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Decision-Making in Frontotemporal Dementia: Clinical, Theoretical and Legal Implications

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Key Words
Frontotemporal dementia · Decision-making · Free will

Abstract
Background: The behavioral variant of frontotemporal dementia (bvFTD) is characterized by progressive changes in personality and social interaction, loss of empathy, disinhibition and impulsivity, most of which generally precede the onset of cognitive deficits. In this study, we investigated decision-making cognition in a group of patients with an early bvFTD diagnosis whose standard neuropsychological performance was within normal range for all variables. ***Methods:*** The Iowa Gambling Task was administered to this group of early bvFTD patients, to a group of early bvFTD patients who had shown impaired performance on the classical neuropsychological battery and to healthy controls. ***Results:*** Decision-making was impaired in both bvFTD patient groups, whether they had shown impaired or normal performance in the classical neuropsychological evaluation. ***Conclusions:*** Patients with early bvFTD may perform normally on standard cognitive tests, and yet develop severe deficits in judgment and decision-making. In many current legal systems, early bvFTD patients showing preserved cognitive functioning who commit unlawful acts run the risk of not being able to plead insane or not guilty on the grounds of diminished responsibility beyond reasonable doubt. This represents a unique legal and ethical dilemma. Our findings have important implications for medicolegal decisions relating to capacity and culpability, and regarding the philosophical concept of 'free will'.

Introduction

In clinical practice, it is not uncommon to find early behavioral-variant frontotemporal dementia (bvFTD) patients who, to a considerable extent, are intellectually unimpaired [1, 2], while relatives and caregivers depict a strikingly different picture: they claim that these patients show severe changes in their behavior and real-life decision-making skills. Although patients with frontal lobe damage usually maintain normal intellectual functioning, they develop difficulties in planning workday and future events, and in choosing friends, partners and activities, and their actions frequently lead to diverse losses in terms of financial status and social standing [3]. For this reason, being able to detect execution-related deficits in bvFTD is fundamental as now the executive domain represents a core feature of the newly proposed diagnostic criteria for bvFTD [4, 5]. Further complicating diagnosis, early bvFTD

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patients may show intellectual functioning within a normal range long after the onset of social and legal problems. Most frequently, mental competence is established by expert legal witnesses via classical neuropsychological batteries or brief cognitive screening tests. While legal regulations concerning patients with dementia currently exist, they are incongruent with the particular case of early bvFTD patients because they are based on the performance profile of patients with dementia of the Alzheimer type whose cognitive and behavioral changes are different both qualitatively and quantitatively.

The Iowa Gambling Task (IGT) was developed to mimic decision-making in real-life scenarios [6] and was initially linked to orbitofrontal cortex dysfunction. While recent studies have confirmed the association of this measure of decision-making with orbitofrontal cortex integrity, they have also highlighted the importance of other prefrontal regions for this task, including the dorsolateral prefrontal cortex, the amygdala, the basal ganglia and the anterior cingulate cortex, among others [7–9]. Our laboratory has recently demonstrated important deficits in decision-making using the IGT in the initial phases of bvFTD [2, 9, 10]. Such deficits seem to stem from the degeneration of the prefrontal cortex typical of this disease [9], which also affects executive functions. In fact, the role of executive functions in decision-making is still controversial [11, 12]. On the one hand, it seems to be the case that impaired executive processes may impact performance on decision-making tasks [8]; on the other hand, correlations between IGT performance and executive tasks have not consistently been found throughout the literature [9], suggesting that the IGT measures an ability to make decisions under the demands of real-life scenarios which goes beyond executive functioning.

In the present study, we report the first detailed analysis of early bvFTD patients who showed selective impairment of decision-making but otherwise performed normally on a standard neuropsychological battery. Their performance was analyzed in detail and compared with a group of early bvFTD patients who had shown impaired performance on neuropsychological tests, as well as with healthy controls.

Patients and Methods

Participants

Forty-three patients with an established diagnosis of bvFTD were recruited for this study. The diagnosis was initially made by two experts in FTD (F.M. and T.T.). Then, each patient was individually reviewed in the context of a multidisciplinary clinical meeting. Patients were only considered for the present analysis if (a) they or their family had signed an informed consent form prior to their inclusion in this study; (b) they fulfilled the Lund and Manchester criteria for bvFTD diagnosis [13]; (c) they did not meet any criteria for specific psychiatric disorders based on the DSM-IV [14] upon interdisciplinary assessment, or a history of head trauma; (d) they were rated by their caregiver as 'mild' or 'below' on the Clinical Dementia Rating Scale (CDR score $\leq$1) [15], and (e) they showed a pattern of frontal atrophy on MRI, and (f) they scored below 9 on the Beck Depression Inventory II (BDI-II) [16]. The interrater reliability of the diagnosis was excellent (Cohen's $\kappa = 0.93$). All patients presented with prominent changes in personality plus social behavior, verified by a caregiver. Patient follow-up as part of our FTD program enabled us to follow these early bvFTD patients longitudinally to confirm that all of them ultimately developed clinical and radiological signs compatible with the full syndrome of bvFTD.

For purposes of comparison, we recruited a group of healthy controls (n = 14) from the same geographical area as the patients, matched for age, gender and level of education. The healthy controls reported no history of psychiatric or neurological disorders, as well as no history of substance abuse.

Procedure

For the purposes of this study, data derived from the neuropsychological battery included tests of (a) general cognitive status by the Mini-Mental State Examination (MMSE) [17] and Addenbrooke's Cognitive Examination-Revised (ACE-R) [18]; (b) verbal memory by the story recall subtest of the Wechsler Memory Scale-Revised (WMS-R) [19] and the Rey Auditory Verbal Learning Test (RAVLT) [20]; (c) visual memory by the Rey Complex Figure Copy [20]; (d) language by the abbreviated version of the Boston Naming Test [21] and semantic fluency (animals) [22]; (e) attention by the forward digit span task of the WMS-R [19] and the Trail-Making Test Part A (TMT-A) [23], and (f) executive functioning by the backward digit span task of the WMS-R [19], phonological fluency (letter P) [22] and the TMT-B [23].

Experimental Task: IGT

The participants were assessed by a task designed to mimic real-life affective decision-making: the IGT [6]. The results of the IGT were not used for diagnosis. In this task, participants are asked to choose cards from four decks (A–D) in order to win as much money as possible throughout the game. The task is completed after 100 selections, although participants are unaware of this. Following card selection, participants receive a certain amount of money (reward), but some card choices also result in loss of money (penalties). Decks A and B are ultimately risky (great immediate reward with severe penalties), while C and D are more conservative (poorer immediate rewards with small penalties). Net earnings may only be obtained by consistently selecting from low-yield decks (C and D). The dependent variable on this task is the net score, calculated as the number of choices from the safe decks (C and D) minus the number of choices from the risky decks (A and B). In order to quantify the progression of decision-making preference profiles throughout the task, a net score is calculated for 5 blocks of 20 consecutive cards.

Statistical Analysis

Individual Z scores were calculated for all neuropsychological variables for which normative data were available based on gen-

der, age and years of education. Performance on each variable was classified as being impaired if the Z score for that particular variable was lower than –2 SD. For tests with a known cutoff score (e.g. 88 points on the ACE-R), performance was classified as impaired if the participants scored below the proposed cutoff score. After all available variables were considered, bvFTD patients were classified as having normal neuropsychological performance (NNP group) if they were impaired in 1 or none of the neuropsychological variables. Patients who showed impaired values on 2 or more scores were classified as having impaired neuropsychological performance (INP group). Similar procedures for classifying 'high'- and 'low'-performance bvFTD patients have previously been reported in the literature [1]. Preliminary analysis revealed that all participants originally recruited for the control group had normal neuropsychological performance, which is why they were all clustered into a unique control group (CTR). Comparisons across the three groups were performed using one-way ANOVA with Bonferroni post hoc tests when relevant. For comparisons between two groups at a time, independent t tests were performed. Categorical data (e.g. gender, Rey Figure recognition) were analyzed using χ^2 tests for 2 × 3 contingency tables. Pearson's correlation coefficients were used to analyze relationships between variables of the neuropsychological battery and scores on the IGT. The α value was set at 0.05, two-tailed for all analyses.

Results

Demographic and Clinical Profile

Based on the aforesaid criteria, of the 43 bvFTD patients, 13 were classified into the NNP group and 30 into the INP group. The 14 participants in the CTR group showed normal performance. As shown by table 1, no significant differences were found across the groups for age ($F_{2, 54} = 1.35$; $p = 0.27$), gender ($\chi^2 = 0.45$; d.f. = 2; $p = 0.80$) or years of education ($F_{2, 54} = 0.52$; $p = 0.60$). No significant differences were found between the NNP and INP groups in their CDR scores ($t_{41} = -0.74$; $p = 0.45$). Moreover, the groups did not differ on their BDI-II scores ($F_{2, 54} = 0.64$; $p = 0.58$).

Neuropsychological Performance

Significant differences were found across the groups in all variables of the standard neuropsychological battery (table 2). In all cases, INP differed significantly from both NNP and CTR, except for forward digit span ($F_{2, 54} = 9.88$; $p < 0.001$) and semantic fluency ($F_{2, 54} = 34.2$; $p < 0.001$), in which INP differed significantly from CTR (both: $p < 0.001$), but not from NNP (forward digit span: $p = 0.19$; semantic fluency: $p = 0.37$). No significant differences were found between NNP and CTR in any of the neuropsychological variables.

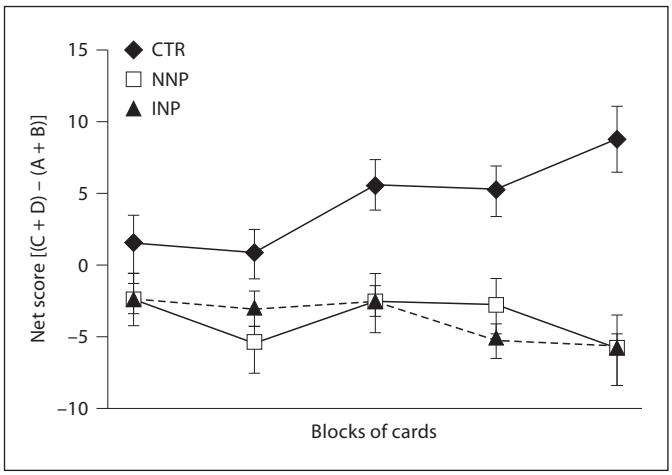

Fig. 1. IGT performance. A significant difference was found between the groups in blocks 3, 4 and 5. NNP and INP did not differ from each other, but both differed from CTR. Error bars: SEM.

Table 1. Demographic and clinical variables for participant groups based on their neuropsychological performance

	CTR (n = 14)	NNP (n = 13)	INP (n = 30)
Age, years	65.5 ± 6.5	67.5 ± 7.2	69.3 ± 7.6
Gender (m:f), n	7:7	7:6	13:17
Education, years	13.9 ± 3.1	14.6 ± 3.7	13.2 ± 4.8
CDR, total score	–	0.63 ± 0.2	0.75 ± 0.4
BDI-II, total score	4.63 ± 4.5	5.4 ± 4.2	5.7 ± 3.9

Values denote means ± SD unless otherwise specified.

Decision-Making Profile

As shown in figure 1, while no significant differences were found across the groups in block 1 ($F_{2, 54} = 1.5$; $p = 0.23$) and block 2 ($F_{2, 54} = 2.4$; $p = 0.10$), a significant difference was found in blocks 3 ($F_{2, 54} = 6.4$; $p < 0.01$), 4 ($F_{2, 54} = 9.2$; $p < 0.001$) and 5 ($F_{2, 54} = 19.1$; $p < 0.001$). For the last 3 blocks, the performance of CTR on the IGT differed significantly from both NNP (block 3: $p = 0.011$; block 4: $p = 0.019$; block 5: $p < 0.001$) and INP (block 3: $p < 0.01$; block 4: $p < 0.001$; block 5: $p < 0.001$). However, no significant differences were found between NNP and INP in these blocks. A total net score was calculated as the sum of the 5 blocks' net scores. The mean ± SD was +21.9 ± 19.9 for CTR, –19.9 ± 23.5 for NNP and –17.8 ± 18.2 for INP. The differences between the groups were

Table 2. Scores for variables of the standard neuropsychological battery

	CTR (n = 14)	NNP (n = 13)	INP (n = 30)	$F_{2, 54}$	p	CTR vs. NNP	CTR vs. INP	NNP vs. INP
ACE-R	94.5 ± 5.2	90.5 ± 4.2	73.8 ± 13.9	22.5	<0.001	n.s.	<0.001	<0.001
MMSE	29.2 ± 1.0	28.4 ± 2.1	24.9 ± 4.2	10.2	<0.001	n.s.	<0.001	<0.01
Story recall – immediate	25.1 ± 8.9	24.3 ± 6.2	11.8 ± 6.4	24.2	<0.001	n.s.	<0.001	<0.001
Story recall – delayed	20.1 ± 8.8	18.9 ± 5.8	4.37 ± 5.1	40.2	<0.001	n.s.	<0.001	<0.001
Story recall – recognition	17.0 ± 2.8	16.6 ± 3.5	10.3 ± 4.4	19.9	<0.001	n.s.	<0.001	<0.001
RAVLT – immediate	42.5 ± 11.7	37.6 ± 9.6	21.4 ± 6.8	33.1	<0.001	n.s.	<0.001	<0.001
RAVLT – delayed	8.93 ± 3.6	6.62 ± 2.2	2.00 ± 2.3	32.1	<0.001	n.s.	<0.001	<0.001
RAVLT – recognition	12.5 ± 2.4	11.6 ± 1.5	8.40 ± 4.4	8.07	0.001	n.s.	0.001	0.023
Rey figure – copy	34.4 ± 1.8	35.1 ± 1.1	27.3 ± 9.4	8.31	0.001	n.s.	<0.01	<0.01
Rey figure – delayed	18.5 ± 8.7	16.5 ± 6.7	6.20 ± 4.5	23.7	<0.001	n.s.	<0.001	<0.001
BNT	19.8 ± 0.4	19.1 ± 1.1	17.2 ± 3.5	5.31	<0.01	n.s.	<0.001	<0.001
Semantic fluency	20.7 ± 5.2	19.2 ± 4.7	9.63 ± 4.7	34.2	<0.001	n.s.	<0.001	n.s.
Phonological fluency	17.5 ± 5.7	17.2 ± 6.3	9.03 ± 5.9	14.0	<0.001	n.s.	<0.001	<0.001
Forward digit span	7.4 ± 1.3	6.4 ± 1.0	5.57 ± 1.4	9.88	<0.001	n.s.	<0.001	n.s.
Backward digit span	5.00 ± 1.1	4.5 ± 1.3	3.10 ± 1.3	13.3	<0.001	n.s.	<0.001	<0.01
TMT-A, s	39.4 ± 16.4	46.0 ± 14.2	100.9 ± 74.2	7.93	0.001	n.s.	<0.01	0.013
TMT-B, s	94.1 ± 44.3	101.2 ± 23.5	246.2 ± 68.4	50.6	<0.001	n.s.	<0.01	<0.001

Values denote means ± SD. F and associated p values are presented for ANOVA comparisons across the groups. Bonferroni post hoc p values are shown on the 3 rightmost columns for group-to-group comparisons. BNT = Boston Naming Test; n.s. = not significant.

significant ($F_{2, 54}$ = 16.6; $p < 0.001$), with CTR outperforming both NNP ($p < 0.001$) and INP ($p < 0.001$), while the bvFTD groups did not differ between each other (p = 0.99).

Correlations

Correlations were established between variables of the neuropsychological battery and both the IGT net score for block 5 and the total net score. These two variables were chosen for the IGT because they represent decision-making behavior toward the end of the task and the overall decision-making profile, respectively. No significant correlations were found within the NNP group between variables of the neuropsychological battery and the net score for block 5 (r range: –0.37 to 0.51; p range: 0.18–0.99), and the total net score (r range: –0.48 to 0.39; p range: 0.13–0.94). However, when correlations were analyzed within the INP group, significant correlations were found between block 5 and the MMSE (r = –0.44; p = 0.015), the ACE-R (r = –0.55; $p < 0.001$), the recognition score of the story recall task (r = –0.49; $p < 0.01$), the immediate (r = –0.52; $p < 0.01$), delayed (r = –0.55; $p < 0.01$) and recognition scores of the RAVLT (r = –0.42; p = 0.021), the delayed score of the Rey Figure (r = –0.39; p = 0.032), as well as phonological (r = –0.38; p = 0.048) and semantic fluency (r = –0.51; $p < 0.01$). Similarly, significant correlations were found between the overall net score and the MMSE (r = –0.40; p = 0.027), the ACE-R (r = –0.43; $p < 0.016$), the immediate score of the RAVLT (r = –0.44; p = 0.013) and semantic fluency (r = –0.43; p = 0.017).

Discussion

The present study demonstrated, for the first time, that a group of early bvFTD patients showed abnormal decision-making, as measured specifically by the IGT, despite a normal performance on standard cognitive tasks. Although previous studies had documented that patients with prefrontal damage as a consequence of acute brain injury displayed severe impairments of real-life decision-making (despite remaining intellectually unimpaired [24, 25]), this had not previously been demonstrated in patients with early bvFTD using this particular task.

These findings have important clinical, theoretical and legal implications. From a clinical perspective, the IGT currently appears to be one of the most sensitive tests for patients with early bvFTD, especially in the context of

cognitive batteries aimed at replicating real-life scenarios more reliably [2, 4, 9, 10]. A recent revision of diagnostic and research criteria for bvFTD was proposed in the hope of achieving higher shared comparability between research groups [5] while providing a more comprehensive clinical profile of this disease. Deficits in executive functions which can be related to decision-making are now considered a core feature [5]. In this respect, the presence and detection of executive dysfunction and/or impairment of decision-making may in itself be particularly useful for diagnosis during the early stages of the disease [26].

Decision-making involves evaluating possible reward and punishment outcomes associated with a variety of response options and the selection of which option one thinks will be most beneficial. Early bvFTD patients were prone to choose from the risky decks, lured by the prospect of immediate reward, but were less sensitive to the future consequences of their choices. This pattern is consistent with the real-life difficulties of frontal patients, and has been called 'myopia for the future' [27]. Decision-making deficits were initially linked to orbitofrontal dysfunction [6], but more recent studies suggest that decision-making implicates indeed a much wider neuronal distributed network recruiting larger prefrontal cortical areas [7–9]. Consistently, patients with bvFTD have a predilection for making decisions based upon instant short-term reward despite the potentially massive long-term risks to their personal health and finances.

An earlier study in a group of patients with more advanced stages of bvFTD [28] had demonstrated that their behavior was genuinely risk appetitive, rather than cognitively impulsive. In the present study, our early bvFTD patients selected the riskiest decks and made choices that were no longer advantageous. Crucially, these are the types of choices that are remarkably different from the kinds of choices they might have made in the premorbid period, as informally reported by relatives. However, against a background of relatively preserved global intellectual function, these patients have abnormalities in emotion and feeling that can affect normal decision-making [29]. The bvFTD patients appear to know what is wrong or right [30]; however, they consistently chose disadvantageously [31]. Accordingly, previous reports have documented that, towards the end of the task, patients stated that they 'could not stop' selecting cards from those decks with which they won more money in spite of their awareness of which were the riskiest decks [28]. The question is clearly whether there is a fundamental defect of impulse control.

From the perspective of jurisprudence, current regulations and laws intended to deal with dementia of the Alzheimer type are rather inadequate in these cases of early bvFTD. Standards for determining 'mental competence' across various jurisdictions or legal systems are typically based upon rudimentary cognitive screening or classical neuropsychological test evaluations [32–36]. Patients with early bvFTD may perform well in these cognitive batteries, and yet exhibit gross deficits in real-life decision-making, accompanied by profound changes in personality. Families of patients with bvFTD can be faced with individuals who behave bizarrely, make financial mistakes that may lead to bankruptcy, or behave sexually towards them, but unfortunately have no insight into their problems. Crucially, they may perform normally on standard tests of intellectual function. For this reason, the present study highlights an urgent necessity to develop a more informed approach to how bvFTD patients should interact with the criminal justice system if necessary.

Under the current legal system, in many jurisdictions, bvFTD patients – whose prefrontal dysfunction may result in unlawful behavior, but who still exhibit preserved cognitive function – might be demonstrated to offend the law in the absence of strong evidence of neurocognitive dysfunction. For example, patients with bvFTD can violate social norms and perform unlawful behavior, but under the modern criminal justice system, which emphasizes the assumption of free will and voluntariness, may not qualify for a defense of 'not guilty by reason of insanity' [37]. In bvFTD, a fundamental issue is that the individual instead appears to be afflicted by a disorder of his or her free will, as evidenced by repeated decisions and actions that are against the person's best interest, and failure to learn from repeated mistakes, in spite of perfectly intact intellect, memory and other cognitive functions [38]. Defining the precise decision-making abnormality is now essential as, in the law, bvFTD patients may be unable to resist an 'irresistible impulse' of abnormal criminal behavior (long established in multiple jurisdictions in the history of the insanity defense). This naturally opens a significantly wider philosophical debate about the concept of free will, which must be cautiously and meticulously approached from an interdisciplinary perspective. As regards the present discussion, however, it still remains a moot point whether the IGT provides reliable (and admissible) information regarding impulsive disorders on the one hand and risk-taking behavior on the other hand. A defense lawyer might even wish to pursue a different defense to 'not guilty by reason of insanity' by arguing 'diminished responsibility'.

Further research in this area is needed in order to contribute to at least two different issues. First, from a neuroscientific point of view, it should be determined whether there is a specific pattern of brain degeneration that is specific to the group of patients who perform as expected on neuropsychological functional tests, yet show very poor performance on a decision-making task. Second, future studies should help develop new evidence-based policy guidelines to help families deal with the potentially devastating consequences of this disease. The development of sensitive yet brief batteries that are readily available for administration is essential [4]. At the heart of the matter is the frustration that both clinicians and relatives experience when a satisfactory cognitive performance appears at odds with material changes in social behavior.

We hope that this new research on human decision-making will ultimately lead to greater clarity in the criminal justice system and, more importantly, start a discussion as to how patients with specific diseases can be held accountable for their own behavior. This will require a synthesis of diverse interdisciplinary approaches, but the benefits to the efficacy of the criminal justice system when dealing with such conditions could be enormous.

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