Frontotemporal dementia and neuropsychology: the value of missing values

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Abstract

Objective—To investigate the effect of missing values due to behavioural disturbances on the neuropsychological test profile in frontotemporal dementia (FTD). The neuropsychological examination of patients with FTD poses a methodological problem. In many patients it is impossible to administer a complete test battery, due to behavioural disturbances inherent to the disease. This study describes the test behaviour of patients with FTD, the number of missing values due to disturbed test behaviour, and its influence on neuropsychological test results.

Methods—Thirty one patients with probable FTD were administered a neuropsychological test battery including measures of memory, intelligence, and executive functioning. Moreover, patients were rated on a global deterioration scale and a test behaviour scale, constructed for this study.

Results—The more disturbing the test behaviour, the less tests were assessable, leading to many missing values. The most disturbing features were “positive symptoms” of FTD, such as perseveration and stimulus boundedness. The effect of test behaviour was largest for tests measuring executive functions and reasoning capabilities. The replacement of the missing values due to behavioural disturbances by the lowest score also showed the largest effect on tests of executive function and reasoning abilities.

Conclusion—Data imputation of missing values due to test behaviour disturbances provides a more differentiated picture of cognitive deficits in FTD.

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Keywords: dementia; frontal temporal; neuropsychological tests; test behaviour

Frontotemporal dementia (FTD) is a form of primary degenerative dementia with characteristic clinical features. The disease is usually seen in the presenium and is highly familial. It presents with progressive personality changes, behavioural alterations, and neuropsychological disturbances.^{1,2} Some studies have investigated these neuropsychological features of FTD.³⁻⁷ Most of these studies have shown a specific profile of cognitive functioning, characterised by progressive deterioration of language and executive functions with secondary memory disorders and initially preserved spatial skills.

Usually, these neuropsychological studies describe small, selected samples of patients who are in the early course of the disease. The neuropsychological examination of patients with FTD poses a methodological problem, because it requires mental effort, attentiveness, and accuracy on the part of the patients. These are precisely the faculties that are disturbed in FTD. In many patients, it is therefore impossible to administer a complete test battery. As a result, the investigator is left with many missing values in the data set. It is plausible that the number of missing values is related to the severity of the behavioural problems. Although probably inherent to the disease, the problem of missing values in this patient group has never been investigated. Most studies on FTD do mention intervening behaviour disturbances during examination, but the reliability of the data set is usually not questioned. Yet, only describing valid test results and disregarding missing values will provide us with an underestimation of the cognitive deficits in FTD.

Therefore, we studied aspects of test behaviour that are characteristic of FTD to determine their relation with missing values and their influence on the profile of neuropsychological test results. We also took age, severity, and duration of disease as possible confounding factors into account.

Patients and methods

METHODS

Inclusion procedure

This study is part of a population based study in The Netherlands on FTD. Inclusion procedure and design have been described in detail elsewhere.⁸ In short, a complete ascertainment of patients with FTD in The Netherlands was attempted between 1 January 1994 and 1 March 1997. All patients were investigated by the neurologist of the study. A detailed clinical history, neuroimaging (CT, MRI, or SPECT; EEG), and laboratory tests were obtained to support the clinical diagnosis of FTD and to exclude other causes of dementia. Symptoms had to be present for at least 1 year. Probable FTD was (in the absence of international criteria) defined as showing symptoms satisfying the criteria of the Lund and Manchester Groups,² and either frontotemporal atrophy (CT, MRI) or frontotemporal hypoperfusion (SPECT) on neuroimaging. The study was approved by the Institutional Review Board of the University Hospital Rotterdam. Informed consent for participation was obtained from the spouse or a first degree relative of each patient.

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Table 1 Characteristics of patients with FTD

	Male		Female		<i>p</i> Value
	Mean (SD)	Range	Mean (SD)	Range	
Age	56.2 (8.8)	36–67	57.7 (9.7)	38–69	0.66
Education (y)	10.0 (3.1)	6–16	8.6 (2.8)	5–16	0.20
Global deterioration scale	4.1 (1.4)	2–6	4.1 (1.1)	2–6	0.95
Disease duration (months)	29.3 (13.2)	8–48	31.9 (16.3)	7–64	0.64

PATIENTS

Seventy four patients were included in the study as having probable FTD. Thirty six of these patients were examined at the outpatient department of the University Hospital, Rotterdam to confirm the diagnosis. In 12 out of these 36 patients neuropsychological testing was not feasible because of severity of disease. After closing of ascertainment, patients suspected of having FTD were still brought to our attention. Seven patients were diagnosed with probable FTD according to inclusion criteria, and were added to this study. The total number of patients in this report is 31. None of these patients had a motor or sensory impairment possibly interfering with neuropsychological testing.

NEUROPSYCHOLOGICAL EXAMINATION

A standard battery of tests was compiled, but depending on the phase of progression of disease, adjustments in protocol were inevitable. Estimation of general cognitive functioning was assessed with an abbreviated version of a Dutch intelligence test, the Groninger intelligentie test (GIT),⁹ which is composed of three subtests. The subtest perceptual puzzles consists of perceptual puzzles increasing in complexity. In the subtest calculation, written addition sums have to be solved in 1 minute. In the subtest verbal reasoning, a logic has to be deducted between two pairs of words and applied to a third word. Abstracting ability was reflected in the subtest similarities and the proverbs taken from the subtest Information, both from the Dutch version of the Wechsler adult intelligence scale (WAIS).¹⁰ Executive (control) functions were tested with trail making part A and part B,¹¹ modified Wisconsin card sorting test (WCST),¹² category fluency

from the GIT (animals and occupations),⁹ and the subtests digit span and digit symbol (WAIS).¹⁰ Verbal memory was tested using the Dutch version of the California verbal learning test (CVLT)¹³ or the Dutch version of the auditory verbal learning test (AVLT).¹⁴ In cases when the CVLT or AVLT were not assessable any more we administered the word list memory test of the CERAD.¹⁵ Orientation was assessed by MMSE questions¹⁶ and confrontation naming by the Boston naming test (short 15 item version from the CERAD).¹⁵ Finally, visuoconstructive functions were tested by drawing a clockface. More elaborate descriptions and references for most of these tests are given by Lezak.¹⁷

Test scores were judged to be valid when a test could be administered and a score could be calculated. When tests could not be administered and we were confronted with missing values we distinguished between missing values due to behavioural disturbances and missing values due to other reasons (missing, other reasons). The second category consists of missing values due to non-behavioural disturbances on the patient's side, such as communication problems or missing values on account of the investigators, such as differences in protocol or time restraints.

BEHAVIOUR RATINGS

Based on a short interview with the patient and on information provided by the care giver or relative, disease severity was rated on the global deterioration scale (GDS).¹⁸ Moreover, we constructed a test behaviour scale (TBS). The test behaviour displayed during administration of tests was rated on a three point scale (normal or absent, present, and present and prominent). The choice for the TBS items was partly based on the Lund and Manchester criteria² and partly on our own experience with the patient population. The items of which the scale consisted of are shown in table 2. The TBS was rated by the examiner after the test session.

STATISTICS

The internal consistency of the TBS was calculated as Cronbach's α . For every patient a

Table 2 Description and frequencies of the items of the test behaviour scale

Item (n=31)	Description	Present and prominent	Present	Normal or not present
Loss of insight	The inability to value own performance on a test	17	14	0
Distractibility	The loss of focused attention on the tests	14	10	7
Loss of mental effort	The decreased amount of effort put into attaining the requirements of the tests	10	15	6
Impulsivity	Acting without thinking or planning ahead	10	13	8
Loss of initiative	No or diminished initiative to carry out purposive acts	9	13	9
Inability to correct	Not being able to correct errors during testing	5	16	10
Perseverative behaviour	Repetition of one act, such as drawing a circle, or repetitive applying of old task instructions to new tasks	9	9	13
Increased associativity	The tendency of connecting one thought to another without relevance to the situation	6	9	16
Loss of compliance	The decreased degree of cooperation of the patient with testing	5	10	16
Restlessness	Inability to sit still for longer periods of time	5	9	17
Disturbed mental speed	A disturbed rate of response, eg a slowed or a hastened, impulsive way of responding.	3	8	20
Response rigidity	The difficulty in adapting answers to changing questions.	7	3	21
Stereotypy of behaviour	A repetitive response in a situation	4	6	21
Stimulus boundedness	The clinging of the attention to the strongest stimulus, usually in the perceptual field	3	5	23

Table 3 Number of valid test scores, missing values due to test behavioural disturbances, and missing values due to other reasons (missing, other reasons)

Tests	Valid	Missing values due to behavioural disturbances	Missing (other reasons)
Orientation	28	2	1
Boston naming test (abbreviated)	27	3	1
GIT (abbreviated)	18	10	3
Similarities (WAIS)	20	9	2
Proverbs (information WAIS)	25	5	1
Digit symbol (WAIS)	18	11	2
Trail making part A	24	6	1
Trail making part B	12	18	1
Modified Wisconsin card sorting test	11	17	3
Category fluency animals (GIT)	29	2	
Category fluency professions (GIT)	26	5	
Digit span (WAIS)	26	2	3
Word list learning tests	21	6	4
Drawing clockface	29	1	1

GIT=Groninger intelligentie test; WAIS=Wechsler adult intelligence scale; word list learning tests: Dutch versions of California verbal learning test and auditory verbal learning test and word list memory test from the CERAD.

TBS score was calculated by summing the scores on the items of the scale, and the number of missing values due to behavioural disturbances was counted. We computed Pearson's correlation coefficients on the TBS, the number of missing values due to behavioural disturbances, the GDS, duration of disease in years, and age. We assessed the coefficients for significance using two tailed tests. To exclude a possible association between missing values due to behavioural disturbances and other factors such as aphasia or short term memory problems we computed the correlation between the number of missing values due to behavioural disturbances and respectively the BNT score and digit span forwards (WAIS).

Because we used three different memory tests, scores were transformed into z scores with the standardisation samples as reference to arrive at a uniform word list learning score.

For all test scores, means (SD) were calculated. Next, we replaced each missing value due to behavioural disturbances by the worst score found on that particular test. After this adjustment, we calculated means (SD) of the adjusted scores. To determine the effect of the adjustment of missing values due to behavioural disturbances we computed the effect sizes of each test variable. The effect size is the difference between the adjusted and observed

means divided by the observed SD. According to Cohen,¹⁹ an effect size of 0.8 SD should be considered as large, an effect size of 0.5 SD as medium, and an effect size of 0.2 SD as small.

Results

Patients (13 men and 18 women) were aged 36 to 69 years (mean 57.0 (SD 9.2)) (table 1). Disease duration was not correlated with GDS, or with age. There was no difference between men and women in age, GDS, disease duration, or years of education.

The TBS showed a good internal consistency (Cronbach's α 0.82). Table 2 shows the frequencies of the behavioural features. All patients showed loss of insight into their performance. Many patients were easily distracted. Mental effort was usually low, although compliance was in the normal range for half of the cases. Most patients showed impulsivity. Loss of initiative and inability to correct were often found. Perseverative behaviour, increased associativity, and restlessness were present in half of the cases. Disturbed mental speed, response rigidity, stereotypy of behaviour, and stimulus boundedness were less often found.

As expected, our patients were often unable to perform certain tests. Table 3 shows the number of valid test scores, the numbers of missing values due to test behaviour disturbances, and the number of missing values due to other reasons (missing, other reasons). Missing values due to behavioural disturbances occurred most often for trail making part B and the modified WCST. Also, digit symbol and the GIT yielded high numbers of missing values. The number of missing values due to behavioural disturbances was strongly associated with the TBS score ($r=0.70$), notably with restlessness, inability to correct, insight into performance and perseverative behaviour, stereotypy of behaviour, and stimulus boundedness (table 4). Moreover, both the number of missing values due to behavioural disturbances and the total TBS score were strongly related to the severity of disease as measured by the GDS score (both $r=0.77$). The correlation between number of missing values due to behavioural disturbances and BNT score was low ($r=-0.19$), and between number of missing values due to behavioural disturbances and the score on digit span forwards (WAIS) was also reasonably low ($r=-0.34$). No significant relation was found between TBS and disease duration ($r=-0.05$), nor between TBS and age ($r=-0.22$).

Table 5 shows the observed and the adjusted scores. The effect of the adjustment was largest for the digit symbol (WAIS) and for the trail making test parts A and B. The effect size was also large for total IQ of the GIT, and for the percentage of perseverative errors on the modified WCST. A medium size effect was seen for the immediate recall of the tests for word list learning. Finally, assignment of lowest scores to missing values due to behavioural disturbances hardly influenced results on the clockface, the orientation questions, proverbs, digit span, the BNT, and category fluency.

Table 4 Correlation of test behaviour features with number of missing values due to behavioural disturbances, global deterioration scale, duration of disease and age

	Number of missing values	Global deterioration scale	Duration of disease	Age
Loss of insight into performance	0.49**	0.46*	-0.06	-0.28
Distractibility	0.43*	0.50**	0.09	-0.08
Loss of mental effort	0.40*	0.46*	-0.35	-0.11
Impulsivity	0.21	0.38*	0.24	-0.22
Loss of initiative	0.29	0.31	-0.09	-0.21
Inability to correct	0.58**	0.75**	-0.10	-0.24
Perseverative behaviour	0.65**	0.75**	-0.07	-0.16
Increased associativity	0.45*	0.37	-0.05	-0.35
Loss of compliance	0.39*	0.53**	0.36*	-0.03
Restlessness	0.51**	0.58**	-0.07	-0.25
Disturbed mental speed	0.44*	0.26	-0.20	0.22
Response rigidity	0.19	0.18	-0.09	0.14
Stereotypy of behaviour	0.48**	0.35	-0.16	-0.31
Stimulus boundedness	0.69**	0.52**	-0.11	-0.27
Test behaviour scale	0.70**	0.77**	-0.05	-0.22
Global deterioration scale	0.77**	10.00	0.14	-0.06

*Correlation is significant at the 0.05 level (2 tailed); **Correlation is significant at the 0.01 level (2 tailed)

Table 5 Observed and adjusted means (SD) and effect size of differences

Tests	Observed mean (SD)	Adjusted mean (SD)	Effect size (<i>d</i>)
Orientation:			
Time	3.2 (1.7)	3.1 (1.7)	-0.1
Place	3.8 (1.6)	3.7 (1.7)	-0.1
Boston naming test (abbreviated)	12.4 (2.8)	12.4 (2.8)	0
GIT-IQ (abbreviated)	83.4 (15.4)	70.5 (23.6)	-0.8**
Similarities (WAIS)	3.5 (4.6)	2.5 (4.1)	-0.2
Proverbs (information WAIS)	0.8 (1.6)	0.7 (1.5)	-0.1
Digit symbol (WAIS)	23.9 (9.9)	15.4 (14.1)	-0.9**
Trail making test A (s)	86.2 (48.0)	111.8 (72.8)	0.9**
Trail making test B (s)	194.9 (77.1)	266.0 (69.7)	0.9**
Modified WCST categories	1.8 (1.5)	1.3 (1.0)	-0.3
Modified WCST perseverations (%)	62.8 (27.6)	84.8 (24.6)	-0.8**
Category fluency animals (GIT)	7.9 (5.7)	7.4 (5.6)	-0.1
Category fluency professions (GIT)	6.1 (4.7)	5.3 (4.8)	-0.2
Digit span forwards (WAIS)	4.8 (.9)	4.7 (1.0)	-0.1
Digit span backwards (WAIS)	2.6 (1.4)	2.4 (1.6)	-0.1
Word list learning total (z score)	-2.5 (1.4)	-3.1 (1.7)	-0.4*
Word list learning recall (z score)	-0.4 (1.0)	-0.4 (0.9)	0
Drawing clockface	1.7 (1.1)	1.6 (1.1)	-0.1

*Effect size is significant ($d \geq |0.4|$; $p \leq 0.05$; 2 tailed).

**Effect size is significant ($d \geq |0.5|$; $p \leq 0.01$; 2 tailed).

GIT-IQ=Intelligence quotient from the Groninger intelligence test; WAIS=Wechsler adult intelligence scale; WCST=Wisconsin card sorting test.

Discussion

In our study, we explored the relation between test behavioural disturbances, missing values, and neuropsychological test results. We found that with increasing disease severity of FTD, there were more behaviour disorders that interfered with testing. The most interfering features were restlessness, perseverative behaviour, and stimulus boundedness. In the words of Hughlings Jackson,²⁰ these features could be considered the “positive symptoms” of FTD. Such positive symptoms apparently lead to more problems in assessing tests than the negative symptoms such as loss of initiative or lack of mental effort. In the second case the tests can often still be administered with extra incitement by the examiner.

In our study, the severity of the behavioural disturbances had no relation with the age of the patient, or with the duration of disease. Younger patients who had the disease for a year could show just as many behaviour problems as older patients who were ill for a much longer period.

The behavioural disorders show the largest effect on tests measuring the executive (control) functions and reasoning capabilities. The trail making test, part B in particular, digit symbol (WAIS) and the WCST, even in its modified form, are tests that seem not assessable any more in an early stage of the disease. This underscores these tests as sensitive markers for impairments of executive function, which is by contrast with a test such as the BNT, which has a concrete, visual stimulus that captures the patient's attention more easily. We replaced the missing values by the lowest observed values. For this we only used the missing values due to behavioural problems and not the missing values due to other reasons such as communication problems or time restraints. The effect of the data imputation was largest for tests measuring executive function and reasoning capabilities. As a consequence, the difference between test results of executive function and memory or constructive functions became larger, and a more differenti-

ated picture of cognitive deficits in FTD is achieved.

Some studies have noted difficulties in differentiating FTD and dementia of the Alzheimer type (DAT) on neuropsychological variables and have questioned the specificity of deficient executive skills in FTD compared with DAT.^{21, 22} Perhaps the problem of the missing values provides a clue for this finding. In our experience, patients with DAT do show behavioural problems during testing, but clearly not to the extent of patients with FTD and usually much later in the disease. Thus neuropsychological tests are assessable for much longer in the course of DAT, providing the investigator with a more complete data set. Studies in which test results of Alzheimer's disease and FTD are compared probably only use cases with valid data, leaving out the patients who are most affected by test behavioural disturbances. In this way the extent of the cognitive deficits in FTD is underestimated and obscures the cognitive differences between DAT and FTD.

In a previous study, Fillenbaum *et al*²³ explored the missing values or non-response on the mini mental state examination. They concluded that non-response is not random and scoring non-response as error is more likely to give a correct classification of severity of dementia.

The method of replacing all missing values irrespective of its cause, however, is not valid and feasible for all patient groups and has to be done with caution. Missing values may be caused by non-behavioural disturbances, such as sensory impairments, aphasia, or factors caused by the examiner. In these cases the failure to complete a test does not indicate a cognitive disturbance, but is more likely to reflect the limitations of neuropsychological testing.

Our patient group with FTD was generally mildly demented and we only replaced the missing values due to behavioural disturbances by the lowest scores. Missing values due to other reasons, such as communication problems or factors caused by the examiner, were not taken into consideration in the data analysis. Therefore, in our study replacing missing values due to behavioural disturbances by the lowest scores is justified.

The method of assigning meaning to missing values is just one step towards unravelling the influence of behavioural disturbances on neuropsychological test results. Another complication is the fluctuating pattern of test behaviour. A patient who shows high distractibility in one point in time, may be less distractible on another occasion, resulting in fluctuating test scores. According to Stuss *et al*²⁴ this “noise” in the data is also part of the cognitive problem of patients with frontal dysfunction. In patients with FTD this could be a subject of further research.

Our results show clearly that missing values due to behavioural disturbances in the context of FTD are important and useful information. With data imputation, a more differentiated picture of cognitive deficits in FTD is given without the need to exclude those patients who

display behavioural disturbances so characteristic of FTD. Consequently, more realistic and valid data will provide a deeper understanding and clues for further research on the clinical picture of FTD and its relation to other dementia syndromes.

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