of intradimensional and extradimensional shifts used to examine ‘attentional set’ in humans [44] and other animals [45].

In this paradigm, initially the subject is required to learn a series of discriminations in which one of two stimuli was correct and the other was not, using feedback provided automatically by the computer. The test is composed of nine stages presented in the same fixed order, represented pictorially in figure 3. The test begins with a simple discrimination (sd) and reversal (sd_r) for stimuli varying in one dimension (i.e. two purple filled shapes). A second, alternative dimension is then introduced (white line configurations) and compound discrimination (cd) and reversal (cd_r) were tested. To succeed, subjects have to continue to respond to the previously relevant stimuli (i.e. purple shapes), ignoring the presence of the new, irrelevant dimension (lines). At the intradimensional shift (id) stage, new exemplars are introduced from each of the two dimensions (new lines and new shapes) and subjects are required to transfer the previously learned rule to a novel set of exemplars from the same stimulus dimension. Thus, to succeed, they have to continue to respond to one of the two exemplars from the previously relevant stimuli (shapes). Following another reversal of contingencies (id_r), the extradimensional shift (ed) and reversal (ed_r) are presented and again, novel exemplars from each of the two dimensions are introduced. However, at this stage, the subject is required to shift ‘response set’ to the alternative (previously irrelevant) stimulus dimension and ig-
nore the previously relevant dimension. At each stage, a change in contingencies only occurs once the subject has learnt the current rule to a criterion of six consecutively correct responses. The subject is only allowed to proceed to each successive stage of the test if he or she reached criterion at the previous stage. This permits a clear and simple method of analysing and presenting the main results.

The proportion of subjects reaching criterion at each stage of the CANTAB attentional set-shifting paradigm is shown in figure 4. Patients with neurosurgical excisions of the frontal lobes are specifically impaired in their ability to shift response set to the previously irrelevant stimulus dimension (i.e. at the ed stage of learning), but not to shift attention to new exemplars of a previously relevant dimension (i.e. at the id stage of learning) [46]. The ed shift is a core component of the WCST, and the pattern of deficits reported in patients with frontal lobe damage on this test may be partly explained in these terms [47]. By comparison, patients with temporal lobe excisions and amygdalo-hippocampectomy patients have been found to be unimpaired in their ability to perform either shift [46], supporting the anatomical specificity of the ed shift. This observation concurred with previous reports that patients with unilateral or bilateral temporal lobe damage and a patient with bilateral hippocampal damage were unimpaired on the WCST [48, 49]. The ed shift stage has also been shown to pose particular difficulties for medicated and nonmedicated PD patients [43] and in patients in the preclinical and early clinical stages of HD [50, 51].

Figure 5 shows the number of errors made at the id and ed stages in the attentional set-shifting paradigm, for subjects who attempt both of these stages. Patients with frontal lobe excisions generally make more errors at the ed shift stage, compared to the id shift stage, and this is borne out as a significant difference in the patients with frontal lobe damage requiring more trials to criterion specifically at the ed shift stage. Figure 5 also demonstrates graphically the lack of deficit at the ed shift stage for temporal lobe excision patients [41] and for patients with DAT [after 52]. It is particularly interesting to observe that patients with mild pDAT, who exhibit significant memory deficits, are no worse than age- and IQ-matched controls at negotiating the attentional set-shifting test [52]. This is a very significant finding, as it implies that the deficits in extradimensional shifting are found patients with basal ganglia disorders. In contrast, the deficits present in early DAT resemble those produced by posterior or cortical, especially temporal lobe damage. A key observation regarding patients with mild fvFTD is that, compared to matched controls, they are unimpaired on the ed shift, both in terms of the number of errors made compared to the id shift and also in terms of the proportion of subjects reaching criterion.

However, if the total number of errors on the nonreversal stages (cd+id+ed) are compared with the total number of errors on the corresponding reversal stages (cd_r+id_r+ed_r), patients with fvFTD are found to show a deficit specific to the reversal stages [U = 8, W = 92.0, P = 0.0115; significant as p < 0.0167]. In preliminary analysis, including only subjects who attempt all stages of the task, this deficit has not been demonstrated in other patient groups (see fig. 6) (FLE: U = 71.5, W = 193, P = 0.216; TLE: U = 114, W = 400, P = 0.080; DAT: U = 4, W = 22, P = 0.248; all n.s. as p > 0.0167). The specific nature of the reversal deficit in patients with fvFTD is shown clearly in figure 6a–d. As the extradimensional shift is known to be more difficult than reversal shifting for normal subjects [42], it is unlikely that the deficit in reversal shifting (or indeed the above-mentioned deficit in extradimensional

**Fig. 4.** Performance on the attentional set-shifting paradigm, assessed in terms of the proportion of subjects reaching each stage of the test by producing six consecutively correct responses. Stages: s_d, simple discrimination; s_r, simple reversal; cp_d, compound discrimination, spatially discontiguous elements; ed, compound discrimination reversal; cd, compound discrimination reversal; id, extradimensional shift; id_r, intradimensional reversal; ed, extradimensional shift; ed_r, extradimensional reversal. Key as shown [data taken from 30, 37, 38, 46, 52].

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**Table 1.** Proportion of subjects reaching each stage of the test by producing six consecutively correct responses. Stages: s_d, simple discrimination; s_r, simple reversal; cp_d, compound discrimination, spatially discontiguous elements; cd, compound discrimination reversal; cd_r, compound discrimination reversal; id, extradimensional shift; id_r, intradimensional reversal; ed, extradimensional shift; ed_r, extradimensional reversal. Key as shown [data taken from 30, 37, 38, 46, 52].

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Cognition and Drug Therapy in Frontotemporal Dementia

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Fig. 5. Errors at the intradimensional (id) and extradimensional (ed) shift stages of the attentional set-shifting paradigm. Panels show errors for (a) frontal variant frontotemporal dementia (fvFTD); (b) frontal lobe excision (FLE); (c) temporal lobe excision (TLE) and (d) mild dementia of the Alzheimer type (DAT) patients. Control groups (Controls) were matched by age and premorbid intelligence with their respective patient groups [data from 41, 52].

Fig. 6. Cumulative errors at the nonreversal (cd+id+ed) and their corresponding reversal stages (cd_r+id_r+ed_r) of the attentional set-shifting paradigm. Panels show errors for (a) frontal variant frontotemporal dementia (fvFTD); (b) frontal lobe excision (FLE); (c) temporal lobe excision (TLE) and (d) mild dementia of the Alzheimer type (DAT) patients. Control groups (Controls) were matched by age and premorbid intelligence with their respective patient groups [data from 41, 52].
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shifting) is simply due to differences in task sensitivity. A recent PET imaging study using an adapted version of the attentional set-shifting paradigm revealed that, compared to the intradimensional shift scans, the extradimensional shift activated the frontal pole on the left side and areas 9/46 on the right, whereas reversal learning engaged neural circuitry associated with the ventromedial prefrontal cortex (e.g. the ventral caudate) [53]. In relation to this work and the nonhuman primate studies by Dias et al. [19, 20] described earlier, the specific reversal learning deficit of patients with fvFTD early in the course of the disease is consistent with the hypothesis that the pathology predominantly affects the orbitofrontal cortex or its connections, rather than the dorsolateral prefrontal cortex.

One intriguing alternative is that the deficits in reversal learning may reflect pathology affecting the caudate nucleus. Divac et al. [54] originally showed in primates that a lesion involving the ventrocaudal neostriatum impaired visual discrimination reversal. The hypothesis has therefore emerged that the ventrocaudal striatum is a critical link in the stimulus response, or habit learning circuit [55]. Neurones which reflect the responses of orbitofrontal neurones considered are found in the ventral head of the caudate nucleus and the ventral striatum, which receive input from the orbitofrontal cortex [56]. The behaviour of patients with fvFTD may also be in keeping with the few reports of the effects of focal caudate lesions. Mendez et al. [57] reported that patients with dorsal caudate lesions exhibited confused and disinterested behaviour, in contrast to patients with ventral caudate lesions who exhibited more disinhibited, euphoric and inappropriate behaviour. The existence of severe atrophy of the caudate in frontotemporal degenerative dementia has long been recognized [58], and one may speculate that it is not merely coincidental that neurones in the orbitofrontal cortex and the ventral head of the caudate may be affected, given the nature of the fronto-subcortical loops. In particular, neuronal degeneration within the orbitofrontal cortex might affect its predominant efferent connections as elucidated in the primate literature [59], for example the temporal lobe and the lateral hypothalamus.

Decision-Making

Although patients with mild fvFTD appear relatively unimpaired on certain probes of dorsolateral prefrontal function (spatial working memory and the ‘one-touch Tower of London’ planning task), these patients do show deficits in an aspect of the attentional set-shifting task sensitive to orbitofrontal or ventromedial function. Another test which can be used to examine cognition in patients with fvFTD is a decision-making task [described in detail in 60], which has previously been found to be sensitive to ventromedial or orbitofrontal function, rather than dorsolateral prefrontal function. The three principal measures in this task are: (a) the speed of decision-making, i.e. how long it takes the subject to decide which colour of box is hiding the token as measured by the mean deliberation time; (b) the quality of decisions: as an ineffective approach is to bet continuously on the least likely of the two possible outcomes, one measure was how much of the time the subject chose the most likely outcome, and (c) risk adjustment, i.e. the rate at which a subject increases the percentage of the available points bet in response to more favourable ratios of red:blue boxes (e.g. 9 red:1 blue vs. 4 red:6 blue). The differences between the patients with mild fvFTD and their age- and IQ-matched controls in these three measures are shown in figure 7a–c.

Using this decision-making task, we have shown that patients with fvFTD are different from their age- and IQ-matched controls in that they are willing to bet a much higher proportion of their accumulated reward at all ratios. Furthermore, they show no significant difference from controls in their tendency to choose the most likely outcome, and exhibit increased deliberation times. Therefore, to summarize, although patients with fvFTD may make accurate probability judgements, they are unable to adjust the levels of their bets accordingly. As they are not merely impulsive in making their decisions, they appear to be true risk-takers. There are broad similarities in the performance of the patients with fvFTD and the patients with ventromedial lesions studied by Damasio and co-workers [18, 61]. Both groups of patients make abnormal decisions that are no longer personally advantageous, and in particular have difficulty planning their future over immediate, medium and long ranges. In general, neither the group described by Damasio and co-workers, nor our patient group, is able to adjust their behaviour successfully and appropriately to the task opportunities available. One explanation that has been proposed for the poor performance in the gambling task of patients with ventromedial lesions described by Bechara et al. [62] is that there exists a failure to anticipate future outcomes, and this may also be a possible reason for the poor performance of the patients with fvFTD in the decision-making task. Of added interest is the observation that similar increases in deliberation times in the decision-making task may be produced in those normal volunteers with acutely reduced tryptophan and reduced 5-HT function who demonstrate the most severe deficits in decision-making [60].
**Fig. 7.** Decision-making task. (a) % bets; (b) deliberation times (ms) and (c) % choice of most likely outcome, shown for mild frontal variant frontotemporal dementia patients and control subjects, matched for age and premorbid intelligence level.

**In Summary:** Patients with mild fvFTD appear unimpaired on neuropsychological assessment on tests of visuospatial mnemonic function (pattern and spatial recognition), which are known to be sensitive to deficits in patients with mild DAT. They may show most marked deficits on tests sensitive to ventromedial or orbitofrontal function (for example, the decision-making task and the reversal stages of the attentional set-shifting task), and be relatively unimpaired on tests sensitive to dorsolateral prefrontal function (for example, the spatial working memory task and the ‘one-touch Tower of London’). These neuropsychological findings may bear some relevance to the behavioural presentation of these patients in the clinic. Certain behavioural symptoms are in particular associated with dysfunction of the orbitofrontal-subcortical circuit, for example disinhibited behaviour, obsessive and compulsive behaviour, and changes in eating behaviour [63]. The presence of these same symptoms in fvFTD, disinhibition [64], compulsive behaviours (in particular repetitive checking activities) [65], and increased sweet and carbohydrate preference [66], is therefore of considerable theoretical interest. Therefore, specific deficits found upon formal neuropsychological assessment can potentially provide important clues as to the neural networks that are compromised in disease, and therefore the neurotransmitter systems involved. This, in the longer term, may help to identify any neurotransmitter systems principally affected by disease, and lead to developments in therapeutic strategies.

**Therapeutic Strategies**

There is currently a need for full-scale studies of the effects of putative cognitive enhancers in fvFTD, in stark contrast to the magnitude of trials currently being carried out with DAT patients. The evidence implicating cholinergic neurones in the decline in memory and cognition in ageing and in DAT has been reviewed elsewhere [67]. However, neurochemical studies concerning fvFTD are rather limited. Francis et al. [68] reported normal levels of noradrenaline (NA), serotonin (5-HT) and dopamine (DA) metabolites in a patient with fvFTD, but low release values of NA (with high release values of 5-HT and DA from autopsy tissue). Coull et al. [69] therefore considered one method of increasing noradrenergic activity by giving patients a moderate dose of an α₂ antagonist, idazoxan (IDZ), which acts presynaptically to elevate synaptic con-
centrations of NA [70]. They found that IDZ produced dose-dependent improvements in performance, particularly on tests of planning, sustained attention, verbal fluency and episodic memory.

In contrast, IDZ produced deficits in performance on a test of spatial working memory, which we have previously described as being sensitive to dorsolateral prefrontal function. The results also indicated that if patients were impaired on the working memory task, the deficit might be further exacerbated by IDZ. It is of particular interest, as can be seen from figure 2, that patients with fvFTD may be relatively unimpaired on the spatial working memory task. This may have some relevance to the detrimental effect of IDZ in fvFTD patients on this task, in that IDZ may somehow have an ‘overdose’ effect upon performance, and highlights further the neural specificity of the deficits in fvFTD. It is notable that IDZ has also recently been found to produce deficits in spatial working memory in patients with pDAT [71].

It may be of some relevance that in aged monkeys with naturally occurring catecholamine depletion, α2 adrenergic agonists such as guanfacine have repeatedly been shown to improve dorsolateral prefrontal cortical function assessed using a spatial delayed response task [72]. The cognitive-enhancing properties of these agonists may be considered to be a consequence of their action at post-junctional noradrenergic receptors. Also, in aged monkeys, improvements in performance on the delayed response task induced by a variety of α2 agonists can be blocked by α2 antagonists such as yohimbine and IDZ, but not by the α1 antagonist, prazosin [73]. However, the detrimental effects of IDZ upon spatial working memory may also be explained in terms of recent developments in elucidating how IDZ interacts with other neurotransmitter systems. It is now known that IDZ is an agonist at 5-HT1A autoreceptors modulating 5-HT synthesis in the rat brain in vivo, causing overall a reduction in the synthesis of 5-HT in the cerebral cortex [74]. It is widely recognized that 5-HT constrains the activity of DA, resulting in an opposing relationship between DA and 5-HT [75], and so a decrease in activity in the serotonergic activity potentially could lead to ‘overdosing’ of the dopaminergic neurotransmitter system. Consistent with this hypothesis, Matsumoto et al. [76] have recently demonstrated that IDZ can induce an increase in DA release in the prefrontal cortex. This is important as excessive DA activity in the prefrontal cortex has previously found to be detrimental to many cognitive functions mediated by the prefrontal cortex, including working memory [77].

The specific nature of cognitive deficits seen in patients with mild fvFTD do, however, provide some important insights into the nature of the neurotransmitter systems which may be compromised early in the disease process. Deficits in reversal learning similar to those seen in patients with fvFTD can be seen with dysfunction of serotonergic neurotransmitter systems in the prefrontal cortex. Normal subjects with low levels of 5-HT centrally induced by a low tryptophan drink, when required to perform a simple rule reversal in the presence of an irrelevant dimension (the cd_r stage), needed more trials to learn this rule, in comparison to subjects receiving placebo [78]. Nomura [79] has reported an analogous effect in rodents: rats given a low tryptophan diet showed impaired learning in an operant type discrimination learning paradigm. In the decision-making task, patients with fvFTD show marked increases in deliberation times, akin to those seen in normal volunteers with acutely reduced 5-HT function.

Miller et al. [66] have recently suggested that some of the symptoms associated with FTD are related to serotonergic dysfunction. Weight gain exceeding 4.5 kg occurred in 64% of FTD patients, and a change in food preference to carbohydrates occurred in 75%. Also, severe compulsions were found in 64% of individuals with FTD. There is indeed currently some neurochemical evidence from postmortem studies to suggest that there exist profound postsynaptic serotonergic receptor abnormalities in patients with FTD in comparison to controls [80]. It is noteworthy that, in this study, reduced total 5-HT receptor binding was found in samples of tissue from autopsy-proven cases of FTD from the frontal pole, temporal pole and the hypothalamus, but not in the cholinergic cells of the nucleus basalis of Meynert, in comparison to controls. In any case, various other studies [68, 81] converge upon the notion that the neurochemical changes of FTD have a profile distinct from that of DAT.

Many of the symptoms of fvFTD are indeed currently treated using serotonin-boosting compounds, including impulsive behaviour [82], depression [83], alterations in eating habits [84], and obsessions and compulsions [85]. Swartz et al. [86] have demonstrated in preliminary studies that it is possible to ameliorate many of these specific symptoms, including impulsivity, depression, carbohydrate craving and compulsions, in fvFTD patients by using 5-HT-boosting compounds. Mild improvements in eating disorders have also been noted. However, as the authors themselves acknowledged, this study suffered from an uncontrolled and unblinded design and the use of three different SSRIs. Clearly, more studies have to be
done in this area to examine objectively the effects of 5-HT-boosting compounds upon behavioural symptoms, and in particular the effect upon these compounds upon cognition given the potential problems that may occur, described earlier for IDZ. It shall also be useful to consider in particular whether a specific pattern of presenting clinical symptoms may predict response to therapy.

The accurate diagnosis of symptoms in patients is therefore extremely important. For example, Levy et al. [87] recently highlighted that apathy did not correlate with depression in a combined sample of patients, including 28 patients with FTD, and hence that distinguishing the two syndromes might have therapeutic implications. This is important given that apathy may be a later presentation in fvFTD [64]; furthermore, apathy may be associated with significantly reduced rCBF in the dorsolateral (rather than the orbitofrontal) prefrontal cortex [88, 89]. Agents used to treat apathy behaviourally have previously included drugs that modify dopaminergic neurotransmission including amphetamine, bromocriptine and methylphenidate [90]. These drugs may also be of some use in treatment of cognitive deficits consequent upon dysfunction of the dorsolateral prefrontal cortex later in the disease process. A landmark study by Brozoski et al. [91] demonstrated that 6-hydroxydopamine lesions of the dorsolateral prefrontal cortex in rhesus monkeys was as devastating to memory performance as removing the cortex itself, and that, importantly, this impaired performance could be reversed by DA agonists such as L-dopa and apomorphine. In relation to this, it is useful to note that Elliott et al. [92] have demonstrated significantly enhanced performance in tests of spatial working memory and planning in healthy young adults, using methylphenidate, a stimulant related to amphetamine [93]. It is therefore clear that much can be accrued from a comparative approach to frontal lobe function not only for our understanding of the neuropsychological deficits in patients with fvFTD, but also for the development of successful therapeutic strategies.

**Conclusions**

Whilst it is understood that various divisions of the prefrontal cortex appear to have different patterns of anatomical connectivity and function, the precise ways in which they interact to control cognition and behaviour in social and nonsocial contexts is still relatively poorly understood. A precise understanding of the nature of frontal lobe function in humans and nonhuman primates, and a precise characterization of cognition and behaviour in patients with early frontal variant frontotemporal dementia, can complement each other not only in addressing this problem, but also in the development of novel rational therapeutic strategies for intervention in patients in the mild stages of disease. It is hoped that this will result in substantial benefits for these patients in terms of their cognition and behaviour.

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