Note

Repeat and Point: Differentiating semantic dementia from progressive non-fluent aphasia☆

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ARTICLE INFO

ABSTRACT

To determine whether a new, simple, quick measure, the Repeat and Point test, reliably differentiates between semantic dementia (SD) and progressive non-fluent aphasia (PNFA).

Fifteen patients with SD, six patients with PNFA and 18 healthy controls were administered the Repeat and Point test. Participants were required to repeat 10 multi-syllabic concrete nouns and, following each repetition, to point to the word's pictorial referent amongst an array of six semantically and perceptually similar foils.

Patients with SD were consistently impaired relative to PNFA patients and controls on the comprehension (pointing) component of the task, whereas patients with PNFA showed no significant deficit on pointing but were impaired at the production (repeating) component. Discriminant function analysis confirmed perfect classification of the individual patients into their respective groups: criteria involving a ratio of the two scores are provided.

The Repeat and Point test is particularly appropriate for routine use in a clinical context: it is quick and easy to administer and score; it reliably discriminated between the two patient groups, SD and PNFA; and it offers a simple rule of thumb, i.e., the Repeat-to-Point ratio, to aid in the diagnosis of these two language variants of frontotemporal dementia (FTD).

1. Introduction

Frontotemporal dementia (FTD) is the second most common cause of dementia in patients under the age of 65 years (Ratnavalli et al., 2002). Three major subtypes of FTD have been identified (Brun et al., 1994; Hodges and Miller, 2001a, 2001b; Neary et al., 1998; Knibb et al., 2006; Hodges et al., 1992): (1) a frontal or behavioural variant (fvFTD), characterized by gradual disintegration of social cognition, behaviour and motivation; (2) semantic dementia (SD), characterized by deterioration of verbal and non-verbal conceptual knowledge: in the verbal domain, there is progressive and eventually profound anomia and impaired word comprehension; and (3) progressive non-fluent aphasia (PNFA), characterized

by phonological and syntactic processing deficits resulting in effortful distorted speech output.

In the past decade, there has been growing interest in the early differentiation of FTD subtypes (Hodges and Patterson, 1996; Perry and Hodges, 2000; Adlam et al., 2006; Rogers et al., 2006). Differentiating fvFTD from the two aphasic variants is relatively straightforward and is based largely upon the identification of a cluster of diagnostic behavioural changes in the context of preserved language function. Identification and separation of SD and PNFA patients, on the other hand, can sometimes be difficult, as both groups are characterized by language problems and anomia. Simple numerical scores on traditional language production tests, such as confrontation naming and verbal fluency, will not distinguish SD from PNFA patients because both groups perform below control levels. At present the differentiation is usually based upon performance on a battery of sophisticated linguistic tests incorporating measures of semantic, phonological and syntactic processing (Hodges and Patterson, 1996; Perry and Hodges, 2000; Adlam et al., 2006; Rogers et al., 2006). Moreover, the presence of similarities (e.g., good episodic memory, intact visuospatial functions) in the two groups adds to the difficulty in differentiating between them (Hodges and Patterson, 1996).

To our knowledge, there have been no reports of a simple clinical test to aid in the differentiation between these two forms of FTD that involve prominent language deficits. The present study describes the development and application of the Repeat and Point test, a neuropsychological assessment that appears to differentiate reliably between SD and PNFA. Based on our clinical experience, we predicted that SD patients would perform better than PNFA patients on the production component of the test, i.e., Repeat, and, conversely, that PNFA patients would perform better than SD patients on the comprehension component, i.e., Point.

2. Methods

2.1. Participants

Fifteen patients with SD and six patients with PNFA were included in this study. All cases were referred to the Early Onset Dementia Clinic at Addenbrooke's Hospital, Cambridge. The clinical diagnoses were established following neurological and comprehensive neuropsychological assessment using a range of language and non-language based tasks, as described in prior publications (Hodges and Patterson, 1996; Hodges et al., 1992; Knibb et al., 2006; Perry and Hodges, 2000; Rogers et al., 2006). It should be noted that the diagnosis was made without reference to performance on the Repeat and Point test. An estimate of disease duration (see Table 1) was calculated based on the reported date of symptom onset. All patients were given a number of standard psychiatric rating scales to exclude major functional psychiatric disorders such as depression and schizophrenia. Classification of patients into PNFA and SD subtypes was done according to the international consensus criteria (Neary et al., 1998). Magnetic resonance imaging (MRI) scans were available for all SD patients and showed typical polar–parahippocampal and inferior temporal lobe atrophy in all cases. Imaging

Table 1 – The sex, age at test and years of education for each of the three participant groups, plus years of disease duration for each of the two patient groups

	SD	PNFA	Controls
Male/female	11/4	3/3	9/9
Age (years)	65.7 (8.1)	68 (6.3)	62.4 (10.3)
Education (years)	11.2 (1.8)	12 (3.0)	11.8 (2.6)
Duration (years)	5.4 (1.8)	6.3 (1.6)	*

SD represents semantic dementia; PNFA represents progressive non-fluent aphasia; and * represents not applicable.

data were available for five of the six PNFA patients and structural changes were observed involving mainly left perisylvian structures, particularly the insular cortex and Broca's area.

Eighteen healthy individuals were recruited to provide control data on the Repeat and Point test. In addition, 20 healthy controls recruited from the Medical Research Council Cognition and Brain Sciences Unit volunteer panel were assessed on the general neuropsychological battery. The study was approved by the Local Research Ethics Committee, and informed consent was obtained from each of the patients and the control participants.

2.2. General neuropsychology battery

The mini mental state examination (MMSE) (Folstein et al., 1983) was used as a measure of overall cognitive function; visuospatial functions were assessed using the dot counting subtest from the visual object and space perception (VOSP) battery (Warrington and James, 1991) and copy of the Rey complex figure (Osterrieth, 1944); executive functions were assessed via letter fluency for letters F, A, and S; recall of the Rey figure (Osterrieth, 1944) was used as a measure of nonverbal episodic memory; short-term memory was evaluated by forward and backward digit span tests; and phonological processing was assessed using a non-word repetition task designed for children (Gathercole et al., 1994) (unfortunately, there were no age-matched control data available for this test). Participants also completed subtests of the Cambridge semantic memory test battery (Bozeat et al., 2000; Garrard et al., 2001, 1998): category fluency (animals, fruit and birds), picture naming (64 common living and manmade items), and a spoken word-to-picture matching task.

2.3. Repeat and Point test development

Twenty-two concrete nouns, varying from 1 to 5 syllables in length, were originally selected for inclusion in the Repeat and Point test. The list was then reduced to 10 by eliminating all words where controls made more than one error ($N = 8$ words) and any word on which PNFA patients were 100% accurate on the repeat task ($N = 4$ words). All further statistical analyses were carried out on this reduced item set ($N = 10$) comprising the following number of words at each syllabic length: two syllables ($N = 1$, ostrich), three ($N = 4$, e.g., stethoscope), four ($N = 4$, e.g., asparagus) and five ($N = 1$, hippopotamus).

In a pilot version of the test, participants were asked to define the repeated item prior to pointing at its pictorial referent. A four point system was adopted for scoring definitions according to the detail and specificity of the response (from 0 = incorrect, or no response, to 3 = referent reliably identifiable from the verbal description given). After a number of attempts to refine and simplify the scoring criteria it was decided to exclude this component from the final test. Both the PNFA and SD patients had difficulty generating definitions, but for different reasons. For example, a PNFA patient having difficulty expressing the meaning of a word, such as *caterpillar*, might concurrently demonstrate an understanding of the concept using pantomime, whereas an SD patient failing to define caterpillar accurately would rarely even attempt to gesture its meaning. As gesture was not part of the instruction, this could not 'count' for or against a patient's performance. Because the goal was to produce a test with a simple scoring system, the (otherwise rather fascinating) definition component of the test was dropped.

2.4. Repeat and Point test administration

The final version of the Repeat and Point test takes between 5 and 10 min to complete. Each word is read aloud by the examiner for each task in turn, e.g., repeat "stethoscope" then point to the "*stethoscope*", to minimise working memory demands. The experimenter/clinician can provide the target word more than once at any stage of the test if the patient requests it. In our assessment study, all sessions were tape-recorded for scoring of repetition attempts, but this is not necessary for routine use of the test.

2.4.1. Repeat
Only the first repetition attempt was scored, and was given a score of 1 if correct and a score of 0 otherwise.

2.4.2. Point
Participants were shown an array of seven pictures and asked to point to the target item named by the examiner, which was presented in a random location. All six foils were chosen to be semantically close to the target (e.g., for the target item *ostrich* all distractors were large wild birds), and in some cases, perceptually similar (see Fig. 1 for an example). Participants were not given any feedback on their performance. Again, only first responses were scored: 1 for a correctly identified item, 0 otherwise.

2.5. Statistical analyses

Scores (percent correct) were analysed with three by two ANOVAs by both subjects (F_s) and items (F_i), with
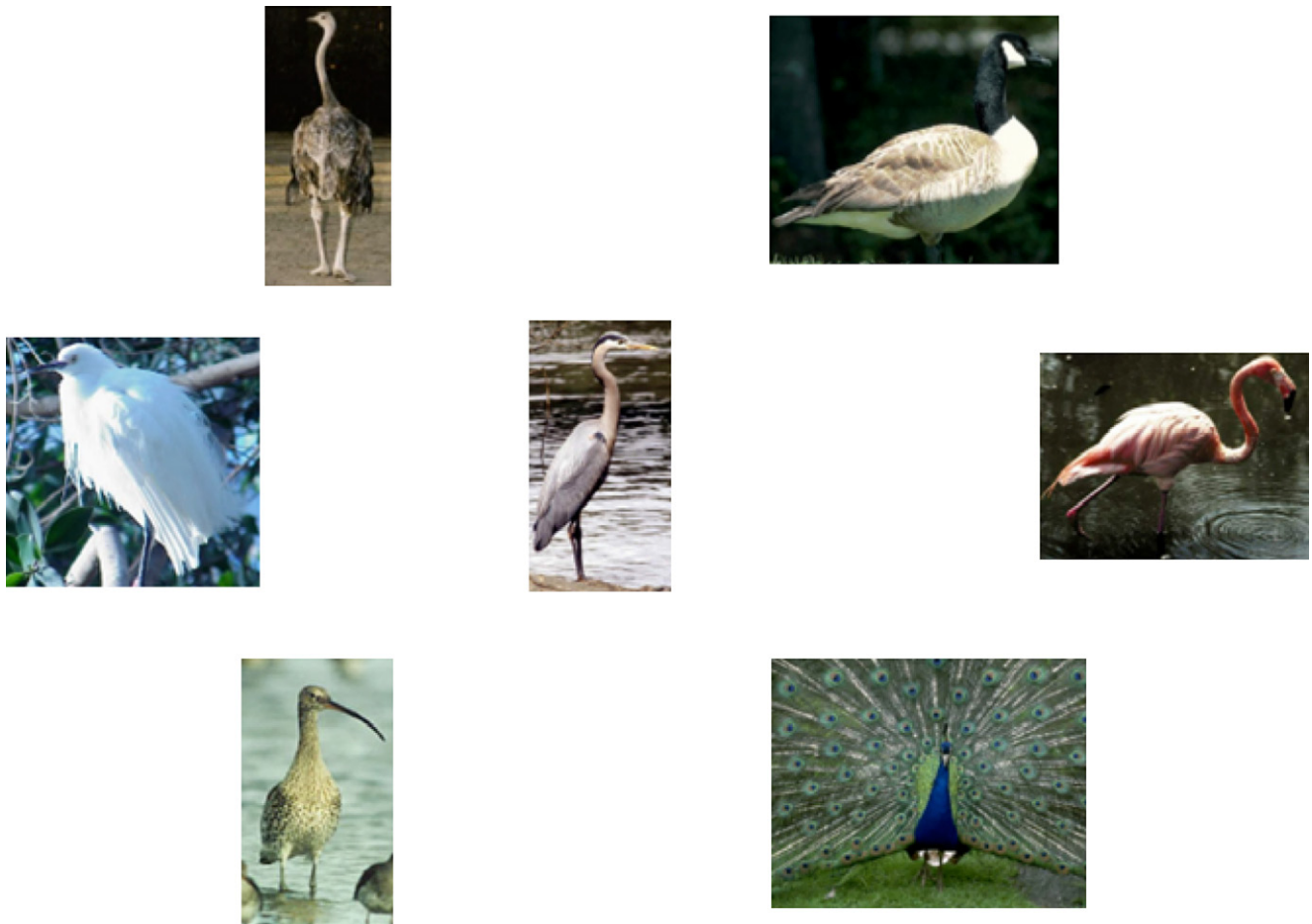

Fig. 1 – An example from the pointing task. The participant is required to point to the ostrich (target) amongst the six semantically related and, in some cases, perceptually similar foils.

a between-subjects and within-items factor of group (control, SD, PNFA) and a within-subjects and within-items factor of task (Repeat, Point). Significant interactions were followed-up by using paired-samples t-tests for the within-item analysis and independent groups t-tests for the between-subjects analysis. Discriminant function analysis was also used to investigate how well the test discriminated between the two patient groups.

3. Results

3.1. Demographics

The demographic characteristics of the patient and the control groups completing the Repeat and Point test are shown in Table 1. The groups did not differ in age at test ($F_{(3,55)} = 1.77$, $p > .05$) or years of education ($F_{(3,43)} = .56$, $p > .05$), and disease duration did not significantly differ between patient groups ($t_{(18)} = 1.04$, $p > .05$).

3.2. General neuropsychology

As shown in Table 2, a series of independent groups t-tests revealed that, consistent with their deficits in auditory verbal short-term memory and phonological processing (Hodges and Patterson, 1996; Grossman et al., 1996; Croot et al., 1998; Tree et al., 2001), the PNFA group was only impaired relative to controls on the measures of fluency (letter and category) and digit span (forwards and backwards). The SD patients, however, were impaired relative to controls on all measures except for the copy of the Rey figure and the dot counting test. The SD patients were also impaired relative to the PNFA patients on picture naming and word–picture matching, but, as expected, performed significantly better than the PNFA patients on the non-word repetition test and the forward condition of the digit span test.

3.3. Repeat and Point

Performance of the three groups for each item is provided in Table 3, with averaged data displayed in Fig. 2. Analyses revealed a highly significant group by task interaction by both subjects ($F_{s(2,36)} = 139.34$, $p < .0005$) and items ($F_{i(2,18)} = 47.61$, $p < .0005$). As predicted, performance (a) in the control group was at ceiling in both conditions, (b) in the SD group was significantly lower for Point than Repeat ($t_{s(14)} = 12.82$, $p < .0005$; $t_{i(9)} = 8.14$, $p < .0005$), and (c) in the PNFA group was significantly poorer for Repeat than Point ($t_{s(5)} = -4.84$, $p = .005$; $t_{i(9)} = 2.89$, $p = .018$).

Multiple comparisons exploring the group effect for each task revealed the following significant contrasts. For the Repeat component, control > SD ($t_{s(15)} = 2.67$, $p = .017$; $t_{i(9)} = 2.44$, $p = .038$), control > PNFA ($t_{s(5)} = 4.82$, $p = .005$; $t_{i(9)} = 6.34$, $p < .0005$) and SD > PNFA ($t_{s(6)} = 3.83$, $p = .009$; $t_{i(9)} = 6.48$, $p < .0005$). For the Point component, control > SD and PNFA > SD ($t_{s(5)} = -9.63$, $p < .0005$; $t_{i(9)} = -6.63$, $p < .0005$) ($t_{s(14)} = 14.33$, $p < .0005$; $t_{i(9)} = 8.80$, $p < .0005$); PNFA patients differed from controls only in the by-items but not the by-subjects analysis ($t_{s(5)} = 1.92$, $p = .111$; $t_{i(9)} = 5.93$, $p < .0005$).

In order to explore whether a combination of Repeat and Point scores would effectively classify patients as having either SD or PNFA, we conducted a discriminant function analysis on the patient data. The discriminant function we obtained was as follows: $y = 1.916 + (-.057 \times \text{Repetition}) + (.057 \times \text{Point})$. The predictive capacity of this function was highly significant ($\chi^2 = 35.34$, $p < .005$) and accounted for 100% of the available variance, indicating perfect classification of patients into their respective groups on the basis of the discriminant scores using the cut-off point of 1.916. Clinically, this function may be applied in the following way. For someone obtaining equal scores on Repeat and Point, the ratio between the two scores would of course = 1. In the present sample of SD patients, this ratio never fell below 1.25, and in the present sample of PNFA patients, this ratio never fell above .9. Hence, for the ratio Repeat/Point, the rule PNFA < .9 and SD > 1.25 may be applied for patient classification purposes.

Table 2 – Summary of the means and standard deviations for the general neuropsychology assessments for each patient group

	SD			PNFA		
	N	Mean	SD	N	Mean	SD
MMSE (/30)	15	22.7	4.4[a]	6	20.7	8.2
Category fluency (total)	14	13.0	12.4[a]	6	19.2	14.9[a]
Letter fluency (total)	13	24.3	16.1[a]	6	19.0	18.1[a]
Naming (64)	15	20.8	18.7[a,b]	6	46.0	21.6
Word–picture matching (64)	14	36.6	19.8[a,b]	5	63.0	1.2
Rey figure copy (36)	15	34.7	2.1	6	26.4	12.9[c]
Rey delayed recall (36)	4	6.9	6.5[a]	5	13.4	5.8
Digit span (forward)	15	6.1	1.2[a]	6	3.7	.8[a,c]
Digit span (backward)	15	4.1	.9[a]	6	3.3	1.0[a]
Dot counting (VOSP) (10)	14	9.9	.4	6	10.0	0
Children's non-word repetition test (40)	15	33.0	7.1	6	16.2	7.8[c]

Significant group differences are indicated as follows: a = lower than controls; b = lower than PNFA; and c = lower than SD.

Table 3 – Mean percentage of correct responses for Repeat and Point on each of the 10 items

Item	Repetition			Pointing		
	Controls	SD	PNFA	Controls	SD	PNFA
Cucumber (3)	100.0	100.0	71.4	100.0	33.3	85.7
Centipede (3)	100.0	100.0	71.4	100.0	13.3	57.1
Rhinoceros (4)	100.0	87.0	14.3	100.0	40.0	85.7
Rhododendron (4)	94.0	93.0	28.6	94.0	20.0	85.7
Ostrich (2)	100.0	100.0	71.4	100.0	6.7	85.7
Asparagus (4)	100.0	80.0	42.9	100.0	26.7	71.4
Helicopter (4)	100.0	100.0	71.4	100.0	86.7	85.7
Hippopotamus (5)	100.0	87.0	14.3	100.0	26.7	85.7
Kangaroo (3)	100.0	100.0	71.4	100.0	60.0	85.7
Stethoscope (3)	100.0	80.0	57.1	100.0	13.3	57.1

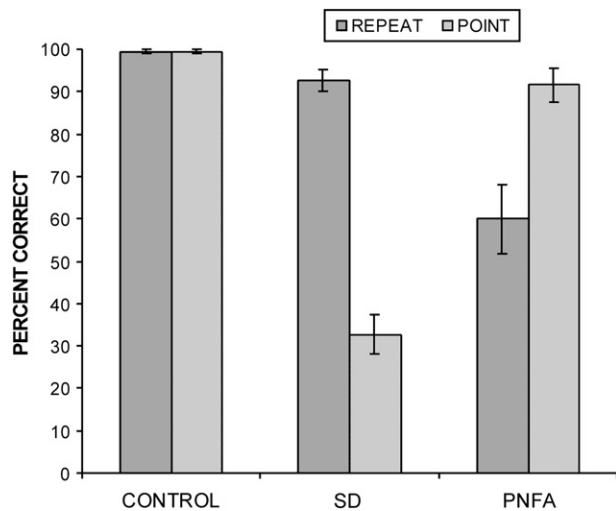The number of syllables is shown for each item.

Fig. 2 – The mean percentage correct responses on the Repeat and Point test. Standard errors are shown for each group.

4. Discussion

The simple 10-item Repeat and Point test was remarkably successful in discriminating between patients previously classified (on existing criteria) as either SD or PNFA. In terms of the group results, a double dissociation was apparent, such that SD patients were significantly better at repetition than pointing, with the reverse pattern for the PNFA patients. Using discriminant function analysis, a perfect classification of patients was achieved based upon their performance on the Repeat and Point tasks, in that all SD patients obtained a Repeat-to-Point ratio of more than one (in fact 1.25) and all PNFA patients obtained a Repeat-to-Point ratio of less than one (in fact .9).

Despite the consistent numerical and statistically reliable superiority of SD > PNFA for the Repeat component, there was a slight, but nonetheless statistically significant, repetition impairment in the SD group relative to controls. Previous research has suggested that knowledge of the meaning of words supports repetition (Patterson et al., 1994): SD patients showed a clear advantage for repeating short sequences of familiar words judged as still 'known' to them (on the basis of naming and comprehension tests) relative to sequences of real words with deteriorated meaning for those specific patients. Although this phenomenon has mainly been observed when there is a fairly substantial "load" on phonological working memory, e.g., repetition of four- or five-word sequences (Jefferies et al., 2004), it is certainly plausible that it might occasionally extend to the repetition of a single multi-syllabic word. Thus the occasional SD repetition errors observed in the current study might be expected given the SD patients' degraded comprehension of the same items (as revealed on the pointing component). Indeed, the SD patients did not accurately point to any of the incorrectly repeated items, although they had a one in seven likelihood of doing so by chance.

The finding that the PNFA patients scored within the normal range on the reasonably difficult comprehension task represented by the Point component reinforces the conclusion that single word comprehension is largely preserved in PNFA (Hodges and Patterson, 1996; Grossman et al., 1996; Karbe et al., 1993). This clearly delineates them from SD patients for whom impaired word comprehension is a defining characteristic (Hodges et al., 1992; Hodges and Patterson, 1996; Adlam et al., 2006; Rogers et al., 2006).

The most striking finding was the discriminant function analysis that resulted in 100% correct patient classification based on a combination of the patients' Repeat and Point scores. This finding indicates high specificity and sensitivity of the Repeat and Point test in the discrimination of PNFA and SD patients. In addition to its specificity and sensitivity, the Repeat and Point test has a number of practical advantages, including: (i) it can be administered in less than 10 min; (ii) the objective nature of the scoring criteria makes this test resistant to interpretation errors; and (iii) for clinical purposes, the cut-off Repeat-to-Point ratio for diagnostic differentiation is approximately 1. Specifically, in the present sample of patients, this ratio never fell below 1.25 for SD patients and never fell above .9 for PNFA patients.

One clear limitation is that the PNFA group was rather small (N = 6). The test was, however, based on extensive clinical experience and evolved from an informal test used in the clinic, prior to formalisation as the Repeat and Point, which very consistently discriminated SD from PNFA. Despite this limitation, we propose that the Repeat and Point test lends itself to common use in a clinical context to aid in accurate diagnosis of SD and PNFA.

A recent large clinico-pathological study, using a statistical modelling method that made no prior assumptions about the data structure, demonstrated that patients with primary progressive aphasia can be divided into two coherent syndromes that closely conform to the clinical descriptions of PNFA and SD (Knibb et al., 2006). Interestingly, the language variables that best differentiated between the two groups included impaired repetition and impaired single word comprehension, i.e., the two components of the Repeat and Point test. It remains to be seen whether there are patients who conform to the broad clinical criteria for progressive aphasia yet who cannot be classified, at presentation, using the Repeat and Point test.

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