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The time course of neurolinguistic and neuropsychological symptoms in three cases of logopenic primary progressive aphasia

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ABSTRACT

Primary progressive aphasia (PPA) is a rare clinical dementia syndrome affecting predominantly language abilities. Word-finding difficulties and comprehension deficits despite relatively preserved cognitive functions are characteristic symptoms during the first two years, and distinguish PPA from other dementia types like Alzheimer's disease. However, the dynamics of changes in language and non-linguistic abilities are not well understood. Most studies on progression used cross-sectional designs, which provide only limited insight into the course of the disease. Here we report the results of a longitudinal study in three cases of logopenic PPA over a period of 18 months, with exemplary longitudinal data from one patient even over 46 months. A comprehensive battery of neurolinguistic and neuropsychological tests was applied four times at intervals of six months. Over this period, deterioration of verbal abilities such as picture naming, story retelling, and semantic word recall was found, and the individual decline was quantified and compared between the three patients. Furthermore, decrease in non-verbal skills such as divided attention and increasing apraxia was observed in all three patients. In addition, inter-subject variability in the progression with different focuses was observed, with one patient developing a non-fluent PPA variant. The longitudinal, multivariate investigation of logopenic PPA thus provides novel insights into the progressive deterioration of verbal as well as non-verbal abilities. These deficits may further interact and thus form a multi-causal basis for the patients' problems in every-day life which need to be considered when planning individually targeted intervention in PPA.

1. Introduction

Primary progressive aphasia (PPA) is a progressive neurodegenerative syndrome affecting predominantly language abilities (Mesulam, 1982). Word-finding difficulties and comprehension deficits despite preserved cognitive functions are characteristic symptoms during the early course of disease, i.e. during the first two years. Preserved cognitive functions distinguish PPA from other dementia types like Alzheimer's disease. Mild impairment in arithmetic operations (dyscalculia), ideomotor and/or buccofacial apraxia, and marginal deficits in constructional abilities can be present at the beginning of the disease but should not affect the normal day activities. At later stages, other verbal and non-verbal cognitive impairments may appear and, finally, the patients loose their ability to communicate verbally because of total loss of language and accompanying severe cognitive deficits. However, the longitudinal development of non-linguistic cognitive deficits accompanying or influencing language, or some of its aspects, remains largely unknown. Therefore, the present study provides a longitudinal, multivariate account on PPA in order to uncover the cognitive dynamics of its progressive nature.

When investigating the longitudinal cognitive characteristics of PPA, it is of note that the status of PPA as a unique clinical entity has been discussed controversially. First, this is due to heterogeneous neuropathological and clinical findings as well as controversial reports on different long-term developments in PPA, such as the average duration of the disease or developing

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co-morbid impairments. Moreover, there is an ongoing discussion whether PPA subtypes can be distinguished, and if so, on the basis of which symptoms. Sonty et al. (2003), Gorno-Tempini, Dronkers, et al. (2004), Rogalski and Mesulam (2007) and others differentiate three PPA-variants: a fluent form (fPPA), characterized by impaired comprehension with preserved syntactic abilities and word-fluency, a non-fluent form (nfPPA), which is labelled by impaired syntactic abilities and word-fluency with intact comprehension, and finally a logopenic variant (lPPA) which is a mixture of the two former variants: it is characterized by frequent disruption of oral fluency because of word-finding difficulties whereas syntactic abilities and comprehension are little impaired. According to Mesulam, Grossman, Hillis, Kertesz, and Weintraub (2003), those three variants of PPA finally converge in the progression of the disease and ultimately lead to mutism. Gorno-Tempini et al. (2006) report, that nfPPA leads earlier to mutism than fPPA and can develop into a corticobasal syndrome (Gorno-Tempini, Murray, Rankin, Weiner, & Miller, 2004). In opposition to this classification of PPA, authors like Snowden, Neary, and Mann (1996) as well as Garrad and Hodges (2000) regard nfPPA and fPPA as two separate disorders. Whereas the non-fluent type (including lPPA) is termed PPA, the fluent variant is called semantic dementia (SD) which is characterized by severe semantic impairment up to the total loss of the ability processing semantic information. Following this account, in order to diagnose fPPA, it is important to test whether or not semantic processing is intact. In Mesulam's classification of the semantic variant of PPA (i.e. fPPA in their terms) the semantic system itself is intact but access to it is impaired. The knowledge of the object is still intact and in case of word-finding difficulties the patient has the chance to make himself understood using circumlocutions or non-verbal expression like pantomime or gesture. In contrast, following the definition of SD by Snowden et al. (1996), representations in the semantic system are impaired. Hence, the patient cannot communicate by non-verbal expression, because the knowledge of meaning and use of objects is lost. In an attempt to unify the field by discussing and integrating the variety of approaches to PPA, Gorno-Tempini et al. (2011) have now published a new guideline paper for the classification of PPA in non-fluent/agrammatic, semantic, and logopenic PPA (for a quantitative template to dissociate these subtype on the basis of their performance in semantic and syntactic tests cf. Mesulam et al., 2009). When describing the relevant recent papers on PPA in the following paragraphs, we stick to the subtype labels originally given by the respective authors of the studies for the sake of scientific correctness; the reader may easily translate these labels to the now valid nomenclature just mentioned.

During the progression of logopenic PPA, the principle linguistic symptoms are increasing word-finding difficulties and comprehension deficits as well as naming dysfunctions. Fluent speech production can become non-fluent because of emerging word-finding problems. Only after the first two years after the onset of PPA, other cognitive impairments such as problems in orienting or memory may develop. Some PPA patients develop striking personality changes characteristic for fronto-temporal dementia. Other patients show signs of corticobasal degeneration (such as extrapyramidal dysfunction) or a motor neuron disease with associated aphasia. Those co-morbid diseases are called PPA-plus syndromes (Mesulam, 2001).

The assessment of neuropsychological abilities is important for a first diagnosis of PPA. At the very onset of PPA, skills like visuo-spatial processing as well as visual memory should be in a normal range. However, light impairment of arithmetic operation, constructional and ideomotor skills as well as light impaired ability of inhibition in go/nogo tasks may exist because of the closeness of the corresponding cortical regions and language-relevant regions. Yet, for the diagnosis of PPA, they should not affect everyday activities (Mesulam, 2001).

Multidimensional neuropsychological assessment may be useful for the distinction between cases of fronto-temporal dementia (FTLD) and Alzheimer's disease (AD) (Giovagnoli, Erbetta, Reati, & Bugiani, 2008), in particular in the domains of memory, attention and visuo-constructive abilities. Similarly, Wicklund, Rademaker, Johnson, Weitner, and Weintraub (2007) reported that the cognitive decline in PPA patients differed predominantly from Alzheimer's dementia and fronto-temporal dementia in the domains of language, verbal memory, and attention. In 2009, Libon et al. investigated the longitudinal course of neuropsychological performance in a large number of patients with AD and subtypes of FTLD (among others, SD and nfPPA) over the course of 100 months. They reported a double dissociation between SD and nfPPA in naming test and executive control, in terms of better results for nfPPA over SD in naming and worse results in letter fluency. Another double dissociation was found between patients with corticobasal degeneration and nfPPA: the nfPPA group performed better in visuo-constructive test than in tasks requiring executive control. However, in this study, no patients suffering from logopenic variant of PPA participated. Moreover, within the test battery, no tests assessing attention and apraxia were included. Considering these factors would thus be advantageous for the better understanding of the time course of the different variants of PPA.

In the case of PPA variants, neuropsychological performance may differ depending on the particular subtype. Gorno-Tempini, Dronkers, et al. (2004) found different patterns of neuropsychological deficits in the three subtypes of PPA. The authors tested verbal fluency, verbal recognition, verbal and non-verbal memory, executive functions, and praxis. For the nfPPA, Gorno-Tempini, Dronkers, et al. (2004) reported significant better performance in verbal memory tasks in comparison to fPPA and lPPA. The nfPPA patients did not differ from the other groups on non-verbal memory or executive functions. However, the nfPPA patients also showed the worst performance in the praxis test. In contrast, the logopenic PPA group had the worst results in tests of verbal recognition. In the test of semantic word recognition they scored significantly worse than the nfPPA but performed best on a test of verbal working memory. Finally, the lPPA group performed worst on immediate and 30-s recall of verbal information.

Such neuropsychological deficits in PPA may not simply co-occur but also intermingle with the patients' language deficits; a distinction between these two options via standard tests is not always possible. Sonty et al. (2003) and Gorno-Tempini, Dronkers, et al. (2004) reported that PPA patients performed significantly worse than healthy controls in a word-fluency task supposed to measure executive functions. Additionally Sonty et al. (2003) report significantly worse performance in naming. Consequently, when applying neuropsychological tests requiring verbal processing, there is a risk that PPA patients score significantly lower than a control sample only because of their aphasic symptoms (Le Rhun, Richard, & Pasquier, 2005; Mesulam et al., 2003; Sonty et al., 2003). Thus, a detailed knowledge of verbal and non-verbal neuropsychological profiles of PPA as well as their development during the progression of the disease seems relevant for the appropriate evaluation of a patient's level of cognitive performance. Such knowledge may, in turn, inform the planning of therapeutic interventions in individual cases. More generally, the data contribute to a better understanding of one subtype of PPA and may thus, in future, help characterize commonalities and differences to other PPA variants.

1.1. Aim of the study

The aim of the present study was to investigate the progression of neuropsychological abilities in three patients with a logopenic

Table 1
Characterization of PPA patients according to sex, age, education, profession, handedness, supposed onset of the disease, and PPA subtype.

Patient	AT	AS	MW
Sex	Male	Male	Female
Age at T1	70	58	73
Education	University	High school[a]	High school[a]
Profession	Physician	Toolmaker	Saleswoman
Handedness[b]	Right (+100)	Right (+100)	Right (+80)
Onset	2004	2006	2007
Subtype	Fluent/logopenic	Fluent/logopenic	Fluent/logopenic
T1	Mar 2008	May 2008	July 2008
T2	October 2008	November 2008	December 2008
T3	April 2009	May 2009	July 2009
T4	October 2009	November 2009	January 2010

[a] High school education (*Volksschule* or *Realschule*) until grade 10 (maximum).
[b] Measured with the Edinburgh Inventory by Oldfield (1971).

variant of PPA. The main focus in this longitudinal analysis was on a comparison of verbal and non-verbal abilities, which may develop differently depending on the patient's linguistic level of performance. In particular, the following questions were addressed: (1) How does verbal and non-verbal performance in logopenic PPA develop over the course of 18 months? (2) Do additional non-verbal impairments develop over time, or, rather, is the dynamics of verbal and non-verbal performance comparable? (3) In which respects are the profiles of the three PPA patients comparable to one another, i.e. is there generalizable trend over the group of logopenic PPA patients which potentially characterizes this particular variant of PPA? In order to achieve this aim, three German logopenic PPA patients were examined four times over the course of 18 months with a test battery comprising those cognitive and linguistic dimensions that were identified in earlier studies as potentially relevant for the characterization of PPA.

2. Methods

2.1. Patients

A total of 7 patients potentially suffering from PPA entered the first examination. Two of them were then excluded from the study because their disorder was different from PPA.[1] A third patient had been diagnosed as non-fluent PPA type but refused further participation in the study. For a fourth patient, the initial diagnosis of PPA could not be confirmed as the only mild speech symptoms did not show any progression over the course of 18 months. Thus, finally, three patients with clear-cut logopenic PPA were included in this report.

These three patients (mean age 67.3 years, one woman) with logopenic PPA were examined a total of four times at intervals of six months with a battery of linguistic and neuropsychological tests. All experimental methods were approved by the ethics committee of Medical Faculty at RWTH Aachen University. All patients gave written informed consent at each examination. Patients were recruited at the Section Neurolinguistics at the Department of Neurology at RWTH Aachen University. The examinations took place between March 2008 and January 2010. An overview of the applied tests and a survey of demographical and clinical data of the patients are given in Tables 1 and 2.

The patients had to meet the following inclusion criteria. At first assessment (T1), no non-verbal cognitive deficits should be present in order to exclude the differential diagnosis of Alzheimer's disease. Provided that the patient was able to perform all planned tests (see below) at first time of assessment, the patient was asked to repeatedly attend. The three cases are now described in detail.

2.1.1. Patient AT

Patient AT, a 70 year old right-handed male retired physician, presented with a history of word-finding difficulties which progressed very slowly for about 4 years before our first examination. The tentative diagnosis of PPA was made by an examination at the Department of Neurolinguistics, RWTH Aachen University, at the end of 2006. Following this diagnosis, AT had since received speech therapy. At the first time of assessment in March 2008, the patient was well oriented with respect to space and time, cordial, cooperative and resilient. His spontaneous language was characterized by word-finding difficulties, aborted sentences, morphological inflection errors, and phonematic paraphasias. His sentence structure was preserved and complex. He described his symptoms as highly fluctuating. During examination, he was able to communicate about nearly all everyday problems with only some help by the examiner, but conversation was difficult because of noticeable difficulties in language abilities. Yet, in the subtest of the Aachener Aphasie Test (AAT; Huber, Poeck, Weniger, & Willmes, 1983) specific language deficits were detected. A non-verbal semantic deficit indicative of semantic dementia could be precluded because of the result in the Birmingham Object Recognition Battery (BORB; Riddoch & Humphreys, 1993), which was in the average range of norm scores.

2.1.2. Patient AS

AS was a 58 year old right-handed male with a two year history of decline in word-finding. Throughout the project, he was still working as a toolmaker. An accompanying bilateral hearing impairment was treated with a bilateral hearing aid. AS was directed to the study by his local speech and language therapist. He started speech therapy by the recommendation of his neurologist before the first contact in our clinic and received therapy during the whole period of our project with one interruption of nine months. During the first examination in May 2008 the patient was cordial, cooperative, resilient and oriented. In contrast to AT, however, he was able to communicate only about familiar topics and only with the aid of the examiner. Often the intended meaning could not be conveyed. AS's spontaneous language was characterized by a strong dialect and simple sentence structure. The patient generally expressed himself in incomplete sentences because of sentence abruption and considerable word-finding problems. Overall, he showed mild aphasia. A non-verbal deficit in terms of semantic dementia could be precluded because of the average results in the BORB.

2.1.3. Patient MW

The third patient was a 73 year old right-handed woman with a one-year history of progressing word-finding problems. Born in Upper Silesia, she has been living in Germany for 35 years. She is a native speaker of German who learned Polish at young age. She was a saleswoman and retired 13 years ago. In 2008, she presented at the Department of Neurolinguistics, RWTH Aachen University, because of the progressing language difficulties. Since the diagnosis of PPA, she had been receiving speech therapy. In particular, MW accidentally replaced German words by Polish words. During the whole examination, MW seemed nervous and little resilient but could be motivated by the examiner. She was able to communicate about nearly all everyday problems with only some help by the examiner. However, conversation was difficult because of noticeable difficulties in language abilities. Spontaneous language was characterized by word-finding problems and sentence abruption as well as many phonematic uncertainties in combination with paraphasias. The sentence structure was complex; the rate of speech was high. MW declared that her language problems are variable depending on respective situation. When she gets nervous, speech problems increase. Altogether, a mild to moderate aphasia was observed. A non-verbal deficit in terms of semantic dementia could be precluded because of the average result in the BORB.

2.1.4. Classification of the patients as logopenic PPA

At first evaluation, all patients showed verbal impairment with mostly intact comprehension and variably affected expressive skills. Verbal expression was still fluent in all three cases. Moreover, a non-verbal semantic deficit could be excluded in each of them. Thus, and in agreement with the classification of vascular aphasics as well as PPA patients that is based on preserved articulatory and syntactic abilities in the AAT (Lange et al., 2012), all patients were characterized as suffering from a fluent variant of PPA. Differences among the patients existed at the level of education, the age of onset and the duration of the disease.

The classification of the patients as logopenic PPA was performed according to the quantitative template for subtyping PPA by Mesulam et al. (2009). This two-dimensional template is based on single-word comprehension (Peabody Picture Vocabulary Test, 4th edition) and grammatical structure of sentences (Northwestern Anagram Test). It results in a subdivision into 4 quadrants using the 60% performance level: an agrammatic variant (PPA-G), a semantic variant (PPA-S), a mixed variant (PPA-M), and a logopenic subtype (PPA-L). As score for single-word comprehension, we converted the raw scores of the AAT subtest auditory single word comprehension into percentage of correct items. In order to quantify syntactic abilities, the raw values of the patients' performance in a German adaptation of Grodzinsky's test of syntactic abilities (Heim et al., 2010; Seidel et al., 2009) was likewise converted into percentage of correct answers. This syntactic test involved sentence–picture matching (e.g. decide which of two picture alternatives correctly depicts the sentence "The king is combed by the boy"), with syntactic complexity being varied both by presence/absence of topicalization (e.g. "It is the boy that the king combs"), mode (active/passive, e.g. "The boy combs the king" vs. "The king is combed by the boy"), and subject/object reference (e.g. "It is the boy that combs the king" vs. "It is the boy that the king combs"). For further details cf. Friedmann and Grodzinsky (1997) and Grodzinsky and Finkel (1998). Following the guidelines by Mesulam et al. (2009), all of our patients can be classified as logopenic subtypes of PPA (cf. Fig. 1).

[1] One patient presented with language difficulties because of a posttraumatic stress disorder and the second patient had an underlying amyotrophic lateral sclerosis.

Table 2
Overview of the applied tests, its abbreviation, the tested functions, and references.

Tests	Abbreviation	Tested functions
Aachener Aphasie Test[a]	AAT	Verbal skills
Aachener Aphasie Test Supplement Texte[b]	AAT supplement texts	Story retelling
Aachener Materialien zur Diagnostik neurogener Sprechstörungen[c]	AMDNS	Speech motor abilities
Birmingham Object Recognition Battery[d]	BORB	Nonverbal semantic processing
Regensburger Wortflüssigkeitstest[e]	RWT	Verbal fluency, executive functions
Leistungsprüfsystem für 50-90jährige[f]	LPS50+	Intelligence
Verbaler und non-verbaler Lerntest[g]	VLT, NVLT	Verbal and non-verbal learning
Wechsler Memory Scale, digit span forward[h]	–	Auditory short term memory
Hamburg-Wechsler-Intelligenztest, digit span backward[i]	–	Auditory short term memory
Hamburg-Wechsler-Intelligenztest, Mosaik-Test	Mosaik-Test	Spatial-constructional abilities
Corsi-Block-Tapping-Test[j]	Corsi	Visual-spatial memory span
Testbatterie zur Aufmerksamkeitsprüfung[k]	TAP	Sustained, selective, and divided attention

[a] Huber et al. (1983).
[b] Huber, Klingenberg, Poeck, and Willmes (1993).
[c] Bülte (2008).
[d] Riddoch and Humphreys (1993).
[e] Aschenbrenner, Tucha, and Lange (2000).
[f] Sturm, Willmes, and Horn (1993).
[g] Sturm and Willmes (1999a, 1999b).
[h] Wechsler (1987).
[i] Tewes (1991).
[j] Smirni, Villardita, and Zappala (1983), Corsi (1972).
[k] Zimmermann and Fimm (2002, 2007).

2.2. Research design

The experiment was a longitudinal multiple case study. All patients were invited for examination four times during the course of 18 months, in intervals of six months. One patient, AT, was even examined at 7 timepoints over a total time of 46 months in order to exemplarily demonstrate the long-term stability of the findings observed in all patients. At each time point (T1, T2, T3, and T4), patients and their spouses stayed at the clinical ward at the Institute for Neurosciences and Medicine (INM, Research Centre Jülich) for three to four days, where they completed the test battery detailed below. The patients were examined by a neurologist (co-author MS). Based on the cognitive functions identified as potentially impaired in, or characteristic of, PPA (Giovagnoli et al., 2008; Gorno-Tempini, Dronkers, et al., 2004; Mesulam, 2001; Wicklund et al., 2007), a battery of German neuropsychological and neurolinguistic tests was assembled in order to test a range of verbal abilities, verbal executive functions, verbal vs. non-verbal learning and memory, intelligence, facets of attention, and ideomotor apraxia. Table 2 lists all tests that were applied at each examination point (for further details of the tests, please refer to Supplementary Materials; Folstein, Folstein, & McHugh, 1975; Heßelmann, 1996; Weiss-Blankenhorn, Werner, & Piefke, 2005). These tests were administered in blocks of ca. 120 min each. The results of all the tests were communicated to the patients on their last day at the ward, and in a written form.

In order to exclude a potential vascular aetiology of the aphasic symptoms or other structural changes, all patients underwent structural MRI (3 T Siemens Tim-TRIO scanner, Siemens, Erlangen, Germany). Anatomical images were acquired with a T1-weighted MPRAGE sequence (176 slices, resolution 1 mm × 1 mm × 1 mm, field-of-view (FOV) = 256 mm, repetition time (TR) = 2.25 s, echo time (TE) = 3.03 ms; flip angle = 9°).

3. Results

This section gives a survey of the results of the neurolinguistic and neuropsychological tests in each patient. For a detailed report of the individual results of every patient the reader is referred to Supplementary Results. Over the course of 18 months different individual profiles as well as similarities were found. Systematic similarities were found in a deterioration of verbal skills, with

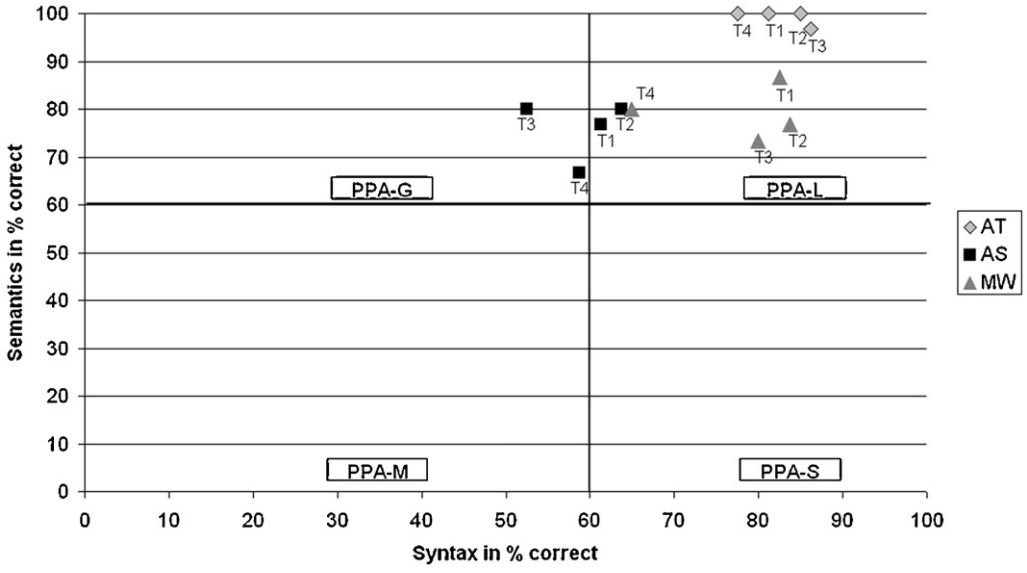

Fig. 1. Two-dimensional quantitative template for subtyping PPA. *Note*: AT's performance is illustrated with a diamond, the results of AS with a square, and MW's results with a triangle. The *y*-axis depicts the values in percentage correct in auditory single-word comprehension, and the *x*-axis shows the values in percentage correct of syntactic abilities. *Abbreviations*: T1, T2, T3, T4, first, second, third, and fourth examination point.

Table 3
Results of the patients in verbal fluency and executive functions.

	AT				AS				MW			
	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
sem. WFL	44	34[a*]	43	43	41	39	30[b,*]	33	41	40	40	30[d*,e*,f*]
lex. WFL	49	52	44	34[d**,e**,f*]	28	36	30	30	33	32	32	30
sem. Change	54	46	50	43	33	30	30	28	48	43	34[b*]	30[d**,e*]
lex. Change	57	30[a***]	46	30[d***,f**]	33	28	28	28	30	32	32	–

Abbreviations: T1, T2, T3, and T4, first, second, third, and fourth examination point; sem. WFL, semantic word-fluency; lex. WFL, formal-lexical word-fluency; sem. Change, semantic change condition; lex. Change, formal-lexical change condition. [a]T2–T1; [b]T3–T1; [c]T3–T2; [d]T4–T1; [e]T4–T2; [f]T4–T3; *$p \leq .05$; **$p \leq .01$; ***$p \leq .001$. *Note*: In T4 data of lexical Change condition is missing for MW because she aborted this test.

Table 4
Results of the patients in the AAT-subtests.

	AT				AS				MW			
	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
TT	69	73	73	73	56	57	56	57	73	73	73	61[d***,e***,f***]
REP	62	58[a**]	59[b*]	56[d***,f*]	47	49	48	45[e**,f*]	62	58[a**]	57[b***]	52[d***,e***,f***]
WRI	72	68[a*]	67[b**]	64[d***,e*,f*]	57	57	55	53[d*,e*]	54	51[a*]	51[b*]	47[d***,e*,f*]
NAM	71	60[a***]	58[b***]	63[d***]	59	53[a***]	51[b***]	49[d***,e*]	61	55[a***]	51[b***,c*]	48[d***,e***]
COMP	78	61[a***]	73	68[d**]	53	49	53	50	65	61	59	54[d**,e*]
AC	80	60	71	69	49	47	55	43	55	57	52	55
RC	64	61	67	63	56	50	50	56	78	63	66	52

Abbreviations: T1, T2, T3, and T4, first, second, third, and fourth examination point; TT, Token Test; REP, repetition; WRI, written language; NAM, picture naming; COMP, language comprehension; AC, auditory comprehension; RC, reading comprehension. [a]T2–T1; [b]T3–T1; [c]T3–T2; [d]T4–T1; [e]T4–T2; [f]T4–T3; *$p \leq .05$; **$p \leq .01$; ***$p \leq .001$.

Table 5
Patients' results in intelligence test.

	AT				AS				MW			
	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
Lexicon	43	44	44	42	35	36	32	34	37	33[a*]	33[b*]	33[d*]
Anagrams	59	62	60	60	48	59	54[c*]	41[d**,e***,f***]	42	38[a*]	38[b*]	38[d*]
phon. WFL	55	54	43[b***,c***]	44[d***,e***]	36	40	35[c***]	34[d*,e***]	39	42	34[b***,c***]	34[d***,e***]
Reasoning	57	55	62	58	50	57	58	48[e**,f**]	50	51	58	55
sp. sense	48	36[a*]	45	42	49	39	47	36[d**,f*]	51	51	62	58
perception	69	67	53[b***,c***]	64[d*]	53	53	50	41[d***,e***,f***]	59	53[a*]	55	53[d*]

Abbreviations: T1, T2, T3, and T4, first, second, third, and fourth examination point; phon. WFL, phonematic word fluency; sp. sense, spatial sense. [a]T2–T1; [b]T3–T1; [c]T3–T2; [d]T4–T1; [e]T4–T2, [f]T4–T3; *$p \leq .05$; **$p \leq .01$; ***$p \leq .001$.

naming tests, in particular. The ability to retell stories was impaired as well. In the apraxia tests, all patients developed mildly to moderate impairments. Furthermore, they worsened significantly in divided attention for auditory stimuli. In intelligence testing, performance for word-fluency on phonemic criteria declined significantly (cf. Table 3) and performance for verbal vs. non-verbal tests differed from each other significantly at each examination point. Performance for non-verbal semantics was average for each patient at each examination, whereby semantic dementia could be precluded at each examination point. Furthermore, deficits in spatial-constructional processing could also be precluded at every examination for each patient.

3.1. Language abilities (AAT aphasia test)

The results of the AAT subtests (cf. Table 4) showed that the patients' performance at every examination point was average or even above average, compared with normative data of vascular aphasics. AT almost continuously reached the best results in comparison to the other two patients, whereas AS scored always below the other two patients in every subtest. Only in the subtest written language MW scored continuously below the other two patients. In naming, the performance of all patients worsened over the period of 18 months. The deterioration of performance in naming and written language was significant in all patients.

3.2. Verbal and non-verbal intelligence

In the course of intelligence testing (cf. Table 5), all three patients showed deterioration in executive word retrieval (word-fluency by phonemic criteria). Moreover, all patients revealed significantly worse performance in verbal than non-verbal subtests at each examination. At T4 MW refused to carry out the verbal subtests.

3.3. Ideomotor skills

With respect to ideomotor skills, all patients showed a decreasing performance. AT and AS showed a light (AT) respectively moderate (AS) ideomotor apraxia at T4. With MW the test could not be finished at T4 because she was very frustrated about her

Table 6
Patients' results in apraxia tests.

	AT				AS				MW			
	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
LA	65	40	43	53	65	53	58	46	62	46	45	–
BA	30	28	30	30	30	29	30	26	30	29	27	22

Abbreviations: T1, T2, T3, and T4, first, second, third, and fourth examination point; LA, limb apraxia; BA, buccofacial apraxia. *Note*: The scores are raw-scores; scores for LA: 72–63: no LA; 62–53: light LA; 52–25: moderate LA; 24–0: severe LA; scores for BA: 30–29: no BA; 28–25: light BA; 24–11: moderate BA; 10–0: severe BA. *Note*: In T4 data LA is missing for MW because she did abort this test.

Table 7
Results of the patients in the Test for Attentional Performance (TAP).

	AT				AS				MW			
	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
Sustained attention												
SAwo	41	28[a***]	24[b***,c***]	24[d***,e***]	28	51	28[c***]	49[e***]	40	35[a***]	29[b***,c***]	21[d***,e***,f***]
SAw	40	33[a***]	28[b***,c***]	30[d***,e***]	28	34	37	29[e***,f***]	42	35[a***]	31[b***,c***]	20[d***,e***,f***]
Selective attention												
RT	45	37[a***]	43[b***]	33[d***,e***,f***]	56	76	65[c***]	73[e***]	68	47[a***]	28[b***,c***]	26[d***,e***,f***]
Omis	63	39[a***]	38[b***]	39[d***]	38	24[a*]	38	33	38	38	29	29
Err	38	41	52	53	41	30	35	28[d*]	35	38	46	35
Divided attention—single task												
RT vis	28	29	40	35[f**]	39	38	36	42	61	66	55[b***,c***]	53[d***,e***]
Omis vis	35	20	53	26	54	53	54	53	35	47	53	47
RT aud	44	24[a***]	20[b***,c***]	20[d***,e***]	36	32[a***]	20[b***,c***]	41	42	40[a*]	34[b***,c***]	28[d***,e***,f***]
Omis aud	40	41	39	39	41	41	41	39	41	41	39	39
Divided attention—dual task												
Omis	30	34	27	29	28	52	41	45	44	50	37	29
Err	38	66	67	67	61	49	49	43	34	32	32	30
RT vis	40	32[a***]	23[b***,c***]	21[d***,e***]	28	34	38	47	38	33[a**]	47	42[f**]
RT aud	33	21[a***]	20[b***]	20[d***]	–	35	29[c***]	55	43	29[a***]	45	27[d***,f***]

Abbreviations: T1, T2, T3, and T4, first, second, third, and fourth examination point; SAwo, sustained attention without warning signal, SAw, sustained attention with warning signal; RT, reaction time; Omis, omissions; Err, errors; RT vis, reaction time on visual stimuli; Omis vis, omissions in visual condition; RT aud, reaction time on auditory stimuli; Omis aud, omissions in auditory condition. [a]T2–T1; [b]T3–T1; [c]T3–T2; [d]T4–T1; [e]T4–T2; [f]T4–T3; $*p \leq .05$; $**p \leq .01$; $***p \leq .001$. *Note*: At T1 the data of RT aud of AS is missing because of data loss during data transfer.

disability to carry out the test and so the test was aborted. In addition, AS and MW developed a light (AS) respectively moderate (MW) buccofacial apraxia (cf. Table 6).

3.4. Attention

In the tests of different facets of attention, heterogeneous results were found (cf. Table 7).

For sustained attention, the performance of the patients for both conditions with and without auditory cue was at T1 nearby (below) average. During progression of the disease, it continuously worsened for AT and MW until it was wide below average at T4. Performance of AS in the condition without auditory cue was in average at T2, but dropped back at T3, and was in average again at T4. In the condition with auditory cue, AS slightly improved, but fell back at T4, so that performance always remained below average. In divided attention tasks, reaction time in both visual and auditory conditions was almost continuously below average. Patient AT scored the worst in reaction time and omissions. However, he committed fewer errors at T2, T3 and T4.

In the go/nogo task and the selective attention task, performance between the patients differed in the course of 18 months. Reaction time of AS was always average or even above average, but he omitted many stimuli and committed many errors. On the other hand, AT's reaction time was at each examination in lower average but during the course he committed less errors and at the same time omitted more stimuli. MW's reaction time worsened continuously, she omitted many stimuli and committed fewer errors during the course. AT and MW significantly worsened in reaction time for auditory stimuli in selective attention, whereas AS scored average at T4 (cf. Table 7).

3.5. Verbal and non-verbal learning

The learning tests (Table 8) showed different dynamics in the three patients: patient AT's performance improved for both verbal and non-verbal learning, but at T4 performance dropped back for verbal learning whereas for non-verbal learning continuously increased. Patient AS shows a fluctuating performance for both verbal and non-verbal learning test. The verbal performance of MW was below average from the beginning at T1, and worsened significantly to T4; her non-verbal performance remained on average level till T3 but was below average at T4.

3.6. Long-term outcome in patient AT

Finally, in Table 9, we report the data from examinations of patient AT from a total of seven time points, covering a period of 46 months. The data demonstrate further decline in language abilities but also in attention, but not in verbal and non-verbal learning.

4. Discussion

In this longitudinal study on the cognitive development of logopenic PPA patients, neurolinguistic and neuropsychological skills of three fPPA patients were examined over the course of 18 months in order to investigate commonalities and discrepancies in the progression of the disease. (1) As a main result, we observed that all three patients showed comparable patterns not only in language processing but also in attention and praxis. In particular, similarities were found in the deterioration of verbal skills, above all in naming as well as in the ability of story retelling. Furthermore, the performance in phonematic word-fluency worsened significantly. (2) As a second main finding, at each examination, verbal performance was systematically worse than non-verbal performance in every patient, including non-verbal semantic abilities. (3) Moreover, all patients developed mild to moderate limb-apraxia. (4) Additionally, the performance on an auditory divided attention task decreased systematically in all patients. These findings are now discussed in detail. (5) Finally, the long-term examination of patient AT corroborates that the pattern of decline observed for all three patients is stable even over a period of 46 months.

4.1. Verbal skills

The spontaneous language scores were stable for each patient over the course of the investigation. One reason could be that the time span between the investigation points was too short to find significant changes in the test investigating spontaneous language. The AAT-scales may not be sensitive enough to detect marginal changes (Grande et al., 2008). Poeck and Luzzatti (1988), who

Table 8
Patients' results in verbal (VLT) and non-verbal (NVLT) learning test.

	AT				AS				MW			
	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
VLT	29	48	52	40[f*]	43	48	30[b*,c**]	35[e*]	42	37	34	28[d*]
NVLT	47	55	56	58	52	41[a*]	37[b**]	41[d*]	47	44	55	39[f**]

Abbreviations: T1, T2, T3, and T4, first, second, third, and fourth examination point; VLT, difference value in the verbal learning test; NVLT, difference value in the non-verbal learning test; [a]T2–T1; [b]T3–T1; [c]T3–T2; [d]T4–T1; [e]T4–T2; [f]T4–T3; $^{*}p \leq .05$; $^{**}p \leq .01$; $^{***}p \leq .001$.

examined three patients twice at intervals between six months to three years used the same test procedure to investigate spontaneous language, and did not find significant changes as well. Moreover, all patients reported that fluency differs at different times of the day and between days, which may further make it difficult or even impossible to detect changes in relatively short intervals of time.

All fPPA patients showed continuous deterioration in the AAT subtest naming. For two of them this decrease was significant. This finding extends data from previous PPA studies (cf. Karbe, Kertesz, & Polk, 1993; Kertesz, Davidson, McCabe, Takagi, & Munoz, 2003; Mesulam et al., 2003; Sonty et al., 2003; Weintraub, Rubin, & Mesulam, 1990) which identified naming difficulties as a core deficit in fPPA. However, even over the course of one and a half

Table 9
Results of the patient AT (T0 = December 2006, T6 = October 2010; time interval: 46 months).

	T0	T1	T2	T3	T4	T5	T6
AAT—subtests							
TT	73	69	73	73	73	67	57[g***,h***]
REP	64	62	58	59	56	54	51[g***,h***]
WRI	70	72	68	67	64	63	62[g***,h***]
NAM	66	71	60	58	63	57	50[g***,h***]
COMP	78	78	61	73	68	63	52[g***,h***]
AC	69	80	60	71	69	57	57[g*,h***]
RC	78	64	61	67	63	66	49[g***,h***]
RWT							
sem. WFL	–	44	34	43	43	36	33[h*]
lex. WFL	–	49	52	44	34	38	44
sem. Change	–	54	46	50	43	38	33[h**]
lex. Change	–	57	30	46	30	34	30[h***]
Intelligence							
Lexicon	46	43	44	44	42	40	37[g***,h***]
Anagrams	57	59	62	60	60	51	62
phon. WFL	51	55	54	43	44	47	46[g***,h***]
Reasoning	–	57	55	62	58	53	51
sp. sense	30	48	36	45	42	48	39[h*]
Perception	51	69	67	53	64	59	57[h***]
Apraxia (raw-scores)							
LA	–	65	40	43	53	45	39
BA	–	30	28	30	30	29	29
Attention							
Sustained attention							
SAwo	37	41	28	24	24	21	21[g***,h***]
SAw	48	40	33	28	30	27	32[g***,h***]
Selective attention							
RT	–	45	37	43	33	30	25[h***]
Omis	–	63	39	38	39	39	33[h***]
Err	–	38	41	52	53	38	41
Divided attention—single task							
RT vis	35	28	29	40	35	49	32
Omis vis	35	35	20	53	26	40	26
RT aud	44	44	24	20	20	20	26[g***,h***]
Omis aud	40	40	41	39	39	41	26
Divided attention—dual task							
Omis	30	30	34	27	29	31	23
Err	45	38	66	67	67	52	52
RT vis	33	40	32	23	21	36	29[g*,h***]
RT aud	36	33	21	20	20	20	[a]
Learning							
VLT	36	29	48	52	40	37	47
NVLT	35	47	55	56	58	48	38

Abbreviations: T0–T6 first till sixth examination point; TT, Token Test; REP, repetition; WRI, written language; NAM, picture naming; COMP, language comprehension; AC, auditory comprehension; RC, reading comprehension; WFL, semantic word-fluency; lex. WFL, formal-lexical word-fluency; sem. Change, semantic change condition; lex. Change, formal-lexical change condition; phon. WFL, phonematic word-fluency; sp. sense, spatial sense; LA, limb apraxia; BA, buccofacial apraxia.
Note: The scores are raw-scores; scores for LA: 72–63: no LA; 62–53: light LA; 52–25: moderate LA; 24–0: severe LA; scores for BA: 30–29: no BA; 28–25: light BA; 24–11: moderate BA; 10–0: severe BA; SAwo, sustained attention without warning signal, SAw, sustained attention with warning signal; RT, reaction time; Omis, omissions; Err, errors; RT vis, reaction time on visual stimuli; Omis vis, omissions on visual stimuli; VLT, difference value in the verbal learning test; NVLT, difference value in the non-verbal learning test; in visual condition; RT aud, reaction time on auditory stimuli; Omis aud, omissions in auditory condition.
Note: "–", no data available.
[g]T0–T6, [h]T1–T6; $^{*}p \leq .05$; $^{**}p \leq .01$; $^{***}p \leq .001$.
[a] Patient ignored all of the auditory stimuli.

years, performance remained within the average range of aphasics with vascular aetiology, indicating that the decrease was constant but not dramatic. Similarly, in phonematic word-fluency, all three patients worsened. This decline became significant from the second to the third examination points. To summarize, as hypothesized, there was a continuous decrease in expressive verbal skills in all three patients, which is the core symptom of PPA (Medina & Weintraub, 2007).

Although this finding was expected on the basis of earlier cross-sectional research, it is only by virtue of the present longitudinal data that the progression of language symptoms can be documented and quantified over the course of 18 months. Most interestingly, whereas vascular aphasics usually tend to improve and become more fluent over time even in the case of overall non-fluent aphasia, one of the PPA patients examined here showed the reverse development, i.e. a change in syndrome. Patient AS was initially fluent but became (and remained) non-fluent during the course of 18 months. This observation, which needs to be replicated longitudinally in more cases, may suggest that, despite the initial presence of distinct PPA subtypes, a transformation from fluent (at least logopenic) into non-fluent may occur over time.

4.2. Learning and memory

In the verbal learning test the patients AS and MW showed the expected decline in performance over a period of 18 months. Their performance was below average after six (MW) and twelve (AS) months. In the non-verbal learning test those two patients also showed the expected profile: the onset of the disease in MW was less than two years ago and her performance in non-verbal learning was still in the average range. Yet, the performance of AS, who reported the first word-finding difficulties more than two years ago, declined over the course of twelve months and at T3 was below average. This corresponds with the typical course of PPA (Mesulam & Weintraub, 1992), which may include non-verbal learning impairments later than 2 years after the onset of the disease.

An unexpected result was found in the performance of AT over the course of 18 months. The onset of the disease was more than four years before he entered the study. Yet, surprisingly, his performance in non-verbal learning was in the average range at each examination and continuously improved. Likewise, his verbal learning performance improved and was in the average range from T2 on. These results are rather surprising in a progressing language disorder. On closer inspection, AT's response behaviour changed during the twelve months: in comparison to the previous examination he made fewer false alarms (which are contrasted with hits), so the average score becomes better. One possible explanation is that AT trained his memory, whereby he used a holistic mnemonic computer program at home. This program works similar to the applied test: he has to press a key when a certain picture of a city appears repeatedly, but not when an unknown picture appears. Therefore, it could be possible that this increasing controlled response behaviour is an effect of training by the computer program. If this would hold true in a larger sample, it would be an easy and straightforward strategy to maintain verbal learning performance in PPA patients.

4.3. Intelligence

A consistent result was found in the deterioration in word-fluency for all of our patients over the course of examination. Furthermore, verbal performance was significantly worse than non-verbal performance at every examination for all patients. This result is in line with and extends earlier findings by Poeck and Luzzatti (1988) who applied the same test procedure for intelligence like the present study. Regarding the progression of intelligence decline, the verbal performances of their three patients also worsened over the period of investigation and were partly below average at the last examination point whereas non-verbal performance worsened within average. Consequently, there was a dissociation between the progress of verbal and non-verbal intelligence. In the light of the decrease in verbal abilities discussed above, this dissociation suggests the increasing importance of non-verbal IQ tests for the objective assessment of the cognitive status of fPPA patients.

4.4. Apraxia, attention, and language

Over the course of 18 months, all patients developed mild (AS) or moderate limb-apraxia. As Joshi, Roy, Black, and Babour (2003) noted, tests of apraxia are rarely part of standard examination of PPA patients despite the acknowledged comorbidity with PPA. Following the definition of PPA by Mesulam (2001), mild limb apraxia or buccofacial apraxia can be present at the beginning of the disease, but do not affect everyday activities. Likewise, Kempler et al. (1990) reported that one of their three patients developed a moderate apraxia as well as the patient of Schwarz, De Bleser, Poeck, and Weis (1998) who developed limb-apraxia in the course of the disease. Along the same lines, Weintraub et al. (1990) describe the development of buccofacial apraxia in two of their three patients. However, several other studies did not report any kind of apraxia in PPA. For instance, none of the three patients of Poeck and Luzzatti (1988) showed signs of limb or buccofacial apraxia. Zakzanis (1999), Caramazza, Papagno, and Ruml (2000) as well as Papagno and Capitani (2001) found no evidence for limb or buccofacial apraxia in fPPA.

One explanation for this heterogeneous pattern could be that the presence or absence of apraxic symptoms is possibly related to the individual pattern of neurodegeneration. Following Leiguarda and Marsden (2000) and Goldenberg (2007), apraxia is (often) associated with damage in particular of left parietal regions in the brain. Due to profound degeneration in the parietal lobes, apraxia could increase or emerge during the course of PPA. Interestingly, different subtypes of PPA show differential patterns of atrophy (Mesulam et al., 2009), with parietal atrophy particularly in the logopenic variant of PPA that is characterized predominantly by phonological deficits. This parietal atrophy in logopenic PPA, which is associated with these phonological deficits, may also explain the increasing apraxia symptoms observed here. This does not preclude more wide-spread atrophy in frontal and parietal regions in individual patients, but, rather, complements the original concept of "fronto-temporal lobar dementia".

The same explanation may also apply to the robust decrease in attention in all three patients. Whereas praxis is generally associated with left-hemispheric regions, attention is associated in particular with right parietal lobe functions (e.g. Arrington, Carr, Mayer, & Rao, 2000; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Raz, 2004). As discussed above for apraxia, degeneration occurs in parietal cortex and may be found in particular in the logopenic variant of PPA (e.g. Gorno-Tempini, Dronkers, et al., 2004; Gorno-Tempini et al., 2008; Rohrer et al., 2010). Thus, the remarkable and persistent decline in the attention domain in all three logopenic PPA patients may be closely linked to parietal atrophy as well.

It is these latter two symptoms, and in particular deterioration of attention, that may characterize the progressive nature of logopenic PPA. Different from findings in aphasic patients with vascular aetiology (e.g. Graf, Kulke, Sous-Kulke, Schupp, & Lautenbacher, 2011, who demonstrated that vascular aphasic patients do not profit from additional training of attention), in logopenic PPA patients, language decline and attention decline

seem to be related, or, at least, co-incidental. This is an important observation, which was possible only by virtue of the longitudinal approach applied in the present study but which could not be obtained cross-sectionally (Zakzanis, 1999). The fact that Zakzanis (1999) attributed only minor importance to the domain of attention in PPA may further be explained by the fact that, at that time, the logopenic variant of PPA had not been identified. As outlined above, it is very likely that the parietal atrophy in logopenic PPA, which may affect phonology, praxis, and attention is singular and that the semantic or agrammatic variants of PPA fail to show such association between language and attention. Consequently, if several subtypes of PPA had been included in the Zakzanis (1999) study, mild cross-sectional impairments of attention in few logopenic PPA patients may have been obscured. Further longitudinal research is required to compare the development of attention in the logopenic variant of PPA to that in the semantic or agrammatic type, as was done in the study by Libon et al. (2009). However, one limitation of the Libon study is that it only included a subset of the cognitive domains and sub-domains that were tested in the present study.

4.5. Limitations and perspectives

The present study provides a multivariate, longitudinal approach to the logopenic variant of PPA. The patients were examined four times over the course of 18 months, using a comprehensive battery of linguistic and neuropsychological tests with and without verbal materials. With such broad and labour-intensive approach, we faced some inevitable limitations. Foremost, the patients' resilience decreased with progressing severity of their disease, making it necessary to include more and more pauses and thus to inflate the total time of examination. Likewise, in particular language-based tests became increasingly difficult and frustrating for the patients. These increasing time demands put constraints on the total number of tests that could be performed with each patient at each examination. Ideally, one would wish to have verbal and non-verbal versions of each test (as we had e.g. for intelligence and learning) in order to be able to compare verbal vs. non-verbal performance. Due to the time constraints, and since tests are not always available to examine verbal and non-verbal performance, an a priori selection of tests had to be made. We focused on such tests that seemed most sensitive and relevant to PPA and thus included, e.g. no test of non-verbal executive functions.

Another limitation was the selection of patients. First, given the low prevalence rate of PPA, large samples are hard to acquire. As outlined in Section 2, less than 50% of the patients potentially suitable for the study could finally be included. It would be desirable to have about the same proportions of logopenic, semantic, and agrammatic PPA patients, and matched healthy controls. At the same time, protection against drop-outs would be ideal in order to generalize findings. In the present study, the availability of a neurological research ward at the Research Centre Jülich helped prevent drop-outs, since patients were in a well-cared environment and could bring their spouses for the duration of their stay.

The three patients reported in the present paper showed consistencies but also some variability over the course of the examination. Potential reasons involve non-uniform progress of the degeneration of neural tissue as well as influence of other variables such as level of education or the kind of intervening speech therapy. However, in the present paper, we focused on the most robust commonalities in the individual cognitive trajectories, providing individual statistics which additionally permit the assessment of inter-patient variance. To address systematically the variability between different variants of PPA is a project for future studies.

5. Conclusion

The present longitudinal study demonstrates the progression in a fluent variant of PPA, which was predominant but not restricted to the verbal domain. In addition to increasing deficits in verbal fluency and naming, and to relatively more severely impaired verbal than non-verbal learning, praxis, and attention were also impaired over the course of the disease. These findings were consistent in all three PPA cases reported here and may thus be used as a basis for hypotheses about the determining features of logopenic PPA. The progression data were further corroborated in the long-term observation of one of the patients over a period of 46 months. Such knowledge will be relevant for future research to better define the syndrome of PPA in general as well as to distinguish its different variants from one another. As a tentative hypothesis, one could expect that the concurrent deficits which result, among others, from atrophy to the parietal lobes (cf. Mesulam et al., 2009) may not simply represent comorbid deficits but, rather, interact. If, as in the case of logopenic PPA reported in the present study, selective auditory attention impacts on the processing of spoken language, the resulting problems in language comprehension might be much bigger than they would be in the case of an isolated phonological processing deficit. In other words, the observed phonological symptoms the patients make in every-day life and in a diagnostic situation could be partly due to the additional interference of partly disturbed auditory attention. Such potential cross-causalities would be of particular importance also for the practitioner who decides how to best plan the individually targeted therapy which may differ from that for aphasics with vascular aetiology (Graf et al., 2011).

Finally, the study has some general implications for neuropsychologists and speech and language therapists working with PPA patients. To practitioners, PPA is almost unknown (Croot, Nickels, Laurence, & Manning, 2009). However, it is likely that the prevalence of PPA will increase due to the increasing life expectancy of the human population. Following the suggestions by Louis et al. (2001), Block and Kastrau (2004), or Croot et al. (2009), PPA should move into the focus of practitioners, with the positive consequences for diagnostics and therapy discussed above. The present multivariate approach may be useful to better understand the spectrum of deficits in PPA for more efficient diagnostics and intervention in the future, with the aim that PPA patients can longer be part of a communicating society.

Future research should enlarge the sample of PPA patients to get more information about the individual focus of the disease in every patient. Moreover, even longer examination period could provide further insight in the progression of the disease and show a change from a fluent to a non-fluent variant of PPA.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuropsychologia.2012.03.028.

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