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ORIGINAL COMMUNICATION

The applause sign in frontotemporal lobar degeneration and related conditions

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Abstract

The applause sign, i.e., the inability to execute the same amount of claps as performed by the examiner, was originally reported as a sign specific for progressive supranuclear palsy (PSP). Recent research, however, has provided evidence for the occurrence of the applause sign in various conditions. The aim of this study was to determine the prevalence of the applause sign and correlate its presence with neuropsychological and MRI volumetry findings in frontotemporal lobar degeneration and related conditions. The applause sign was elicited with the three clap test (TCT), with a higher score indicating poorer performance. Data were recorded from 272 patients from the cohort of the German consortium for frontotemporal lobar degeneration (FTLDc): 111 with behavioral variant frontotemporal dementia (bvFTD), 98 with primary progressive aphasia (PPA), 30 with progressive supranuclear palsy Richardson's syndrome, 17 with corticobasal syndrome (CBS) and 16 with amyotrophic lateral sclerosis with frontotemporal dementia (ALS/FTD). For comparison, 29 healthy elderly control subjects (HC) were enrolled in the study. All subjects underwent detailed language and neuropsychological assessment. In a subset of 156 subjects, atlas-based volumetry was performed. The applause sign occurred in all patient groups (40% in PSP, 29.5% in CBS, 25% in ALS/FTD, 13.3% in PPA and 9.0% in bvFTD) but not in healthy controls. The prevalence was highest in PSP patients. It was significantly more common in PSP as compared to bvFTD, PPA and HC. The comparison between the other groups failed to show a significant difference regarding the occurrence of the applause sign. The applause sign was highly correlated to a number of neuropsychological findings, especially to measures of executive, visuospatial, and language function as well as measures of disease severity. TCT scores showed an inverse correlation with the volume of the ventral diencephalon and the pallidum. Furthermore the volume of the ventral diencephalon and pallidum were significantly smaller in patients displaying the applause sign. Our study confirms the occurrence of the applause sign in bvFTD, PSP and CBS and adds PPA and ALS/FTD to these conditions. Although still suggestive of PSP, clinically it must be interpreted with caution. From the correlation with various cognitive measures we suggest the applause sign to be indicative of disease severity. Furthermore we suggest that the applause sign represents dysfunction of the pallidum and the subthalamic nucleus, structures which are known to play important roles in response inhibition.

Keywords Applause sign · Frontotemporal lobar degeneration · Progressive supranuclear palsy · Atlas-based MRI volumetry · Subthalamic nucleus · Pallidum

Abbreviations

ALS/FTD	Amyotrophic lateral sclerosis with frontotemporal dementia
bvFTD	Behavioral variant frontotemporal dementia
CDR-SOB	Clinical Dementia Rating Scale Sum of Boxes
CBS	Corticobasal syndrome
FTLD	Frontotemporal lobar degeneration
HC	Healthy control
LI	Laterality index
PPA	Primary progressive aphasia
PSP	Progressive supranuclear palsy

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SPM12	Statistical parametric mapping 12
STN	Subthalamic nucleus
TCT	Three clap test

Introduction

The applause sign, the inability to execute the same amount of claps as performed by the examiner, was first described by Dubois and colleagues [13] who suggested it as a specific sign of progressive supranuclear palsy (PSP). To test for its occurrence one usually performs the three clap test (TCT). Recent studies have described the applause sign in various conditions such as frontotemporal dementia, amyotrophic lateral sclerosis and Alzheimer's disease [3, 23, 30]. There have also been case reports of the applause sign in lymphoma or infarction of the basal ganglia [18, 43]. The pathophysiological basis of the applause sign, however, remains unclear. A possible role of apraxia has been suggested [45] as well as of frontal lobe dysfunction [29]. The current study aimed to determine the frequency of the applause sign in frontotemporal lobar degeneration and related neurodegenerative conditions and to correlate it with neuropsychological and MRI volumetry findings.

Materials and methods

Ethics statement

Ethical approval for conduction of the study has been obtained at the coordinating site at the University of Ulm and all participating centers of the German consortium for frontotemporal lobar degeneration. Written informed consent was obtained from every participant. The study was performed according to the Declaration of Helsinki.

Subjects

272 patients from the cohort of the German consortium for frontotemporal lobar degeneration (FTLDc), funded by the German Federal Ministry of Research [33], were included in the study. 111 had been diagnosed with behavioral variant frontotemporal dementia (bvFTD), 98 with primary progressive aphasia (PPA; 35 nonfluent agrammatic PPA, 27 semantic variant PPA, 18 logopenic variant PPA, 18 not further classified), 30 with PSP Richardson's syndrome, 17 with corticobasal syndrome (CBS) and 16 with amyotrophic lateral sclerosis with frontotemporal dementia (ALS/FTD), according to the respective diagnostic criteria [4, 19, 27, 34, 40]. A *c9orf72* mutation was present in 9 bvFTD and 3 ALS/FTD patients. For comparison we investigated 29 cognitively healthy elderly control subjects (HC). HC were defined by having no diagnosed neuropsychiatric illness, the absence of deterioration of behavior or cognition by observation or history provided by a knowledgeable informant, a normal neurological examination, the absence of language difficulties and a normal neuropsychological assessment (e.g., MMSE > 26).

Clinical test battery

Patients and HC underwent detailed language and neuropsychological assessment. Severity of dementia was assessed with the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) score. To check for additional motor symptoms part III of the UPDRS was performed. UPDRS scores were not available for the ALS/FTD and the HC study group.

The presence of the applause sign was assessed with the three clap test (TCT), which was administered by the attending physician, who was not blinded to the diagnosis, at the respective study centre. Subjects were asked to clap three times as quickly as possible after the examiner had demonstrated three rapid hand claps. Clapping performance was scored as follows: score 0 = subject claps exactly three times, score 1 = subject claps 4 or 5 times, score 2 = subject claps more than 5 times but stops on his/her own, score 3 = subject does not stop applauding. The test was considered abnormal when the score was ≥ 1 [14]. To ensure that the subject correctly understood the instructions one exercise trial was performed first and only the second trial was analyzed. Medians and prevalences of the resulting scores were calculated. For better comparability to previous studies we also calculated means and standard deviations. In addition, we determined sensitivity, specificity and positive predictive value.

MRI acquisition

Simultaneously (0.2 ± 1.4 months) with the clinical examination, a subset of 156 subjects (51 bvFTD, 61 PPA, 11 PSP, 7 CBS, 4 ALS and 22 HC) underwent whole-brain T1-weighted MRI on a 3T scanner. An array head coil with a minimum of 8 channels was used. 3D T1-weighted-sequences were acquired in sagittal orientation with a spatial resolution of $1 \times 1 \times 1$ mm.

MRI data processing and volumetric analysis

After pseudonymization and conversion from DICOM to ANALYZE 7.5 format the 3D T1-weighted images were processed by a fully automated and observer-independent method of atlas- and mask-based MRI volumetry using the Statistical Parametric Mapping 12 (SPM12) software (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm). The method has been described in detail elsewhere [21, 22, 32] and is established

in neurodegenerative diseases [16, 17, 20, 22, 24, 36]. In short, each T1 image is normalized to Montreal Neurological Institute template space using diffeomorphic anatomical registration through exponentiated Lie algebra [8] and segmented into gray matter, white matter, and cerebrospinal fluid components using the 'unified segmentation' algorithm of SPM12 with default parameters. The volumes of specific brain structures and compartments are calculated by voxel-by-voxel multiplication and subsequent integration of normalized and modulated component images with predefined masks in the same space. Modulation of the normalized component images compensates for the effect of spatial normalisation (i.e., extension or shrinkage of the investigated structure) so that after multiplication of a specific mask with the 'modulated' gray or white matter image the computed volume represents the volume of the original structure in native space. The masks are derived from different probabilistic brain atlases, such as the LONI Probabilistic Brain Atlas (LPBA40) provided by the Laboratory of Neuroimaging (LONI) at the University of California, Los Angeles, USA (http://www.loni.ucla.Atlases) [38], and the Neuromorphometrics (NMO) atlas included in SPM12. The maximum probability tissue labels of the NMO atlas are derived from the "MICCAI 2012 Grand Challenge and Workshop on Multi-Atlas Labeling" (https://masi.vuse.vanderbilt.edu/workshop2012/index.php/Challenge_Details), the MRI data originate from the OASIS project (http://www.oasis-brains.org) and the labeled data are provided by Neuromorphometrics, Inc. (http://Neuromorphometrics.com) under academic subscription (cf. SPM12's release notes).

Target structures were chosen a priori. As a fronto-subcortical disconnection has been suggested to be causative for the applause sign [1, 25], regions of interest to be analyzed were the frontal, temporal, parietal and occipital lobe of the LPBA40 atlas as well as caudate nucleus, putamen, pallidum and ventral diencephalon of the NMO atlas.

For each region of interest the individual volume was determined in milliliters. For comparison, the volumes measured were corrected by individual intracranial volume (ICV) and standardized to the mean ICV of healthy controls.

To assess left–right-differences of each target structure volume a laterality index (LI) defined as the ratio [(left–right)/(left + right)] was calculated [37]. The LI ranges from − 1 to + 1, a positive value indicating leftward asymmetry.

Statistical analysis

Data were analyzed using SPSS 23. Non-dichotomized mean scores of demographic data and TCT scores were analyzed by Kruskal–Wallis test and post-hoc Bonferroni corrected Mann–Whitney tests. Chi square analysis was used to check for differences in gender distribution across all groups. Standard statistical significance was set at $p < 0.05$.

Spearman's test was used to explore correlations between TCT scores and neuropsychological variables and volumetric data, respectively. For group comparisons of neuropsychological data a Kruskal–Wallis test was performed. Significance levels for both tests were adjusted according to Bonferroni correction. Results of post-hoc tests were regarded significant if they survived an additional Bonferroni correction for multiple pairwise comparisons. As in some patient groups only few neuroimaging data were available, no group comparison of volumetric data was performed. Kruskal–Wallis and post-hoc Bonferroni-corrected Mann–Whitney tests were performed to check for significant differences of volumetric data of patients with an applause sign compared to patients showing no applause sign and HC.

Results

Demographics

Patients with bvFTD were significantly younger than PSP patients. Kruskal–Wallis test detected significant group differences of education level; however, post-hoc Mann–Whitney tests did not show significant pairwise differences. Gender distribution and disease duration were similar in all groups. For demographic data see Table 1.

Table 1 Demographics of the study sample

	bvFTD $n = 111$	PPA $n = 98$	PSP $n = 30$	ALS/FTD $n = 16$	CBS $n = 17$	HC $n = 29$	χ^2
Age (years)	62.7 (9.7)[c]	66.4 (7.6)	70.5 (6.6)[a]	68.1 (8.2)	67.4 (8.7)	65.5 (8.9)	20.3 (s.)
Education (years)	13.4 (2.9)	13.7 (3.7)	12.2 (3.0)	12.9 (2.6)	11.9 (3.3)	13.3 (3.3)	11.1 (s.)
Sex (male/female)	69/42	48/50	17/13	7/9	10/7	15/14	4.8 (n.s.)
Disease Duration (years)	4.0 (3.4)	3.2 (1.9)	4.0 (3.1)	4.4 (6.6)	3.9 (2.6)		2.8 (n.s.)

Significantly different compared to [a]bvFTD, [b]PPA, [c]PSP, [d]ALS/FTD, [e]CBS, [f]HC

bvFTD behavioral variant frontotemporal dementia, *PPA* primary progressive aphasia, *PSP* progressive supranuclear palsy, *ALS/FTD* amyotrophic lateral sclerosis with frontotemporal dementia, *CBS* corticobasal syndrome, *HC* healthy controls, *s.* significant, *n.s.* not significant

Neuropsychological data

The patterns of language and neuropsychological impairment kept with the expected clinical specificities in that PPA patients performed worst in tests for language assessment, while patients with the extrapyramidal syndromes CBS and PSP performed worse than other patient groups in CERAD Trail Making Test A and had higher UPDRS part III scores. bvFTD patients showed significantly higher CDR-SOB scores than PPA patients (Table 2).

Group comparisons of the applause sign

The applause sign was observed in all patient groups (40.0% in PSP, 29.5% in CBS, 25.0% in ALS/FTD, 13.3% in PPA (14.3% in nonfluent agrammatic PPA, 14.8% in semantic variant PPA, 5.6% in logopenic variant PPA, 16.7% in not further classified aphasia) and 9.0% in bvFTD) (Table 3; Fig. 1). PPA subtypes did not differ significantly from one another concerning the frequency of the applause sign and the TCT score and were therefore pooled in the analysis. The applause sign was significantly more frequent in the PSP ($\chi^2 = 27.662$, $p < 0.0001$) group

Table 2 Neuropsychological data

	bvFTD $n=111$	PPA $n=98$	PSP $n=30$	ALS/FTD $n=16$	CBS $n=17$	HC $n=29$	χ^2
CERAD Plus							
Semantic Fluency	12.3 (6.5)[b]	9.2 (5.7)[a,e]	10.4 (4.9)	8.7 (4.0)	14.5 (6.1)[b]	25.8 (5.2)	20.6 (s.)
Boston Naming Test (15 items)	12.7 (2.8)[b,d]	8.7 (4.4)[a,b,e]	12.3 (2.5)[b]	10.2 (2.7)[a,e]	13.6 (1.5)[b,d]	14.2 (2.8)	58.6 (s.)
MMSE	24.1 (4.9)	22.4 (6.6)	24.4 (4.0)	23.7 (4.4)	23.3 (5.4)	29.1 (0.9)	3.5 (n.s.)
Word List Memory	14.2 (5.2)	13.6 (6.3)	15.0 (4.4)	13.4 (4.3)	14.0 (6.1)	22.2 (5.2)	1.5 (n.s.)
Constructional Praxis	9.5 (2.0)	9.6 (2.0)	8.2 (2.6)	8.9 (2.1)	7.5 (3.1)	10.5 (2.1)	17.0 (n.s.)
Wort List Recall	4.7 (2.3)	4.3 (2.7)	4.1 (2.4)	4.7 (2.3)	3.9 (3.2)	7.8 (2.6)	5.7 (n.s.)
Word List Recognition	8.6 (2.2)	8.8 (1.7)	9.2 (1.1)	8.9 (2.0)	8.2 (1.9)	9.5 (1.9)	5.6 (n.s.)
Recall of Constructional Praxis	5.7 (3.8)	6.6 (3.5)	5.0 (3.6)	5.3 (3.5)	4.9 (3.4)	9.2 (2.6)	6.7 (n.s.)
TMT A	74.3 (40.2)[c]	71.7 (35.5)[c]	110.7 (45.0)[a,b]	77.0 (38.6)	100.7 (52.3)	34.0 (12.0)	19.8 (s.)
TMT B	175.4 (83.7)	188.3 (81.5)	229.4 (74.2)	217.6 (59.2)	195.4 (96.5)	71.6 (31.8)	6.9 (n.s.)
TMT A/B	2.8 (1.1)	3.0 (1.0)	2.4 (0.6)	3.7 (1.0)	2.7 (1.2)	2.0 (0.6)	13.8 (n.s.)
Phonemic Fluency	7.5 (4.9)	5.8 (3.9)	5.4 (4.0)	4.2 (2.5)	7.3 (4.6)	17.6 (4.5)	13.1 (n.s.)
Digit Span							
Forward	6.2 (1.8)[b]	4.7 (2.4)[a]	5.9 (2.1)	5.2 (2.2)	5.2 (2.1)	8.1 (2.5)	25.5 (s.)
Backward	4.1 (1.7)	3.7 (2.2)	3.7 (1.8)	3.5 (1.1)	3.7 (1.3)	6.3 (1.9)	5.5 (n.s.)
Corsi Block Tapping Test							
Forward	5.8 (2.3)	6.4 (2.3)	5.9 (1.8)	6.5 (2.1)	5.4 (2.5)	7.7 (2.1)	5.1 (n.s.)
Backward	5.1 (2.3)	5.4 (2.4)	4.6 (1.9)	4.9 (1.9)	4.1 (2.2)	6.9 (2.3)	6.0 (n.s.)
Repeat and Point							
Repeat	9.6 (1.2)[b]	8.3 (2.2)[a]	9.1 (2.0)	8.4 (3.0)	9.0 (2.3)	8.9 (3.1)	38.1 (s.)
Point	8.4 (2.1)	7.7 (2.5)	8.1 (1.6)	8.1 (1.6)	8.1 (2.3)	8.9 (3.1)	6.4 (n.s.)
Stroop Test Errors	1.9 (3.7)	1.7 (3.5)	2.6 (3.1)	0.9 (1.7)	2.8 (3.1)	0.5 (1.2)	8.9 (n.s.)
Hamasch 5 Point Test	69.7 (26.4)	77.1 (22.0)	70.2 (25.4)	55.1 (20.1)	75.5 (21.9)	90.0 (18.3)	12.5 (n.s.)
Cognitive Estimation Task	9.1 (3.2)	9.0 (3.4)	7.7 (3.3)	7.5 (2.8)	8.4 (3.7)	11.7 (3.3)	7.0 (n.s.)
Theory of Mind	10.8 (3.8)	11.0 (3.1)	11.0 (2.6)	8.9 (1.9)	12.7 (3.5)	16.1 (4.1)	7.6 (n.s.)
Cookie Theft	9.6 (3.4)	8.7 (4.0)	8.0 (3.6)	8.2 (3.5)	9.2 (3.9)	6.6 (7.2)	4.5 (n.s.)
Token Test	3.8 (6.9)[b]	7.9 (9.5)[a,c]	2.9 (6.5)[c]	7.9 (10.6)	6.7 (10.3)	0.0 (0.0)	17.2 (s.)
Written Language	83.1 (13.7)[b]	78.7 (14.9)[a]	71.6 (21.8)	77.0 (12.7)	76.8 (16.2)	80.6 (27.8)	19.8 (s.)
CDR-SOB	5.7 (3.8)[b]	3.0 (2.8)[a]	5.8 (4.4)	4.0 (2.6)	4.8 (3.8)	0.1 (0.2)	28.9 (s.)
UPDRS Part III	9.7 (14.7)[c,e]	4.4 (8.7)[c,e]	34.9 (11.9)[a,b]		27.5 (13.3)[a,b]		47.9 (s.)

Significantly different compared to [a]bvFTD, [b]PPA, [c]PSP, [d]ALS/FTD, [e]CBS

For comparison neuropsychological data of HC are listed

bvFTD behavioral variant frontotemporal dementia, *PPA* primary progressive aphasia, *PSP* progressive supranuclear palsy, *ALS/FTD* amyotrophic lateral sclerosis with frontotemporal dementia, *CBS* corticobasal syndrome, *HC* healthy controls, *s.* significant, *n.s.* not significant

Table 3 Prevalence of the applause sign, TCT scores, sensitivity, specificity and positive predictive value of the applause sign compared to the other patient groups

	bvFTD $n=111$	PPA $n=98$	PSP $n=30$	ALS/FTD $n=16$	CBS $n=17$	HC $n=29$
N (%) of applause sign	10 (9.0%)	13 (13.3%)	12 (40.0%)	4 (25.0%)	5 (29.4%)	0 (0.0%)
N (%) of score 0	101 (91.0%)	85 (86.7%)	18 (60.0%)	12 (75.0%)	12 (70.6%)	29 (100%)
N (%) of score 1	5 (4.5%)	8 (8.2%)	9 (30.0%)	2 (12.5%)	3 (17.6%)	0 (0.0%)
N (%) of score 2	2 (1.8%)	1 (1.0%)	1 (3.3%)	2 (12.5%)	2 (11.8%)	0 (0.0%)
N (%) of score 3	3 (2.7%)	4 (4.1%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Median	0	0	0	0	0	0
Mean	0.2 ± 0.6	0.2 ± 0.7	0.6 ± 0.9	0.4 ± 0.7	0.4 ± 0.7	0.0 ± 0.0
Sensitivity (%)	9.0	13.3	40.0	25.0	29.4	
Specificity (%)	78.9	82.2	86.8	84.4	84.7	
Positive predictive value (%)	22.7	29.5	27.3	9.1	11.4	

bvFTD behavioral variant frontotemporal dementia, *PPA* primary progressive aphasia, *PSP* progressive supranuclear palsy, *ALS/FTD* amyotrophic lateral sclerosis with frontotemporal dementia, *CBS* corticobasal syndrome, *HC* healthy controls

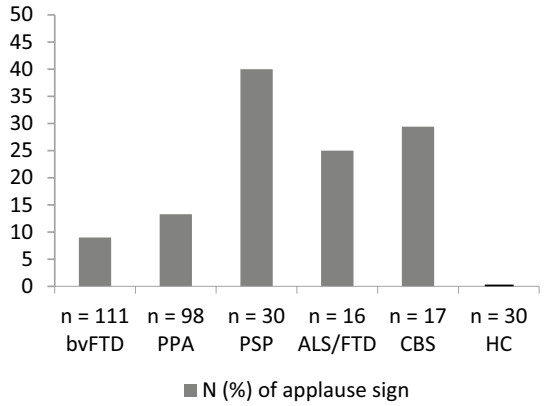

Fig. 1 Percentage of subjects with an applause sign in each study group

compared to the bvFTD ($p<0.0001$), PPA ($p=0.0013$) and HC ($p=0.0002$) groups. No healthy control subject displayed the applause sign. Kruskal–Wallis test showed significant differences of TCT scores between the six groups compared ($\chi^2=26.349$, $p<0.0001$). At Mann–Whitney tests, PSP patients differed significantly from bvFTD, PPA, and HC (each $p<0.0001$). There was no statistically significant difference of TCT scores between PSP and CBS as well as between PSP and ALS/FTD patients. No difference was found between the other patient groups. Apart from PSP, TCT scores failed to discriminate bvFTD, PPA, CBS and FTD/ALS patients from healthy controls.

Calculated sensitivity and specificity of the applause sign in distinguishing the neurodegenerative diseases under analysis from HC were 16.2% and 100% respectively. Comparing the different diagnostic categories, sensitivity and specificity were highest in PSP (Table 3) and lowest in bvFTD. Positive predictive values were quite low in all patient groups. The highest values were found in the PPA patient group (29.5%).

Correlation analysis

Correlation analysis performed within the whole study sample showed a negative correlation of TCT scores with the scores of the Cognitive Estimation Task ($r_s=-0.223$, $p=0.0002$), subtests of the CERAD plus battery (Figure Copying ($r_s=-0.210$, $p=0.0003$) and MMSE ($r_s=-0.236$, $p=<0.0001$)), the Written Language Subtest ($r_s=-0.263$, $p<0.0001$) from the Aachen Aphasia Test and the Cookie Theft Picture Description Task ($r_s=-0.205$, $p=0.0014$). A higher score of these neuropsychological items indicates better cognitive performance.

TCT scores were positively correlated with the results of Trail Making Test A ($r_s=0.227$, $p=0.0002$), CDR-SOB ($r_s=0.262$, $p<0.0001$) as well as with the UPDRS ($r_s=0.477$, $p<0.0001$) score. A higher score of these items reflects poorer performance. There was no correlation of TCT scores with demographic data, disease duration or other measures of cognitive function.

In bvFTD patients, TCT scores were negatively correlated with results of MMSE ($r_s=-0.356$, $p=0.0002$), Figure Copying ($r_s=-0.320$, $p<0.0008$) and the Cognitive Estimation Task ($r_s=-0.343$, $p=0.0004$) and positively correlated with CDR-SOB ($r_s=0.337$, $p=0.0013$). No correlations of the applause sign with neuropsychological or demographic data were found in the other groups.

Volumetric analysis

Kruskal–Wallis test revealed significant group differences of the volumes of the frontal, temporal and parietal lobe as well as the caudate nucleus, putamen, pallidum and ventral

diencephalon. No significant differences could be detected for the occipital lobe as well as all examined LIs.

Post-hoc Mann–Whitney tests showed that patients with an applause sign had reduced volumes of all target structures compared to HC and had reduced volumes of the pallidum and ventral diencephalon compared to patients showing no applause sign. For the pallidum this was also the case when excluding PSP patients ($p = 0.002$) whereas the ventral diencephalon still showed a trend towards significance ($p = 0.013$). Patients showing no applause sign had smaller volumes of the frontal, temporal and parietal lobe as well as the caudate nucleus compared to HC.

Pooling volumetric data of HC and patients showing no applause sign in the analysis revealed that subjects with an applause sign had significantly smaller volumes of the pallidum and ventral diencephalon compared to subjects that do not show the applause sign (Fig. 2).

In addition the volume of the pallidum ($r_s = -0.3337$, $p < 0.0001$) and the ventral diencephalon ($r_s = -0.315$, $p < 0.0001$) were negatively correlated with TCT scores. No significant correlations of the other target structure volumes investigated and their respective laterality indices could be detected.

Discussion

The aim of this study was to determine the prevalence of the applause sign in frontotemporal lobar degeneration and related neurodegenerative conditions and correlate its presence with neuropsychological and with atlas-based MRI volumetry findings.

The frequency of the applause sign was highest in PSP (40.0%). It was, however, much lower compared to previous studies, where prevalences had been reported ranging from 70 to 90% [14, 25, 30]. The prevalence of the applause sign was also lower in our CBS (29.4%) and bvFTD (9.0%) samples than reported previously [12, 23, 30]. A possible explanation is that in earlier studies the TCT was performed only once, whereas we performed an initial learning trial to ensure that the subject has understood the instruction and analyzed only the second trial. This stricter approach might have led to a lower prevalence of the applause sign in our cohorts. Another possible explanation may be the lack of further subdivision of bvFTD. A previous study [28] had shown that the applause sign is a frequent finding in the disinhibited and stereotypical variants of bvFTD whereas it is a rare finding in apathetic bvFTD. Our data extend previous observations that the applause sign is not specific for PSP. Nevertheless, TCT scores were still able to discriminate PSP from bvFTD, PPA and HC. Yet except for PSP, TCT scores failed to discriminate the neurodegenerative disorders examined from one another as well as from HC.

The sensitivity and specificity of the applause sign to distinguish patients with the neurodegenerative diseases under study from healthy controls were 16.2% and 100.0%, respectively. Sensitivity and specificity of the applause sign in distinguishing one specific disease from others were highest for PSP. Positive predictive values were quite low in all patient groups indicating that the applause sign does not

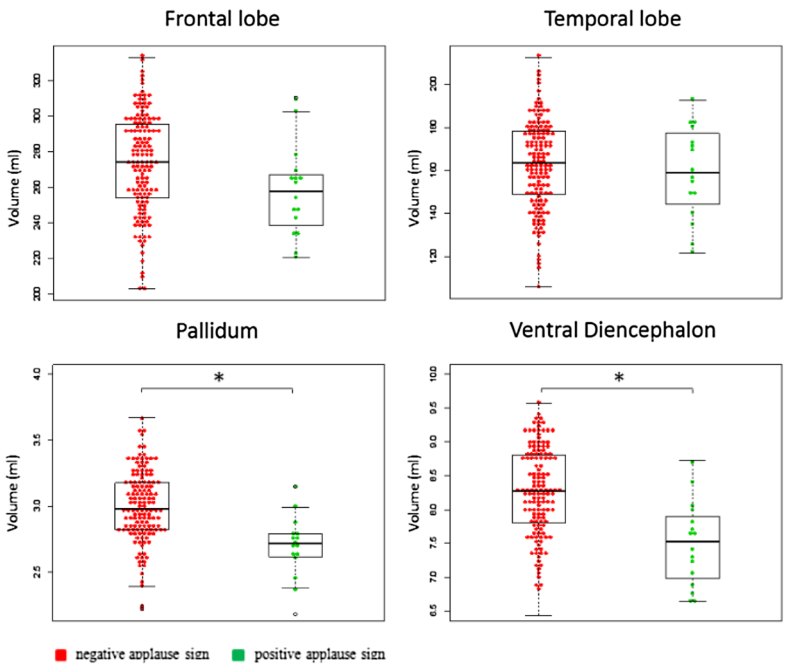

Fig. 2 Target structure volumes of subjects showing no applause sign compared to subjects with an applause sign. * indicates significant differences

Table 4 Number of participants in our study compared to previous studies

	bvFTD	PPA	PSP	ALS/FTD	CBS	Other	HC	Overall
Schönecker et al.	111	98	30	16	17	–	29	301
Abdo et al. [1]	–	–	5	–	2	85	149	241
Anneser et al. [3]	–	–	–	–	–	22	22	44
Dubois et al. [14]	24	–	42	–	–	17	37	120
Isella et al. [23]	–	–	–	–	16	50	30	96
Luzzi et al. [30]	15	–	10	–	–	29	23	77
Luzzi et al. [29]	–	–	–	–	–	105	42	147
Luzzi et al. [28]	41	–	–	–	–	–	25	66
Somme et al. [39]	–	–	23	–	–	106	–	129
Tomic et al. [42]	–	–	–	–	–	30	–	30
Wu et al. [45]	–	–	19	–	9	47	21	96

bvFTD behavioral variant frontotemporal dementia, *PPA* primary progressive aphasia, *PSP* progressive supranuclear palsy, *ALS+FTD* amyotrophic lateral sclerosis with frontotemporal dementia, *CBS* corticobasal syndrome, *HC* healthy controls

reflect a specific disease. Therefore, the applause sign may be indicative of PSP but should be interpreted with caution.

In contrast to previous reports we demonstrated a correlation between TCT scores and a number of neuropsychological measures, especially measures of executive, visuospatial and language function as well as disease severity. The higher sample size of our study might be the reason (Table 4) [39, 42]. As the occurrence of the applause sign was correlated with diverse measures of cognitive and language function as well as with measures of disease severity we interpret its presence as an indicator of disease severity rather than of specific cognitive dysfunction.

A number of hypotheses concerning the pathophysiology of the applause sign have been proposed. Wu et al. [45] suggested that the applause sign may represent a form of apraxia, yet it has also been observed in non-apractic patients [30]. Also, frontosubcortical disconnection has been suggested as possible correlate of the applause sign [1, 25].

In our study cohort pallidal volume and the volume of the ventral diencephalon were significantly correlated with TCT scores and were significantly smaller in patients with an applause sign. Among others, the subthalamic nucleus (STN) is part of the ventral diencephalon. Previous studies have shown that in addition to the frontal lobe, particularly the right inferior frontal gyrus [7] and the pre-supplementary motor area [41], the STN and the pallidum play an important role in response inhibition [6]. It has been hypothesized that a stop process could be generated by the inferior frontal gyrus which leads to activation of the STN. The pallidum on the other hand could be activated via a projection from the STN which in turn leads to inhibited thalamocortical output, reducing activation in motor cortex [5]. Therefore atrophy both of the STN and the pallidum may lead to motor perseveration. Further evidence for the involvement of the STN in response inhibition was obtained from experiments in rodents. Excitotoxic subthalamic lesions lead to impaired stopping in a "stop-signal reaction-time task" [15]. Also, functional imaging studies in healthy participants have shown an increased BOLD signal in frontal cortex and STN during "stop-signal tasks" [26]. Impaired response inhibition has also been observed in Parkinson's disease patients treated with deep brain stimulation of the STN [44]. Local field potential studies in Parkinson's disease demonstrated changes in STN activity and cortico-subthalamic coherence in relation to the inhibition of voluntary movements [2, 35].

Apart from PSP and CBS, an involvement of the subthalamic nucleus has been described in patients presenting with frontotemporal lobar degeneration or amyotrophic lateral sclerosis [11, 31]. We therefore propose that the applause sign reflects dysfunction of the subthalamic nucleus and pallidum. This hypothesis is supported by the fact that TCT scores were significantly correlated with the UPDRS part III scores, an indicator of basal ganglia dysfunction. As lesions of the STN are associated with premature responding [9, 10] subthalamic atrophy could also account for spontaneous applauding prior to any instructions as described by Abdo et al. in parkinsonian patients [1]. Further studies, especially neuroimaging and neuropathologic studies that investigate additional subregions such as the inferior frontal gyurs, will be needed to clarify the underlying pathology of the applause sign.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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