

The applause sign in cortical and cortical-subcortical dementia

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Abstract The “applause sign” is a motor perseveration described in focal and neurodegenerative disorders and characterized by fronto-subcortical dysfunction. Most previous formal investigations focused on Parkinson’s disease or progressive supranuclear palsy. We assessed the prevalence of the applause sign in patients affected by Alzheimer’s disease (AD), Lewy body dementia (LBD), corticobasal syndrome (CBS), and posterior cortical atrophy (PCA), with the aim to verify its contribution to the differential diagnosis. We enrolled 20 patients with AD, 20 with LBD, 16 with CBS, and ten with PCA, and 30 healthy controls. The three clap test (TCT) was used to elicit the applause sign, and was scored by raters blinded to the diagnosis. Correlation with motor (extrapyramidal) and cognitive measures was also performed. A maximum 40 % prevalence of a positive applause sign was found in the two parkinsonian syndromes, which could be discriminated from the two cortical groups with a positive predictive value of 82 % and a negative predictive value of 55 %. According to our findings, a diagnosis of LBD or CBS, rather than of AD or PCA, is highly probable in the presence of an abnormal TCP, but cannot be ruled out based on a negative result. No relevant correlates emerged that could clarify the origin and nature of the applause sign.

Keywords Applause sign · Clap test · Dementia · Extrapyramidal disorders

Introduction

The “applause sign” [1] is elicited by asking the patient to quickly clap his/her hands for a limited number of times, and is considered to be positive when the subject is unable to stop, and violates the constraint. This motor abnormality has been interpreted as a perseverative behavior by most authors [1–7], with a putative fronto-subcortical neural substrate [2, 7–9] (but see [5] and [10] for evidence of a purely cortical underpinning).

Repeated formal investigations of the applause sign have been conducted using the three clap test (TCT) [1] in idiopathic Parkinson’s disease (PD) or progressive supranuclear palsy (PSP), while data concerning other parkinsonian syndromes, or cortical dementias, are more scattered [1, 2, 5, 9, 10].

In the present study, we evaluated the prevalence of an abnormal performance at the TCT in typical Alzheimer’s disease (AD), corticobasal syndrome (CBS), Lewy body dementia (LBD), and posterior cortical atrophy (PCA), and explored its extrapyramidal and neuropsychological correlates. Moreover, we computed inter-rater and test–retest reliability for the clap test.

Lewy body dementia is the second most common degenerative dementia after AD, and its differential diagnosis with respect to AD may be challenging due to the possible overlap of clinical presentation at onset [11]. Being characterized by both cortical and basal ganglia involvement, LBD is likely to show a significantly higher prevalence of applause sign with respect to AD, yet no previous study has assessed the sign in this disorder.

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Only a very small pool of CBS patients has been included in previous studies on the clap test [2, 10]. In our survey, we chose to compare their performance at the TCT with that of patients affected by PCA, a purely cortical syndrome that may have a similar, parietal, cognitive profile [12], and in which the applause sign has never been investigated.

Subjects and methods

Patients were recruited consecutively from the memory and movement disorders clinics of S. Gerardo Hospital, Monza, Italy. They had to have a diagnosis of AD, PCA, LBD, or CBS according to standardized criteria [13–16], and a Mini Mental State Examination (MMSE) adjusted score ≥ 16.0 . Controls were patients' or personnel's acquaintances with no relevant neuropsychiatric or medical illness, and an MMSE adjusted score ≥ 26.0 . All participants were unpaid volunteers and signed a written informed consent to participate. The study has been approved by S. Gerardo Hospital ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Patients underwent the motor section of Unified Parkinson's Disease Rating Scale (UPDRS) and an extensive neuropsychological battery including digit span, attentional matrices, Rey's 15 words list immediate and delayed recalls, the token test, letter and category verbal fluency, copy of Rey-Osterrieth complex figure, Raven's colored progressive matrices, the frontal assessment battery, and De Renzi's test of ideomotor apraxia [17].

The TCT was administered and scored according to instructions provided by Dubois et al. [1]. Patients were asked to repeat the task immediately after the first execution for the purpose of measuring test–retest reliability. The performance was video recorded and tapes were viewed by two independent raters blinded to the diagnosis, who were instructed to count the number of hand clappings and to attribute a score from 3 (three clappings), 2 (four clappings), 1 (5–10 clappings), or 0 (more than ten clappings). The test was considered abnormal when the score was ≤ 2 . The final score was established by consensus, in case of inter-rater discrepancy.

Statistical analysis

Statistical analysis was performed with PASW statistics, release version 18.0.0 (SPSS Inc., Chicago, IL, USA, <http://www.spss.com>). Univariate analysis of variance (ANOVA), Kruskal–Wallis test, Mann–Whitney test or Chi-square analysis were used to compare discrete and continuous variables, as appropriate. Inter-rater reliability

was evaluated using Kappa statistic, and test–retest reliability using Spearman rho correlation coefficient. Two-tailed standard significance level was set at $p < 0.05$. Correlation between TCT scores and neurological and neuropsychological variables was carried out using Spearman rho coefficient; significance level was adjusted according to Bonferroni correction.

Results

Out of a total of 73 patients meeting inclusion criteria, seven had to be excluded due to consent withdrawal ($n = 3$) or missing data ($n = 4$). The final study sample was composed by 66 subjects, whose socio-demographic, clinical, and neuropsychological features are shown in Table 1. Twenty were diagnosed with AD, 20 with LBD, 16 with CBS, and ten with PCA. They did not differ at MMSE. Differences in UPDRS and cognitive measures generally reflected the expected clinical specificities. PD subjects had worse motor scores. Memory and semantic fluency were significantly more impaired in AD patients, while performance at visuo-spatial and construction tests was poorer for the other three groups. Only PCA and CBS patients were apraxic. FAB scores were surprisingly low in PCA, in most cases because of difficulties at motor items.

The control group included 14 men and 16 women, with a mean age of 75.0 ± 7.2 years, 11.7 ± 4.0 years of education on average, and a mean MMSE adjusted score of 28.5 ± 1.3 . They were slightly younger than AD patients and older than PCA and CBS subjects, and more educated than all clinical groups but PCA; gender distribution was comparable; their MMSE score was higher with respect to all patients.

The Kruskal–Wallis test showed a statistically significant difference among groups for TCT scores ($p = 0.001$). At Mann–Whitney tests, AD patients (mean clap score 2.9 ± 0.3) did not differ from PCA patients (2.8 ± 0.6) ($p = 0.933$), and LBD patients (2.4 ± 0.9) did not differ from CBS patients (2.4 ± 0.9) ($p = 0.942$); the former two groups were thus pooled into a “cortical” sample, and the latter two into a “cortical-subcortical” sample. Cortical patients' clap score overlapped with healthy subjects' score (3.0 ± 0.0) ($p = 0.078$), while cortical-subcortical patients performed significantly worse than both cortical patients ($p = 0.007$) and normal controls ($p = 0.000$) (Table 2). The TCT discriminated between cortical and cortical-subcortical patients with a sensitivity of 39 %, a specificity of 90 %, a positive predictive value of 82 %, a negative predictive value of 55 %, and a total accuracy of 62 %.

The percentage of subjects with a positive applause sign was also significantly different across groups ($\chi^2 = 18.800$, $df = 4$, $p = 0.001$). Given the similar prevalence found in

Table 1 Comparison of socio-demographic, clinical, and neuropsychological features of patients' groups. Cognitive tests scores are raw

	Cut-off score	AD n = 20	PCA n = 10	LBD n = 20	CBS n = 16	F/x ²
Age	–	78.8 ± 5.5 ^b	63.2 ± 6.9 ^c	77.1 ± 6.0	70.1 ± 6.2 ^{a,b,c}	12.565
Education (years)	–	7.2 ± 3.3	9.4 ± 4.6 ^c	5.1 ± 1.3	7.0 ± 3.4	12.964
Sex (no. of men/women)	–	11/9	6/4	5/15	11/5	7.945
Disease duration (years)	–	3.5 ± 2.9	4.1 ± 3.5	2.9 ± 1.9	3.6 ± 3.3	0.950
UPDRS motor score	–	7.4 ± 6.1	9.8 ± 7.0	16.1 ± 11.4 ^{a,b}	27.3 ± 11.4 ^{a,b,c}	7.398
Adjusted MMSE	≥24.0	20.8 ± 2.8	21.1 ± 3.7	22.5 ± 4.1	21.6 ± 4.9	22.381
Attentional matrices	≥31.0	29.0 ± 8.8	29.6 ± 6.5	27.6 ± 10.3	22.9 ± 10.7	1.292
Digit span	≥3.8	3.9 ± 0.9	4.2 ± 0.9	4.2 ± 0.8	3.9 ± 0.8	0.650
Word list recall:						
Immediate	≥28.5	11.1 ± 5.0 ^{b,c,d}	23.8 ± 7.5	21.3 ± 7.2	20.6 ± 7.9	10.286
Delayed	≥4.7	0.3 ± 0.7 ^{b,c,d}	2.4 ± 2.5	1.9 ± 2.2	2.9 ± 2.2	6.023
Token test	≥26.5	26.9 ± 4.3	27.0 ± 4.9	25.3 ± 5.1	24.4 ± 5.0	0.907
Verbal fluency:						
Letter	≥17.0	15.8 ± 8.0	18.6 ± 9.0	15.5 ± 5.3	10.5 ± 6.6 ^{a,b,c}	2.979
Category	≥25.0	13.3 ± 5.9 ^b	21.8 ± 10.8 ^d	17.0 ± 5.7	15.1 ± 7.4	3.380
Copy of ROCF	≥28.9	18.5 ± 5.3 ^{b,c,d}	11.6 ± 10.3	12.8 ± 6.4	8.4 ± 8.1	8.012
RCPM	≥19.0	17.6 ± 5.4 ^b	11.1 ± 4.8 ^{c,d}	16.3 ± 3.8	16.4 ± 6.5	3.007
FAB	≥13.5	8.5 ± 2.9	10.2 ± 3.0	9.9 ± 3.1	9.1 ± 3.6	0.977
Limb apraxia:						
Right arm	≥53.0	60.9 ± 6.6	51.3 ± 11.8	59.3 ± 8.2	42.3 ± 16.8 ^{a,c}	8.589
Left arm	≥53.0	60.4 ± 7.9	46.7 ± 16.2 ^{a,c}	59.4 ± 9.4	40.5 ± 18.7 ^{a,c}	7.943

Mean ± standard deviation

AD Alzheimer's disease, PCA posterior cortical atrophy, LBD Lewy body disease, CBS corticobasal syndrome, UPDRS Unified Parkinson's Disease Rating Scale, MMSE Mini Mental State Examination, ROCF Rey-Osterrieth complex figure, RCPM Raven's color progressive matrices, FAB frontal assessment battery

p < 0.05 versus ^aAD, ^bPCA, ^cLBD, ^dCBS

Table 2 Performance at the three clap test of healthy controls and of AD + PCA and LBD + CBS pooled groups

Three clap test	AD + PCA n = 30	LBD + CBS n = 36	Controls n = 30
Mean score ± standard deviation	2.9 ± 0.4	2.4 ± 0.9	3.0 ± 0.0
Cases with score			
3	90.0 %	61.1 %	100.0 %
2	6.6 %	16.7 %	0.0 %
1	3.4 %	19.4 %	0.0 %
0	0.0 %	2.8 %	0.0 %
Total number of cases with an abnormal score	10.0 %	38.9 %	0.0 %

See text for results of comparison analyses

AD Alzheimer's disease, PCA posterior cortical atrophy, LBD Lewy body disease, CBS corticobasal syndrome

AD and PCA patients (10 % for both), and in LBD (40 %) and CBS (37.5 %) patients, the groups were again pooled into two samples. Frequency in AD + PCA patients was not

significantly higher than in controls, none of whom showed a positive applause sign ($\chi^2 = 3.158$, $df = 1$, $p = 0.076$). The LBD + CBS group presented a higher prevalence with respect to both healthy individuals ($\chi^2 = 14.808$, $df = 1$, $p = 0.000$) and cortical patients ($\chi^2 = 7.141$, $df = 1$, $p = 0.008$). LBD + CBS subjects also showed a high frequency of worst TCT scores (Table 2).

Correlation analysis performed within the whole patient sample evidenced only a significant association between TCT and the copy of ROCF (Spearman $\rho = 0.49$, $p = 0.000$); the same relationship approached significance in LBD patients ($\rho = 0.57$, $p = 0.013$). Two other correlations showed a trend towards significance: letter fluency within the AD group ($\rho = -0.52$, $p = 0.018$), and word list immediate recall in CBS patients ($\rho = 0.62$, $p = 0.019$).

Inter-rater reliability was found to be $\kappa = 0.87$ ($p = 0.000$) (95 % CI 0.802, 0.928). Test and retest mean scores for the whole patients sample were 2.7 ± 0.7 and 2.7 ± 0.8 , respectively ($p = 0.379$). Test–retest reliability was $\rho = 0.51$ ($p = 0.000$).

Discussion

We administered the TCT to patients affected by AD, PCA, LBD, and CBS of comparable severity, and to matched healthy controls. The applause sign was significantly more frequent in LBD and CBS, and had the same prevalence in these two conditions.

No previous data from LBD and PCA patients are available for comparison, as performance at the TCT has never been investigated before in these two disorders. As to AD and CBS, our findings are in disagreement with past evidence.

In Luzzi et al.'s patients with AD [5], the frequency of the applause sign was three times higher than in our AD group (30 vs. 10 %). Luzzi's cases were more impaired than our patients only at letter fluency. Interestingly enough, this task was significantly correlated with their score at the TCT (a trend towards significance for such correlation was also evident in our AD group). We thus hypothesize that greater frontal or fronto-subcortical impairment might be responsible for the worse clap performance obtained in Luzzi et al.'s study.

The frequency of the applause sign was also higher in Wu et al.'s CBD patients [10], than in our CBS group (78 vs. 38 %). Perhaps, once again, greater disease severity in Wu's sample might account for this major prevalence of an abnormal TCT, but the authors do not provide details about the cognitive status of their cases.

In spite of these discrepancies, the trend highlighted by our study is in keeping with the general pattern emerging from the literature [1, 2, 5, 9, 10]. Moving across the spectrum of degenerative motor and cognitive disorders, from the "cortical-only" condition of AD, to the "subcortical-only" disorder of PD, the applause sign seems to be most frequent in conditions characterized by cortical-subcortical dysfunction, such as LBD, CBS, or PSP [1, 5]. One possible exception might be frontotemporal dementia, as in one study prevalence of an abnormal TCT in this disease was 70 % [5]; however, a previous investigation with a larger sample reported no positive case [1].

In agreement with this picture, the applause sign was not invariably positive in our extrapyramidal cases, nor was it unique to them, but it was more frequent than in cortical dementias, and the two parkinsonian disorders were not reliably discriminated by the TCT.

PSP was not investigated in our study, but previous publications report a prevalence of the sign ranging from 70 to 90 % in this disorder [1, 5, 9]. These values are significantly higher than those found in our CBS and LBD groups. It would be interesting to clarify why this motor abnormality develops more often in PSP than in other Parkinson plus syndromes.

In the present study, we did not find significant correlations with extrapyramidal motor impairment, apraxia, or

executive dysfunction; a very mild association emerged only with poor letter fluency in AD. A significant association with the copy task (particularly prominent in LBD) was indeed present. However, we tend to interpret this finding as a correlation with disease severity, rather than with the specific cognitive function tapped by the test; visuo-spatial tasks may in fact reflect disease stage more precisely than MMSE in syndromes like LBD, CBS, or PCA.

The low prevalence of the applause sign may partly explain this lack of correlations, but previous literature also failed to demonstrate a strong or consistent relationship between motor or cognitive measures and the clapping task [1, 5, 10].

Our reliability data (the first ever published about the TCT) also deserve a comment. While k statistic showed an almost perfect inter-rater agreement, test-retest consistency was unexpectedly low. Retest mean scores were no better than test scores, discarding the possibility of a practice effect as unique explanation. Maybe in some case repetition of the task might raise the risk of failure in patients with a dysfunctional motor control system.

We are aware that our PCA and CBS groups were small, and that socio-demographic features were different across study groups. However, published series of low prevalence dementia syndromes were not more numerous [2, 5, 9, 10], and factors such as education or sex very unlikely influence hand clapping ability.

Ultimately, our findings suggest that a diagnosis of LBD or CBS, rather than of AD or PCA, is highly probable in the presence of an abnormal Clap test, but cannot be ruled out based on a negative TCT. Further studies would be needed to clarify the origin and nature of the applause sign in these Parkinson plus disorders.

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Conflicts of interest None.

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