Journal of Neural Transmission (2022) 129:1039–1048
https://doi.org/10.1007/s00702-022-02524-2

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

Differences in aphasia syndromes between progressive supranuclear palsy–Richardson's syndrome, behavioral variant frontotemporal dementia and Alzheimer's dementia

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Received: 30 March 2022 / Accepted: 12 June 2022 / Published online: 12 July 2022

Abstract

Language impairments, hallmarks of speech/language variant progressive supranuclear palsy, also occur in Richardson's syndrome (PSP-RS). Impaired communication may interfere with daily activities. Therefore, assessment of language functions is crucial. It is uncertain whether the Aachen Aphasia Test (AAT) is practicable in PSP-RS, behavioral variant frontotemporal dementia (bvFTD) and Alzheimer's dementia (AD) and language deficits differ in these disorders. 28 PSP-RS, 24 AD, and 24 bvFTD patients were investigated using the AAT and the CERAD-Plus battery. 16–25% of all patients failed in AAT subtests for various reasons. The AAT syndrome algorithm diagnosed amnestic aphasia in 5 (23%) PSP-RS, 7 (36%) bvFTD and 6 (30%) AD patients, Broca aphasia in 1 PSP-RS and 1 bvFTD patient, Wernicke aphasia in 1 bvFTD and 3 (15%) AD patients. However, aphasic symptoms resembled non-fluent primary progressive aphasia in 14 PSP-RS patients. In up to 46% of PSP-RS patients, 61% of bvFTD and 64% of AD patients significant impairments were found in the AAT subtests spontaneous speech, written language, naming, language repetition, language comprehension and the Token subtest. The CERAD-Plus subtest semantic fluency revealed significant impairment in 81% of PSP-RS, 61% of bvFTD, 44% of AD patients, the phonemic fluency subtest in 31, 40 and 31%, respectively. In contrast to bvFTD and AD, severity of language impairment did not correlate with cognitive decline in PSP-RS. In summary, the patterns of aphasia differ between the diagnoses. Local frontal language networks might be impaired in PSP-RS, whereas in AD and bvFTD, more widespread neuropathology might underly language impairment.

Keywords Progressive supranuclear palsy · Behavioral variant frontotemporal dementia · Alzheimer's dementia · Non-fluent agrammatic primary progressive aphasia · Cognitive impairment

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Introduction

Prototypical progressive supranuclear palsy (PSP), originally described by Steele et al. (1964), later named Richardson's syndrome (PSP-RS), is characterized by vertical gaze palsy, postural instability, parkinsonism, pseudobulbar palsy, cognitive and behavioral deterioration and typical neuronal, astroglial and oligodendroglial fibrillary neuropathology (Steele et al. 1964; Litvan et al. 1996; Williams and Lees 2009; Respondek et al. 2014). Clinical subtypes of PSP were identified including speech and language variants (PSP-non-fluent/agrammatic primary progressive aphasia (nfaPPA) and progressive apraxia of speech) (Steele et al. 1964; Litvan et al. 1996; Boeve et al. 2003; Williams and Lees 2009; Respondek et al. 2014; Höglinger et al. 2017). However, speech and language deficit may also occur in PSP-RS (Podoll et al. 1991; Rosser and Hodges 1994; Litvan et al. 1996; Williams and Lees 2009).

Multi-domain cognitive decline and impairments of speech and language are related to widespread cortical and subcortical degeneration in PSP-RS (Steele et al. 1964; Litvan et al. 1996; Williams and Lees 2009; Respondek et al. 2014). In Alzheimer's dementia (AD) and behavioral variant frontotemporal dementia (bvFTD), cognitive decline and language impairments also result from extended neurodegeneration (McKhann et al. 2011; Rascovsky et al. 2011). Data on clinical language assessment in PSP patients are limited. Moreover, it has so far not been examined whether language impairments and aphasia syndromes differ in early to moderately advanced PSP-RS, AD and bvFTD (Cummings et al. 1985; Lang et al. 1991; Blair et al. 2007; McKhann et al. 2011; Rascovsky et al. 2011). Because of clinical and neuropathological specificities, language deficits are presumably different in these disorders, yet correlate with cognitive decline.

Diagnosis of speech and language impairments and cognitive deterioration is mandatory in clinical practice to assess communication difficulties and to take suitable measures including speech therapy and personal support. The Aachen Aphasia Test (AAT) was primarily conceived for the diagnosis of aphasia syndromes after stroke. It is validated in several languages and widely used (Huber et al. 1983). By analogy to studies using the AAT and similar aphasia tests or test components (Western Aphasia Battery or SAND Battery, naming, fluency, writing, language repetition tasks, etc.) we hypothesized that the AAT might be practicable and useful in neurodegenerative disorders (Lang et al. 1991; Blair et al. 2007; Catricalà et al. 2019; Picillo et al. 2019) such as in PSP-RS, AD and bvFTD.

The aims of the present study were (1) to compare language deficits and aphasia syndomes in PSP-RS, AD and bvFTD, (2) to find out, whether language impairments are related to multi-domain cognitive decline, and (3) to evaluate the practicability of the AAT for clinical aphasia diagnosis in mild to moderately advanced PSP-RS, AD and bvFTD.

Methods

Patients

Between 2009 and 2018, patients with PSP (Litvan et al. 1996; Williams and Lees 2009; Respondek et al. 2014; Höglinger et al. 2017), corticobasal syndrome (Armstrong et al. 2013), bvFTD (Rascovsky et al. 2011), and primary progressive aphasia (Gorno-Tempini et al. 2011) and their caregivers were asked to participate in a local registry study (Fronto-temporal lobar atrophy-(FTLA)-registry), which focused on clinical progression, neuroimaging, activities of daily living and caregiving (Guger et al. 2021; Kellermair et al. 2021). The protocol was approved by the local ethics committee (Ethikkommission Land Oberösterreich, application number 254) and conducted according to the 1975 Helsinki declaration. Patients and caregivers gave their informed written consent. As of 2013, also patients with probable AD (McKhann et al. 2011) participated in the study.

Between 2013 and 2017, on average one year after inclusion in the FTLA registry study, 28 consecutive patients fulfilling the diagnostic criteria of PSP-RS (Litvan et al. 1996; Williams and Lees 2009; Respondek et al. 2014; Höglinger et al. 2017), 1 patient with PSP-pure akinesia and gait freezing/progressive gait freezing (PSP-PGF) (Respondek et al. 2014; Höglinger et al. 2017), 24 bvFTD patients (Rascovsky et al. 2011), 9 AD patients (McKhann et al. 2011) from the FTLA registry, and 15 AD patients from the memory clinic of the Kepler University Hospital Linz consented to participate in the present aphasia study protocol, which had been conceived as addendum to the original FTLA registry protocol. Three PSP patients had been referred to the Kepler University Hospital Linz from the Department of Neurology, Medical University of Graz, the remaining patients had been recruited at the Kepler University Hospital.

Diagnostic procedures

The baseline examination is summarized and cited in a previous publication (Kellermair et al. 2021). It comprised history taking, general medical, neurological and psychiatric examinations, rating of motor symptoms (Unified Parkinson's disease Rating Scale III, UPDRS-III; Tinetti Performance Oriented Mobility Assessment, Tinetti), neuropsychological tests (Consortium to Establish a Registry for Alzheimer's Disease, CERAD-Plus (Schmid et al. 2014),

including the Mini-Mental State Examination, MMSE; Frontal Assessment Battery, FAB) and neuropsychiatric scales (Frontal Behavioral Inventory, Geriatric Depression Scale, Neuropsychiatric Inventory), assessment of instrumental and basic activities of daily living (ADL) (Lawton and Brody, Barthel), dependency, social parameters, caregiver burden, neuroimaging (in most patients MRI) for corroboration of the clinical diagnoses and exclusion of other significant pathologies, and routine blood and serum laboratory including vitamin B12 and folate levels, TSH, HIV and TPHA serology. Follow-up examinations were performed at 6–12-month intervals for 2 years unless patients or caregivers dropped out from the FTLA-registry study because of withdrawal of consent, immobility, intercurrent disease, admission to a nursing home or death (Guger et al. 2021; Kellermair et al. 2021).

Included *PSP patients* fulfilled the diagnostic criteria of PSP-RS (Williams and Lees 2009; Respondek et al. 2014; Höglinger et al. 2017). On clinical examination vertical gaze palsy or severely impaired vertical and horizontal saccades were noted in all PSP-RS patients, horizontal gaze palsy in the minority of patients. Corrected vision was normal. Quantitative measurements of oculomotor functions were not performed. Neuroimaging (MRI 26, CT 3 patients) revealed midbrain atrophy as well as frontotemporal and insular atrophy and an enlarged third ventricle. The Magnetic Resonance Parkinsonism Index was > 13.55 (Quattrone et al. 2008; Mangesius et al. 2018). Sequelae of cerebral trauma, infarcts, Fazekas grade 2 or 3 white matter hyperintensities and neoplasms were ruled out.

BvFTD patients exhibited disinhibition, loss of empathy, apathy, and stereotypical behavior. The clinical, neuropsychological and neuroimaging findings (MRI in 22, CT in 2 patients) corresponded to the diagnostic criteria of probable bvFTD (Rascovsky et al. 2011).

Short-term memory and naming problems interfering with routine activities were the leading symptoms of the AD patients (McKhann et al. 2011). Clinical examination revealed dementia. Language deficits and neuropsychiatric symptoms were absent or mild. The neuropsychological profile and neuroimaging findings (MRI in 20, CT in 4 patients; mesiotemporal and temporo-parietal cortical atrophy) were typical for probable AD (McKhann et al. 2011).

Testing of language functions

The AAT (Huber et al. 1983) was used as our main tool to diagnose language impairments and aphasia syndromes.

The AAT is validated in aphasia patients and normal control subjects (scores of historical normal controls see Table 2) and classifies sum scores of AAT subtests as normal, or mildly, moderately, or severely impaired (Huber et al. 1983). An algorithm of the AAT summarizes the subtests and categorizes language impairments according to syndromatic principles as Broca, Wernicke, amnestic or global aphasia, or no evidence of a classical aphasia syndrome. For aphasia syndrome classification, all AAT subtests need to be completed.

The *AAT* comprises the following subtests:

Spontaneous speech: The examinee responds to questions about the disease, occupation, family and leisure. *Communication behavior, articulation and prosody, speech automatisms, semantic structure, phonematic structure and syntactic speech structure* are rated from 5 to 0 (score 5: no impairment, 4: mild, 3: moderate, 2: marked, 1 and 0: severe impairment). The optimal sum score is 30.

Token test: The examinee is orally requested to select and arrange rectangles and circles differing in color and size (tokens). Incorrect responses are counted and corrected for age (Huber et al. 1983). The best possible sum score is zero.

Language repetition: The examinee repeats each ten spoken sounds and mono-syllable, loan, foreign, and compound words and sentences. The optimal sum score is 150.

Written language: The examinee reads words and sentences and replicates spoken words and sentences by composing letters and word cards. Further, handwriting after dictation is tested. 90 is the optimal sum score.

Naming: Naming of drawn objects (single and compound nouns, color descriptions) and interpretation of drawings of situations, actions and stories is tested. The optimal sum score is 120.

Language comprehension: The examinee selects one out of four drawings corresponding to a target word or a sentence spoken by the examiner. The optimal score is 120.

We also applied the CERAD-Plus subtests *semantic fluency* (animals) and *phonemic fluency* (s-words) and *object naming* (short form of the Boston Naming Test) to complete the testing of language functions (Schmid et al. 2014).

Neuropsychological and language testing was performed at the Kepler University Hospital Linz or in the homes of the patients. All members of the study team testing language functions and cognition (A.F., R.K., L.R., S.R.-T.) were affiliated to the Kepler University Hospital Linz, Department of Neurology 2. They were not informed about the diagnoses. Diagnosic procedures including neuropsychological and aphasia testing were coordinated and supervised by the corresponding author (G.R.).

Statistical analyses

A two-sided p value ≤ 0.05 was taken as the uncorrected statistical level of significance. In the case of multiple comparisons, the statistical level of significance was adapted according to Bonferroni (critical p value: 0.05 divided by the number of comparisons). Between-group differences in categorical variables were compared using the χ^2 test.

Normally distributed continuous variables were compared using the Student's *t*-test. For non-normally distributed and ordinal scaled variables the Kruskal–Wallis ANOVA and the Mann–Whitney-*U* test were applied. To assess potential univariate correlations between variables Spearman's rank correlations were calculated. Test scores beyond the means plus or minus 1.3 times the standard deviation from the means of normal controls indicated statistically significant impairment. Online statistics were applied (www.socscistatistics.com).

Results

Demographics, education, clinical and neuropsychological findings

Age, sex, disease duration and years of education are summarized in Table 1. There were no differences between PSP, bvFTD and AD ($p > 0.05$). The neuropsychological results (MMSE raw sum scores, *z*-sum scores, CERAD-Plus *z*-sum scores, FAB sum scores) were comparable between the groups (critical *p* value corrected for multiple-comparison 0.012). Substantial motor impairment was found in PSP-RS patients (UPDRS-III, Tinetti) and moderate to marked neuropsychiatric and behavioral symptoms were reported by caregivers, mainly in the bvFTD group (Neuropsychiatric inventory, NPI), and impaired ADLs.

Practicability of the AAT

7 out of 28 PSP-RS patients (25%) were unable to perform the *handwriting task* because of severe akinesia of the dominant hand. One of these patients refused to complete the *language comprehension* subtest. The PSP-PGF patient was severely akinetic and dysarthric and spoke unintelligibly. Therefore, only his *Token test* and his *language comprehension* test were evaluable. 5 of 24 bvFTD patients (20%) did not complete all AAT subtests because of lack of motivation due to cognitive difficulties: 2 patients *written language, naming, language comprehension* and *Token test*, 2 patients *written language*, and 1 patient *written language, naming and language repetition*. 4 out of 24 AD patients (16%) failed to complete all AAT subtests because of cognitive impairments and lack of motivation: 1 patient *spontaneous speech*, 1 patient *language repetition* and *written language*, 1 patient *written language*, 1 patient *written language* and *language comprehension*.

Aphasia syndromes (Tables 2 and 3)

Knowing well that the AAT was not genuinely standardized for the syndromic assessment of degenerative language

Table 1 Demographic and clinical parameters and education years

	PSP *N* = 29	bvFTD *N* = 24	AD *N* = 24	*p* values*
Age	73.9 ± 6.6 (75)	71.5 ± 8.1 (72.5)	78.1 ± 10.1 (77.5)	n.s.
Sex (m/f)	16/13	10/14	13/11	n.s.
Disease duration (Mo)	48.3 ± 36.8 (37)	46.5 ± 36.0 (41)	35.1 ± 24.9 (30)	n.s.
Education years	11.1 ± 4.5 (11)	10.8 ± 3.0 (11)	10.1 ± 2.9 (9.5)	n.s.
MMSE				
Raw Scores	25.4 ± 3.69 (27)	22.8 ± 5.3 (24.5)	22.3 ± 5.3 (25.5)	n.s.
z-Scores	− 1.81 ± 1.46 (− 1.9)	− 3.20 ± 2 (− 3.75)	− 3.18 ± 2.15 (− 2.6)	n.s.
CERAD-Plus *z*-sum scores	− 6.89 ± 4.71 (− 7.7)	− 9.35 ± 7.74 (− 7.9)	− 8.82 ± 5.15 (− 7.6)	n.s.
FAB§	12 ± 7.73 (12)	12.47 ± 6.05 (14)	–	n.s.
UPDRS-III§	42.8 ± 19.22 (44)	22.5 ± 18.15 (16)	–	0.0012*
Tinetti§	14.5 ± 2.95 (15)	20.9 ± 11.5 (23)	–	< 0.0001*
Neuropsychiatric inventory	8.7 ± 10.5 (4)	27.5 ± 25.9 (27)	6.6 ± 7.6 (4.5)	
IADL§	6.5 ± 3.4 (6)	5.2 ± 4.8 (4)	–	
Barthel Index§	80.3 ± 15.6 (80)	78.2 ± 28.2 (92.5)	–	

Means ± standard deviations (medians)

AD Alzheimer dementia, *bvFTD* Behavioral Variant Fronto-temporal Dementia, *CERAD-Plus* Consortium on the Establishment of a Registry in Alzheimer's Disease Plus, *FAB* Frontal Assessment Battery, *m/f* male/female, *IADL* Instrumental activities of daily living, *MMSE* Mini-Mental State Examination, *Mo* months, *n.s.* not significant ($p > 0.05$), *PSP* Progressive Supranuclear Palsy, *UPDRS-III* Unified Parkinson's Disease Rating Scale-Motor scale

§FAB, UPDRS-III,Tinetti, IADL and Barthel index: scores of AD patients are not shown. They were assessed only in single AD patients

*Statistically significant after correction for multiple comparisons

Table 2 Aachen Aphasia Test and CERAD-Plus subtests

Aachen Aphasia Test subtests	PSP	bvFTD	AD	Historical normal controls	*p* values
Spontaneous speech (30;27)	26.3 ± 2.7 (27)	25.1 ± 6.4 (27)	27.5 ± 3.5 (29)	27.34 (28.05)	n.s.
Token test (0;4)	2.8 ± 8.3 (0)	7.7 ± 12.1 (1.5)	6.2 ± 10.6 (3)	1.25 ± 1.64 (0.48)	n.s.
Language repetition (150;141)	143.2 ± 7.5 (146)	132 ± 28.0 (140)	135.5 ± 13.0 (138)	146.08 ± 3.75 (147.17)	n.s.[&]
Written language (90;82)	84.0 ± 8.4 (87)	78.5 ± 23.4 (88)	78.5 ± 16.4 (86)	86.96 ± 3.07 (87.67)	n.s.
Naming (120;104)	103.4 ± 11.3 (107.5)	93.8 ± 26.0 (103)	98.7 ± 13.8 (104)	111.09 ± 5.38 (111.64)	n.s.
Language comprehension (120;95)	100.7 ± 8.0 (101.5)	89.2 ± 282 (99)	92.4 ± 19.8 (94)	107.35 ± 8.81 (109)	n.s.
CERAD-Plus (z-scores)	*N* = 26	*N* = 24	*N* = 17		
Semantic fluency	− 1.93 ± 0.84 (− 1.9)	− 1.6 ± 1.29 (− 1.7)	− 1.46 ± 1.05 (− 1.2)		n.s.
Phonemic fluency	− 1.10 ± 1.07 *(− 1.1)*	− 0.83 ± 1.26 (− 1.1)	− 0.67 ± 1.31 (− 0.9)		n.s.
Object naming	− 1.29 ± 1.27 (− 1.3)	− 1.43 ± 1.1 (− 1.5)	− 1.35 ± 1.41 (− 0.55)		n.s.

Means ± standard deviations and medians (numbers in brackets) of the test scores in the AAT and in the CERAD-Plus battery of PSP, bvFTD and AD patients and AAT historical normal control values. Left column: numbers in brackets behind the Aachen Aphasia Test (AAT) subtests indicate the optimal test scores; cut-off scores. Numbers of persons finishing AAT subtests see text "Results" section-Practicability of the AAT. Remaining abbreviations see Legend Table 1

[&]Statistical trends, details see text, "Results" section, AAT subtests: Comparisons of PSP-RS, bvFTD and AD

Table 3 Numbers of persons and percentages scoring statistically significantly beyond the normal range of AAT and CERAD-Plus subtests

AAT subtests		PSP	bvFTD	AD	Historical normal control scores[§]
Spontaneous speech:	Scores*	*N* = 28	*N* = 24	*N* = 23	*N* = 100
Communication behavior	3,2,1 or 0	6	5	5	4.7 ± 0.55 (4.83)
		21%	*21%*	*22%*	
Articulation and prosody	3,2 or 1	13	3	0	4.61 ± 0.73 (4.81)
		46%	*12%*	*0%*	
Speech automatisms	3,2 or 1	2	3	2	4.59 ± 0.63 (4.72)
		7%	*12%*	*8%*	
Semantic structure	3,2,1 or 0	2	3	2	4.4 ± 0.62 (4.44)
		7%	*12%*	*8%*	
Phonemic structure	2 or 0	0	2	0	4.57 ± 0.67 (4.72)
		0%	*8%*	*0%*	
Syntactic structure	3 or 2	4	7	1	4.47 ± 0.58 (4.53)
		14%	*29%*	*4%*	
Token Test		*14%* (4/29)	*41%* (9/22)	*46%* (11/24)	1.25 ± 1.64 (0.48)
Language repetition		*25%* (7/28)	*61%* (14/23)	*64%* (15/23)	146.1 ± 3.7 (147.2)
Written language		*27%* (6/22)	*26%* (5/19)	*33%* (7/21)	87.0 ± 3.1 (87.7)
Naming		*39%* (11/28)	*52%* (11/21)	*50%* (12/24)	111.1 ± 5.4 (111.6)
Language comprehension:		*32%* (9/28)	*41%* (9/22)	*37%* (13/23)	107.4 ± 8.8 (109)
CERAD-Plus subtests					
Semantic fluency		*81%* (21of 26)	*61%* (13 of 21)	*44%* (8 of 18)	
Phonemic fluency		*31%* (9 of 26)	*40%* (8 of 20)	*31%* (5 of 16)	
Object naming		*52%* (14 of 27)	*60%* (12 of 20)	*33%* (6 of 18)	

Numbers of persons and percentages *(italics)* scoring statistically significantly beyond historical normal scores (means plus/minus 1.3 times the standard deviation). For the numbers of persons performing the AAT subtests Token test, language repetition, written language, naming and language comprehension see Table 2

*Scores range between 5 (normal) and 0 (most severe impairment). For each score below 5 impairments are described in detail in the AAT handbook, corresponding roughly to 4 = minimal, 3 = mild, 2 = moderate, 1 = marked impairment. A score of 3 indicates significant, a score of 4 minimal, but statistically insignificant impairment

[§]Mean ± standard deviation (median)

disorders (Huber et al. 1983) this proof-of-principle study investigated whether the AAT allowed a syndromic assessment. 4 out of 22 PSP-RS patients (18%) fulfilled the AAT criteria (Huber et al. 1983) of amnestic aphasia, 1 patient of probable amnestic aphasia (90% probability, together 5 patients; 23%), and 1 PSP-RS patient of Broca aphasia. 7 out of 19 bvFTD patients (36%) fulfilled the criteria of amnestic aphasia, 1 of Broca, 1 of Wernicke, and 1 of global aphasia. In 5 of 20 AD patients amnestic aphasia was diagnosed, in 1 AD patient possible amnestic aphasia (probability 67%, together 6; 30%), and in 3 AD patients (15%) Wernicke aphasia.

All 5 PSP-RS patients diagnosed with amnestic aphasia exhibited statistically significantly impaired *naming*, 4 of these patients also *language repetition and written language*. Moreover, 10 PSP-RS patients (including 1 patients with amnestic aphasia) had statistically significant *fluency* and *naming* problems and minimally to markedly impaired *articulation/prosody* (AAT scores 4 to 1 of 5), 8 of these patients minimal to moderately severe (scores 4 to 2) impairment of *syntax*, 9 of these patients *effortful speech*, 4, severely impaired *sentence comprehension*. In 4 PSP-RS patients impaired *prosody/articulation* (AAT scores 3 and 4) and significantly deficient *fluency,* in 2 of them significant *naming* and minimal *syntactic difficulties* (score 4) were noted. Phonological errors and apraxia of speech were not observed. In summary, in around half of the PSP-RS patients aphasia resembled mild to moderate non-fluent primary progressive aphasia (PPA-G) and PSP-nfaPPA (Rohrer et al. 2010; Gorno-Tempini et al. 2011; Mesulam et al. 2014; Respondek et al. 2014; Peterson et al. 2021). Impaired *articulation/prosody, naming, fluency, syntax, language comprehension* was also found in 4 bvFTD patients, in 1 of these patients combined with severe (score 2) *phonological difficulties*.

Results of PSP-RS patients in the AAT

In the *spontaneous speech* subtest, most *PSP-RS patients* exhibited delayed speech initiation, speech adynamia, shortening and paucity of sentences (63%), and dysarthria and dysprosodia (75%). Minimal impairments (score 4 of 5) in *communication behavior* subcategories were found in 7–43% of the PSP-RS patient (*Communication behavior* 12*, articulation and prosody* 9, *speech automatisms* 2, *semantic structure* 6*, phonemic structure* 2, *syntactic structure* 10 PSP-RS patients). Further results including PSP-RS patients scoring 3 or less in *communication behavior* subcategories (equivalent to statistically significant impairment) are summarized in Tables 2 and 3. Language repetition, but not spontaneous speech and naming tended to correlate with the UPDRS-III score (Spearman, $r_s = 0.529$, $p = 0.019$, not significant after correction for repeated measurements), Normal results in all AAT subtests achieved 8 patients (36%). The medians of age (74), disease duration (34 months), years of education (11.5) and the UPDRS-III sum scores (45) of these patients were similar and the medians of the MMSE and CERAD z-sum scores (− 0,95 and − 7.0) slightly higher than in the remaining PSP-RS patients. The PSP-PGF patient achieved normal results in the *Token test,* while *language comprehension* was moderately impaired (score 95 of 120).

Results of AD and bvFTD patients in the AAT

Minimal impairments (score 4) in spontaneous speech subcategories were found in 0–45% of the bvFTD and in 4–39% of AD patients. Further results including bvFTD and AD patients scoring 3 or less in *spontaneous speech* subcategories (statistical significant impairment) are summarized in Tables 2 and 3. Impairment if *articulation and prosody* was observed in more PSP-RS than bvFTD and AD patients, difficulties in *syntax* in more bvFTD than PSP-RS and AD patients (Table 3).

AAT subtests: comparison of PSP-RS, bvFTD and AD

Mild impairments in AAT subtests were found in 10–60% of PSP-RS and bvFTD and 20–65% of AD patients, moderate deficits in 0–18% of the subtests of PSP-RS, 0–27% of bvFTD and 8–20% of AD patients (Huber et al. 1983). In the *spontaneous speech* subcategory *articulation* and *prosody,* bvFTD and AD patients achieved better results than PSP-RS patients (Table 2; Mean ± SD (median): bvFTD 4.4 ± 1.1 (5); AD 4.8 ± 0.4 (5); PSP-RS 3.6 ± 1.1 (4). Kruskal–Wallis-ANOVA: $p = 0.00021$. Statistical significance after correction for multiple comparisons. Mann–Whitney-*U* test: PSP-RS versus bvFTD: $p = 0.0045$. PSP-RS versus AD: $p < 0.0001$). The scores for *language repetition* were statistically insignificantly lower in bvFTD and AD compared to PSP-RS (Kruskal–Wallis-ANOVA: $p = 0.0076$, critical p after correction for multiple measurements 0.004. Mann–Whitney-*U* test: $p = 0.006$ and 0.011). In the remaining *communication behavior* subcategories and AAT subtests, no statistically significant differences were found between the groups.

CERAD-plus subtests: comparison of PSP-RS, bvFTD and AD

26 PSP, 24 bvFTD and 17 AD patients completed all CERAD-Plus subtests (Table 2). In all groups, *semantic fluency* was mildly to moderately impaired. 21 PSP-RS, 13 bvFTD and 8 AD patients scored below the cut-off, however, the differences between the groups were not statistically significant ($p > 0.05$). *Phonemic fluency* was normal (*z*-scores within 1.3 times the negative standard deviation of

the mean of normal controls) without statistically significant difference between the groups ($p > 0.05$). *Object naming* was borderline and comparable in all groups ($p > 0.05$).

Correlations between language deficits and measures of multidimensional cognitive impairment

In each patient group, the scores of each AAT subtest were ranked, the ranks of all subtest scores of each patient summarized, and the summarized ranks of all patients correlated with the MMSE and the CERAD-Plus *z*-sum scores. In bvFTD and AD, the summarized ranks correlated significantly with MMSE and CERAD-Plus z-sum scores (bvFTD: $r_s = 0.619$ and 0.559; $p = 0.006$ and 0.024, respectively. AD: $r_s = 0.467$ and 0.689; $p = 0.037$ and 0.009, respectively), which was not the case in PSP-RS ($r_s = 0.153$ and 0.002; $p = 0.495$ and 0.928, respectively).

Discussion

To our knowledge, a comparative study on language impairments and aphasia syndromes in patients with PSP-RS, AD and bvFTD has so far not been published. Moreover, the AAT has not yet been tested for practicability in such a context. The AAT and the CERAD-Plus subtests for fluency and naming revealed language deficits in PSP-RS, bvFTD and AD patients, which were not detectable and quantifiable through a clinical examination alone. In up to 25% of the patients, the AAT was not feasible, which is in accordance with studies using the SAND battery (Catricalà et al. 2019; Picillo et al. 2019). Failures were due to motor and visual impairment, apathy, cognitive deficits and lack of motivation. However, comparable language and cognitive tests have been applied in the literature for aphasia testing in PSP and degenerative dementias (Western and SAND Aphasia Batteries, SYDBAT, Boston Diagnostic Aphasia Exam, tests for fluency, spontaneous speech, naming, language repetition and comprehension, reading, writing, semantic knowledge, etc.) (Rosser and Hodges 1994, Blair et al. 2007, Santos-Santos et al. 2016, Burrell et al. 2018, Barker et al. 2018, Catricalà et al. 2019, Picillo et al. 2019; Peterson et al. 2019, Jokel et al. 2019). Avoiding motor elements and confrontative testing might have reduced test failures. Questionnaires for caregivers, elements of gamification, tests specifically designed to detect grammatical deficits and automated quantitative narrative speech analysis would probably reveal further language deficits (Mesulam et al. 2014; Catricalà et al. 2019).

The CERAD-Plus subtests for *word fluency* and *naming* were of added diagnostic value to the AAT. The AAT algorithm for syndromatic aphasia classification does not comprise nfvPPA (PPA-G) or PSP-nfaPPA (Huber et al. 1983). However, a synopsis of the language tests without algorithmical evaluation and clinical language analysis revealed that in around one half of the PSP-RS patients and in 4 bvFTD patients language deficits resembled mild to moderate nfvPPA (Rohrer et al. 2010; Gorno-Tempini et al. 2011; Mesulam et al. 2014; Peterson et al. 2021).

The AAT and similar aphasia batteries have previously been applied for aphasia diagnosis in neurocognitive disorders (Lang et al. 1991; Blair et al. 2007; Catricalà et al. 2019; Picillo et al. 2019). The AAT is validated in German and several other languages. Our results are probably applicable to studies using the AAT in other languages than German. In fact, most results of the PSP-RS patients and the AD and the bvFTD groups in the AAT correspond to the literature (Lang et al. 1991; Podoll et al. 1991; Rosser and Hodges 1994; Litvan et al. 1996; Blair et al. 2007; Hardy et al. 2015; Santos-Santos et al. 2016; Barker et al. 2018; Burrell et al. 2018; Catricalà et al. 2019; Dodich et al. 2019; Jokel et al. 2019; Peterson et al. 2019; Picillo et al. 2019). Except for the limitations noted in the "Results" section (test failures in around one quarter of the patients, non-fluent agrammatic aphasia not detectable by the AAT syndromatic classification) our study underscores the clinical utility of the AAT in neurodegenerative disorders.

In *PSP-RS semantic fluency* was more impaired than *phonemic fluency*, which corresponds to a recent study (Barker et al. 2018) and contrasts to other publications (Rosser and Hodges 1994; Peterson et al. 2019), but performance in semantic and verbal fluency tests may vary between PSP patients (Santos-Santos et al. 2016). Despite visual scanning deficits and impaired auditory sentence comprehension most PSP-RS patients achieved normal results in the *Token test*. Mild impairment of *language repetition* and mild to moderate impairments of *written language* (additions, distortions and omission of letters or words, syntactic difficulties, observed in around one quarter of our PSP-RS patients) were found. These results correspond to the literature (Santos-Santos et al. 2016; Barker et al. 2018; Burrell et al. 2018; Catricalà et al. 2019; Jokel et al. 2019; Peterson et al. 2019; Picillo et al. 2019). Moreover, *sentence comprehension* and *naming* (probably due to impaired word retrieval, semantic processing, picture recognition or attentional difficulties) were impaired in around 50% of PSP-RS patients, which is also in accordance with the literature (Santos-Santos et al. 2016; Barker et al. 2018; Burrell et al. 2018; Catricalà et al. 2019; Jokel et al. 2019; Peterson et al. 2019; Picillo et al. 2019). Fatigue might have aggravated *language comprehension* deficits since *language comprehension* is the last subtest of the AAT.

Observed speech and language impairments fully or partly resembled language impairments in mild to moderate PSP-nfaPPA and aphasia in nfvPPA (PPA-G); however,

apraxia of speech and phonetic/phonemic paraphasia were not observed and *agrammatic impairments* were only mild to moderate (Rohrer et al. 2010; Gorno-Tempini et al. 2011; Mesulam et al. 2014; Peterson et al. 2019). *Syntax* was impaired in 14 PSP-RS patients, and significant dysgraphic errors were noted in the *handwriting* task. Impairments of *naming*, *sentence comprehension and language repetition* fit into the concept of nfvPPA (Rohrer et al. 2010; Gorno-Tempini et al. 2011; Mesulam et al. 2014; Peterson et al. 2019). Slowing of cognitive processing might partially explain impaired *speech initiation and fluency* (Dubois et al. 1988; Barker et al. 2018).

Impairment of *articulation (dysarthria) and prosody* is probably related to neurodegeneration in basal ganglia circuits, pons and cerebellum (Williams and Lees 2009; Peterson et al. 2019; Kovacs et al. 2020), *fluency* deficits to atrophy in the frontal lobe, the premotor cortex and subcortical white matter (Rohrer et al. 2010; Mesulam et al. 2014; Kovacs et al. 2020; Peterson et al. 2021). Speech initiation might be particularly impaired in dysarthric patients. In our study, language repetition tended to be negatively correlated with the UPDRS-III sum score. Neurodegeneration in the temporal and the parietal lobe might explain deficits in memory-related language functions, such as *language repetition, comprehension* and *naming*. However, neurodegeneration is on average mild in the temporo-parietal region in PSP-RS (Kovacs et al. 2020). On the other hand, language repetition could also depend on fronto-striatal language networks, which are probably affected in PSP (Kovacs et al. 2020).

Impairments of *fluency, naming, sentence comprehension, language repetition, writing, and semantic impairments* observed in our bvFTD and AD patients are in agreement with the literature (Cummings et al. 1985; Lang et al. 1991; Blair et al. 2007; McKhann et al. 2011; Rascovsky et al. 2011; Hardy et al. 2015).

The AAT revealed a trend to statistically significant differences between PSP-RS, bvFTD and AD in the *language repetition* subtest, which tests attention, phonological short-term memory and the integration of articulatory processes (Table 2), and significant impairments of *articulation and prosody* in the PSP group. In contrast to bvFTD and AD, severity of language impairment did not correlate with cognitive decline (MMSE and CERAD-Plus *z*-sum scores) in PSP-RS. These differences between groups suggest that language networks are differently affected in PSP-RS compared to AD and bvFTD. A synopsis of the CERAD-Plus subtests for *fluency and naming* and of the AAT subtests suggests that in around 50% of our PSP-RS patients language deficits resembled mild to moderate PSP-nfaPPA and nfvPPA (PPA-G) (Rohrer et al. 2010; Gorno-Tempini et al. 2011; Mesulam et al. 2014; Peterson et al. 2021). However, apraxia of speech and significant phonological errors of speech were not noted. NfvPPA results from cortical and subcortical neurodegeneration in the frontal gyrus, which is also the case in PSP-RS (Williams and Lees 2009; Dodich et al. 2019; Whitwell et al. 2019; Kovacs et al. 2020). It is likely that in early to moderately advanced PSP-RS mainly local frontal lobe language networks are affected; whereas in early to moderately advanced prototypical AD, more widespread neurodegeneration occurs in the temporal and parietal lobes, and in bvFTD in the frontal and temporal lobes, which in both diseases might combinedly affect language and cognitive networks (Paternico et al. 2016; Perry et al. 2017; Mascali et al. 2018). However, this hypothesis needs to be verified in future comparative PET and structural and functional MR studies.

The AAT algorithm diagnosed amnestic aphasia in 5 PSP-RS patients, Broca aphasia in 1 PSP-RS patient. The AAT algorithm does not provide the diagnosis *non-fluent agrammatic aphasia* (Huber et al. 1983). In nfvPPA (PPA-G), impairment of *fluency* may precede deterioration of *syntax* and *grammar*, which could also be the case in PSP-RS, and contrasts to post-stroke Broca aphasia, which is characterized by concomitant *fluency* and *grammar* deficits (Huber et al. 1993, Rohrer et al. 2010; Mesulam et al. 2014). In post-stroke Broca aphasia infarcts usually involve major proportions of the left inferior frontal lobe (Mesulam et al. 2014). These areas are only mildly affected in PSP-RS (Kovacs et al. 2020). Certain language deficits in our PSP-RS patients, such as disturbed *naming* and *language repetition*, may result from impaired verbal memory, which may lead to the diagnosis *amnestic aphasia*. However, deficits of *naming* and *language repetition* also occur in nfvPPA (PPA-G) (Rohrer et al. 2010; Mesulam et al. 2014), and the temporoparietal region, which is usually involved in amnestic aphasia, is only mildly affected by neurodegeneration in PSP-RS (Kovacs et al. 2020). In contrast to bvFTD and AD, Wernicke aphasia was not diagnosed in our PSP-RS group. Language comprehension, in particular sentence comprehension, was mildly impaired. Semantic knowledge problems and empty fluent language was not observed in PSP-RS patients (Cummings et al. 1985; Nicholas et al. 1985; Lang et al. 1991; Blair et al. 2007; Hardy et al. 2015; Jokel et al. 2019). This observation corresponds to the study by Kovacs et al. (2020) which demonstrated that the left anterior temporal lobe and the temporal Wernicke's area are only mildly affected in PSP-RS.

The included PSP-RS patients are most likely representative for this disorder. They were consecutively recruited, diagnosed according to validated clinical, neuropsychological and neuroradiological criteria, and age, disease duration and clinical characteristics correspond to other studies (Rosser and Hodges 1994; Litvan et al. 1996; Santos-Santos et al. 2016; Burrell et al. 2018; Catricalà et al. 2019; Dodich et al. 2019; Picillo et al. 2019). The sample sizes are small, yet similar to other studies (Rosser and Hodges 1994; Nicholas et al. 1985; Lang et al.

1991; Blair et al. 2007; Santos-Santos et al. 2016; Burrell et al. 2018; Catricalà et al. 2019; Dodich et al. 2019; Picillo et al. 2019; Jabbar et al 2020). The study might be underpowered to substantiate language deficits in the three groups in further detail. Neuropathological verification of the diagnoses is missing. Therefore, the diagnoses are probable and not definite. Our results are cross-sectional. However, more than 50% of our PSP and bvFTD patients dropped out from the FTLA registry during the first year after the first language testing (second year in the FTLA registry) (Guger et al. 2021; Kellermair et al. 2021). For statistical reasons re-testing was not meaningful. Similar disease duration in the three diagnostic groups does not necessarily mean similar stages of disease progression. Therefore, longitudinal studies are needed to comparatively assess the progression of aphasia in these diseases.

Conclusion

The AAT in combination with CERAD-Plus subtests for fluency and object naming revealed language deficits in PSP-RS, bvFTD and AD, which probably would not have been clarified without these language tests. Significant differences in aphasia syndromes were found between the groups. In PSP-RS the AAT syndromatic aphasia classification did not coincide with clinical findings; the prevailing aphasia syndrome (in one half of the PSP-RS) resembled mild to moderate nfvPPA (PPA-G) overlapping with PSP-nfaPPA. Longitudinal studies are needed to verify if in PSP-RS aphasia develops apart or before multi-domain cognitive decline, which together with relatively preserved language comprehension and repetition could facilitate speech therapy. Language and speech difficulties impair communication and interfere with activities of daily living. Early assessment of language functions is important to overcome communication difficulties. The hypothesized differential involvement of language networks in mild to moderately advanced PSP-RS, AD and bvFTD should be verified in future comparative morphological and functional studies.

Author contributions Conceptualization: LR, GR; methodology: LR, GR; formal analysis and investigation: LR, AF, SR-T, RK, MK, PS, FF, MG, CE; writing—original draft preparation: LR; writing—review and editing: MK, PS, FF, MG, CE, RD, SM, GR; funding acquisition: GR; resources: GR; supervision: RD, GR.

Funding The study was supported by the Jubilee Funds of the Austrian National Bank, Project number 13240.

Availability of data and materials The datasets generated and/or analyzed during the current study are available from the first and corresponding author on reasonable request.

Declarations

Conflict of interest Lucia Ransmayr, Alexandra Fuchs, Sibylle Ransmayr-Tepser, Romana Kommenda, Franz Fellner, Christian Eggers, Robert Darkow and Stephanie Mangesius have nothing to declare. Mariella W. Kögl received honoraria as a speaker and consulting honoraria from AbbVie GmbH. Petra Schwingenschuh received consulting honoraria from AbbVie GmbH and Bial. Michael Guger received support and honoraria for research, consultation, lectures and education from Almirall, Bayer, Biogen, Celgene, Genzyme, MedDay, Merck, Novartis, Octapharma, Roche, Sanofi Aventis, Shire and TEVA ratiopharm. Gerhard Ransmayr received research support from the Jubilee Funds of the Austrian National Bank and the Austrian Research Promotion Funds, honoraria as speaker and for consultations from AbbVie GmbH, Alpine Market Research, Biogen, Grünenthal, MedAhead, Novartis Pharma GmbH, Ratiopharm, Roche Austria GmbH, Sanofi Aventis GmbH, Stada Arzneimittel-Gesellschaft, UCB Pharma GmbH. There are no competing financial or non-financial interests of the authors.

Ethics approval The study was conducted according to the Declaration of Helsinki and approved by the local ethics review board (Ethikkommission des Landes Oberösterreich; FTLA Study, Protocol Number 254).

Consent to participate Written informed consent was obtained from the patients and their caring family members.

Ethical approval The study was approved by the Ethikkommission des Landes Oberösterreich (application number 254) and conducted according to the 1975 Helsinki declaration. Participants gave their informed written consent.

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