Abstract
The applause sign is a tendency to continue applauding following a request to clap three times after demonstration, and its occurrence has been related to multiple neurological disorders. This review aims to outline the disorders in which the phenomenon was described and propose a pathophysiological mechanism for its basis considering the pattern of affection.

A review of MEDLINE was performed with the inclusion of relevant data from each article. Progressive supranuclear palsy and other parkinsonian disorders and frontotemporal dementia were the most mentioned diseases as causes of the applause sign. Other disorders such as Alzheimer’s disease and idiopathic normal pressure hydrocephalus are also related.

The applause sign appears to be a form of perseverative behavior related to frontostriatal dysfunction common to several conditions besides neurodegeneration.

We conclude that the applause sign can be considered a clinical observation similar to other frontal release signs, present in several disorders other than progressive supranuclear palsy.
Introduction

The applause sign, also known as clap test, clapping test, or signe de l’applaudissement, is described as a propensity to begin clapping indefinitely when requested to clap three times (this being commonly called the ‘three-clap test’). There is a tendency to describe the applause sign as positive or negative. Being a neurological sign, we consider that one should accurately refer to it as either present or absent in response to the three-clap test (TCT), similarly to a present or absent Babinski sign in response to plantar stimulation.

This finding was originally described in a study by Dubois et al (1995). A subsequent study showed that 30 out of 42 patients with progressive supranuclear palsy (PSP) responded with the applause sign to TCT, while patients with frontotemporal dementia (FTD) or Parkinson’s disease (PD) showed a normal response. Initially the sign was considered positive when the patient clapped more than three times in response to the examiner’s TCT, but later clinical observations led to the inclusion of a less than three claps response as a ‘non-clap sign’ with possible significance in certain FTD variants.

The test gained increased popularity over recent years, despite its clinical value still being not fully grasped, with several pathological processes of distinct etiology being associated with it. It is predominantly related to neurodegenerative diseases, which, given the expected increase in the prevalence of dementia in the aging population with greater life expectancy, may prompt the need for actively incorporating the search for the applause sign in the diagnostic toolkit of both the neurologist and non-neurologist. Further studies about the diagnostic properties of applause sign must come forward to clarify its practical utility and correlation with prognosis.

The purpose of this review is to summarize the existing evidence on the applause sign, concerning the diseases it is related to and the proposed pathophysiology for its occurrence.

Methods

A review of MEDLINE was performed with the last search data of February 3 of 2021. The search strategy included the terms “applause sign”, “applause test” and “clapping sign”. All the articles were included, with no criteria-based exclusion being implemented ad initium.

The following information was extracted: recruiting setting, sample size, number of participants with respective diagnoses, the prevalence of the applause sign in each group, and neuropsychological tests used. We also registered if each study found a correlation with any of the neuropsychological tests used and the MMSE score, and if discriminative measurements (sensitivity and specificity) were calculated.

Results

Our search strategy yielded 77 studies. No Medical Subject headings (MeSH) were applied for this issue. After removing 16 duplicates, 61 articles were screened. Forty articles were excluded from this selection after title and abstract analysis for being unrelated to the subject, including 3 articles referring to the Eastchester Clapping Sign, a test for hemineglect. One additional article was included as relevant for being the first description of the applause sign and referenced in multiple articles. In total, 22 articles were fully analyzed (Fig. 1).

Table 1, summarizes the findings from the 16 cross-sectional studies included.

Figure 1. Article selection process.

Clinical correlations of the applause sign

The first study where the applause sign was reported linked its occurrence specifically to PSP, as a seemingly reliable differentiator from PD and FTD. Following this finding, the research group studied 120 patients with either PSP, PD, FTD, or normal controls, in order to evaluate if the applause sign was related to degenerative diseases with a predilection for mainly cortical (FTD) or subcortical (PSP and PD) structures. Thirty of 42 (71%) PSP patients presented the sign, compared to none from
Table 1. Comparison between the cross-sectional studies included from the literature review

<table>
<thead>
<tr>
<th>Study</th>
<th>Recruiting setting</th>
<th>Sample</th>
<th>Subgroups</th>
<th>NP evaluation</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HC</td>
<td>AD</td>
<td>ALS/FTD</td>
</tr>
<tr>
<td>Abdo et al (2007)</td>
<td>Outpatient clinic</td>
<td>241*</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anneser et al (2015)</td>
<td>Outpatient clinic</td>
<td>44</td>
<td>22</td>
<td>-</td>
<td>22</td>
</tr>
<tr>
<td>Bonello et al (2015)</td>
<td>Outpatient clinic</td>
<td>275</td>
<td>152</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dubois et al (2005)</td>
<td>US</td>
<td>120</td>
<td>37</td>
<td>-</td>
<td>24</td>
</tr>
<tr>
<td>Isella et al (2015)</td>
<td>Outpatient clinic</td>
<td>96</td>
<td>30</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Isik et al (2018)</td>
<td>Outpatient clinic</td>
<td>354</td>
<td>261</td>
<td>63</td>
<td>-</td>
</tr>
<tr>
<td>Kaya et al (2020)</td>
<td>Hospital</td>
<td>423</td>
<td>325</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Koc Okudur et al (2019)</td>
<td>Outpatient clinic</td>
<td>357</td>
<td>237</td>
<td>61</td>
<td>-</td>
</tr>
<tr>
<td>Luzzi et al (2011)</td>
<td>US</td>
<td>77</td>
<td>23</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>Luzzi et al (2012)</td>
<td>US</td>
<td>147</td>
<td>42</td>
<td>105</td>
<td>-</td>
</tr>
<tr>
<td>Luzzi et al (2014)</td>
<td>US</td>
<td>77</td>
<td>25</td>
<td>-</td>
<td>52</td>
</tr>
<tr>
<td>Schönecker et al (2018)</td>
<td>Cohort of National</td>
<td>301</td>
<td>29</td>
<td>16</td>
<td>111</td>
</tr>
<tr>
<td>Somme et al (2013)</td>
<td>US</td>
<td>129</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tomic et al (2013)</td>
<td>Hospital</td>
<td>30</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Weekamp et al (2014)</td>
<td>Nursing Home</td>
<td>73</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Wu et al (2008)</td>
<td>Outpatient clinic</td>
<td>96</td>
<td>21</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

ACD – All-Cause Dementia; AD – Alzheimer’s Disease; ALS – Amyotrophic Lateral Sclerosis; BADL – Basic Activities of Daily Living; bvFTD – behavioral variant of frontotemporal dementia; BWS – Bisyllabic Word Span; CBD – Corticobasal degeneration; CBS – Corticobasal syndrome; CDR - Clinical Dementia Rating; CDT - clock-drawing test; CET - Cognitive Estimation Task; DM – Discriminative measurements (sensitivity, specificity); DR – De Renzi’s test of ideomotor apraxia; DRS – Dementia Rating Scale; DS – Digit Span test; FAB – Frontal Assessment Battery; FTD – Frontotemporal Dementia; HSP – Hamach 5 Point Test; HC – Healthy Controls; HD – Huntington Disease; IADL - Instrumental Activities of Daily Living; INHP – Idiopathic normal pressure hydrocephalus; LBD – Lewy Body Dementia; MCI – Mild cognitive impairment; MHV – Mill Hill Vocabulary test; MMSE – Mental state examination; MSA – Multiple systems atrophy; NP – Neuropsychological; PCA – Posterior cortical atrophy; PD – Parkinson’s disease; PPA – Primary progressive aphasia; PSP – Progressive supranuclear palsy; RAVLT – Rey AuditoryVerbal Learning Test; RCPM – Raven’s colored progressive matrices; ROCF – Rey-Ostrich Complex figure; RR – Rey’s 15 words list recalls; SMC – Subjective memory complaints; US – Unspecified; VaP – Vascular parkinsonism; VF – Verbal Fluency; VOSP – Visual Object and Space Perception test.

* - included four patients with unspecified a typical parkinsonism.
the other groups. Abdo et al (2007) studied the diagnostic value of the TCT in a sample of 44 typical and 48 atypical parkinsonism patients and controls (n = 214). All patients were tested in the off-period of medication. They found that the prevalence of applause sign was 63% in atypical parkinsonism and 29% in PD, calling into question its value as a diagnostic surrogate for PSP. Despite shifting the previous view on specificity for a single disease, this finding still supported the notion of dependence in subcortical regions. In fact, Wu et al (2018) studied the occurrence of the applause sign in other parkinsonian disorders in a sample of 91 patients. It was present in approximately 12.5% of PD (n = 24), 52.6% of PSP (n = 19), 53.9% of multiple systems atrophy (MSA) (n = 13) and 77.8% of cortico-basal degeneration (CBD) (n = 9). Ten patients with Huntington’s disease (HD) were also included, of which 20% presented the applause sign. Interestingly, TCT was unable to discriminate patients with PSP from parkinsonian disorders, and patients with CBD from those with MSA. A study by Somme et al (2013) revealed that the applause sign was present in 85% of PSP (23) and approximately 22% of PD patients (106), reiterating the previous finding on the absence of specificity. The association of the applause sign with PD has been repeatedly reported. Interestingly, the phenomenon was also reported in 15 out of 73 of the residents from a PD institution (20.5%)9, suggesting that it could be a common finding in the spectrum of advanced parkinsonian diseases, which includes PSP.

However, a study of prevalence with an intuitive design grouped the neurodegenerative disorders by their structural affinity. They reported the occurrence of the applause sign in 10% of the patients affected by cortical dementias – which included patients with AD and posterior cortical atrophy (PCA) – contrasting with the 39% of prevalence in cortico-subcortical dementias - Lewy body dementia (LBD) and corticobasal syndrome (CBS). Despite many of the clinical expressions of these subcortical diseases being associated with extrapyramidal symptoms, the applause sign was not invariable associated with them and neither was able to discriminate between both diseases (LBD and CBS). Moreover, a cross-sectional analysis from Luzzi et al (2011) assessed the presence of this sign in cortical dementias unrelated to parkinsonian disorders. From 77 patients, including 23 controls and 29 Alzheimer disease (AD) cases, the prevalence of prolonged applause was 80% in PSP, 70% in FTD, and 31% in AD, extrapolating that the applause sign could also assume a significant presence in diseases with mainly cortical affection. They further hypothesized whether there was an association with stages of cortical dementia progression. They found that the sign was present in 37.8% of mild AD (n = 37), 36.8% of moderate AD (n = 38), and 60% of severe AD cases (n = 30), despite the lack of statistical significance. Nonetheless, the sign may be present in the early stages of neurodegenerative diseases, as reported by a study in a sample of 275 patients of which 72% of the individuals with any form of cognitive impairment – mild cognitive impairment (MCI) and dementia, irrespective of the type – responded positively to the TCT.

The applause sign has also been reported in diseases of the spectrum of FTD. Luzzi et al (2014) reported the sign to be present in 80% of the patients with the disinhibited subtype of the behavioral variant of FTD (bvFTD). Interestingly, the researchers noted that bvFTD patients of the apathetic subtype displayed a propensity to clap less than three times, in what was described as the non-applause sign. This has implications related to the motor initiative that separates the two types of bvFTD and can help establish the pathophysiology of the sign. Schönecker et al (2019) further widened the spectrum to other neurodegenerative disorders related to FTD, with prevalence values of 40.0% in PSP, 30% in CBS, 25% in amyotrophic lateral sclerosis (ALS) and 13% in PPA. Another work with 22 ALS patients showed a prevalence of 23% for the applause sign, which must be understood taking into account the common concurrence between ALS and FTD. Kaya et al (2020) have recently studied the presence of the applause sign in idiopathic normal pressure hydrocephalus (INPH). They showed that it was present in 28.8% of INPH patients, compared to 40% of bvFTD used for reference, showing that the difference was not statistically significant.

Finally, the applause sign has also been described in three case reports, namely: a case of CBS secondary to TDP-43 proteinopathy with atypical findings; A patient with scattered white matter lesions in the MRI secondary to diffuse large B cell lymphoma; and in vascular disease leading to acute bilateral lenticular infarction.

Discussion

The reviewed literature included cross-sectional studies from mainly outpatient settings but of specific...
differentiation, such as memory and movement disorders clinics. Two studies selected patients from a hospital context.\textsuperscript{2,5,6} and 5 were not clear in regard to the setting of selection.\textsuperscript{2,3,7,11,12} The sample sizes and the healthy controls were highly variable between studies, ranging from studies with 423\textsuperscript{16} to studies with 308 participants. As shown in Table 1, several disorders were studied with inconsistent parameters such as the neuropsychological tests measured between studies. Given this baseline discrepancy, we opted not to pursue a systematic analysis on this review, focusing on the evidence for associating the applause sign with specific disorders and possible biological explanations. Discriminative measurements such as sensitivity and specificity calculated for the applause sign in each study were also dependent upon inconsistent study settings, preventing its comparison. Of note, the reported specificity of the applause sign in studies that compared its presence in a disease with that of healthy controls was commonly near 100\%, which just reflects, anecdotally, that the sign is absent in healthy individuals.

Many of the published studies offered insights into the pathophysiology underlying the applause sign. Altogether, it most likely reflects a type of perseverative behavior.\textsuperscript{1,2,5,11}

This response meets the definition of continuous perseveration, an abnormal prolongation of current activity.\textsuperscript{20} Dubois et al (2005) postulated that the applause sign may be associated with dysfunctional basal ganglia that are unable to properly interrupt the ongoing activity. They further added that the preserved behavior contemptuates itself in a decreased ability to plan a specific program of three claps, which would be linked to frontal disfunction.\textsuperscript{2} In the study by Abdo et al (2007), the presence of the applause sign was associated with the presence of signs of frontal disinhibition, namely the snout reflex and the masseter reflex in a group of PD patients. The concept of frontostriatal disconnection syndrome was suggested, in which mirror neurons of the inferior frontal gyrus and cortical frontal areas of motor preparation (important in imitation behavior) stop receiving basal ganglia input, resulting in an uninhibited response of this imitation processing circuitry.\textsuperscript{5} Since PSP is associated with lesions in the frontal cortex and subcortical structures simultaneously, this explanation may reflect the elevated prevalence of this sign in PSP patients in the literature.\textsuperscript{2,3,7,11,14} Despite its original link with the disorder, the applause sign is clearly not specific for PSP, but common to several disorders that disrupt inferior frontal and striatal structures, either isolated or together (as in CBD). Moreover, continuous perseveration has previously been found to be most common in patients with basal ganglia damage, whereas recurrent perseveration is generally related to a posterior left-hemispheric injury.\textsuperscript{20} No study directly assessed the prevalence of the applause sign in PSP relative to other parkinsonian disorders, which would further clarify the subject of frontostriatal disconnection as opposed to a predominantly striatal process.

The majority of studies in parkinsonian patients gave no information about the medication status of the subjects.\textsuperscript{2,4,7,9,11} Whether PD patients on and off treatment differ in the presence of the applause sign is still unknown, and it would be interesting to analyze the treatment response in terms of this sign and other reflexes (such as snout and masseter).

Neuropsychological tests correlated with the applause sign in some studies,\textsuperscript{8,12} while in others it showed no significant association.\textsuperscript{2,15} Overall, the applause sign is not related to performance in tests exploring motor planning and motor execution,\textsuperscript{15} but shows some correlation with tests of executive function, such as the Stroop test.\textsuperscript{12} In agreement, specific components of the FAB, namely verbal fluency and inhibitory control show the most correlation to the sign’s presence.\textsuperscript{7,10} Despite the composition of the test batteries used in each study being highly variable, deeming them unfit for a structured comparison, we believe that these findings correlate with the clinical concept of disruption between frontal and subcortical areas of the brain which most likely underlie the phenomenon. Tomic et al (2013) reported an association between the applause sign and the Initiation/Preservation task of the Dementia rating scale, which are measures of executive function.\textsuperscript{8} These findings oppose the hypothesis of the applause sign as a form of apraxia, in which other neuropsychological test components would be expected to be associated. Wu et al (2008) show that apraxia is unusual in HD patients, in which the applause sign is also seldomly expressed, suggesting that it could be associated with apraxia.\textsuperscript{6} However, this evidence conflicts with other studies that found no correlation between apraxic and non-apraxic patients in terms of applause sign frequency.\textsuperscript{12} Furthermore, as we referred to, the majority of the published neuropsychological test results in the reported studies do not support this apraxia-related hypothesis.
In 5 of the included studies, the presence of the applause sign was related to a lower MMSE score. 5,7,9,16,21 This is more likely to reflect the overall advanced stage of the diseases and the age of the patients, rather than a specific impairment in executive function, which is not accurately assessed by this test. Isik et al (2018) found a correlation with Instrumental Activities of Daily Living and Basic Activities of Daily Living scales, which are also batteries of a general character. It is likely that patients with neurodegenerative disorders that display perseverative behaviors also have diffuse cortical and/or subcortical involvement that causes impairment in overall function. The use of a Rapid Cognitive Screen (RCS-T) combined with a Triple Test comprising head-turning sign, attending alone sign, and the applause sign has been suggested as sensible and specific in identifying cognitive impairment, despite the applause sign not being particularly valuable as an individual measure. 22,23 This emphasizes the importance of the phenomenon as a “clue” rather than a diagnostic test by itself, acting as a valuable clinical observation. The applause sign is present in AD, in which prominent frontal degeneration is characteristic of advanced stages of the disorder. 12 When studied in a high prevalence setting, the applause sign was present in patients with MCI and all-cause dementia. 13 The fact that there was no postmortem confirmation for the diagnosis is particularly unfortunate for the early AD cases. This study used only broad diagnostic categories, and primarily frontal neurodegenerative disorders, as opposed to the more common dementia type (AD), could be biasing the results. It is unlikely, given the proposed mechanism for its generation, that the applause sign serves as a screening measure for MCI in the community setting, with the risk of not identifying patients with milder phenotypes of cognitive impairment.

The applause sign is presumably detectable in any frontal lobe disease to some extent, 11 which is supported by the presence of this phenomenon in INPH, 16 FTD, 3,14,15 and ALS. 15 INPH may be associated with underlying neurodegenerative diseases, 19 causing difficulties in attributing the sign to the first or the former. We believe that the frontostriatal disconnection concept still plausibly explains the occurrence of the applause sign in frontal disorders without an outstanding subcortical affection. Other studies support this view, given that the inhibitory input from the subcortical structures (subthalamic nucleus and pallidum) may be initiated by the frontal lobe. 14 This could effectively explain why both diseases with a predominantly frontal or a predominantly subcortical involvement display the sign. Fronto-striatal dysfunction is characteristic of the disinhibited subtype of bvFTD, with the applause sign being frequent in this group. Furthermore, the non-applause sign first reported in apathetic variants of bvFTD may reflect dorsolateral frontal atrophy, as reported by Luzzi et al (2014). 3 Unfortunately, only 4 articles included the non-applause response to TCT, 6,9,16,21 limiting further conclusions. Neuroimaging and neuropathology studies on FTD patients would be of great interest in further exploring these pathways. In agreement with these considerations, in the case reports included in this review, MRI studies revealed a pattern of frontoparietal atrophy, white matter lesions in the anterior striatal and supralenticular regions, 18 and T2 hyperintensities involving the lentiform nucleus bilaterally (infarction in DWI). 19 Post-mortem autopsy in one of the cases revealed asymmetric cortical and subcortical atrophy. 17 The formal inclusion of the applause sign in protocols of evaluation of demented patients that further undergo brain biopsy studies would be enlightening in this subject.

Conclusion

Our work shows that the applause sign is associated with a wide variety of neurodegenerative disorders, including PSP (the first in which it was considered), CBD, LBD, MSA, PD, FTD (and its variants), ALS, and AD. It is also related to non-degenerative states, such as INPH, CNS lymphoma, and cerebral infarction. Taking this into account, we propose that the applause sign reflects a perseverative behavior that represents a frontostriatal disconnection syndrome elementary to the described disease states.

In this sense, it may not have a specific diagnostic value, but rather be interpreted as a clinical observation similar to the glabellar, masseter, and palmovertical signs.

We propose that the applause sign may be a useful bedside test of frontal-subcortical involvement in clinical situations not directly related to dementia, where it is normally incorporated in the evaluation.

Further studies with neuroimaging and neuropathological analysis for correlation with the clinical aspects are necessary in order to fully unravel the pathophysiology behind this sign.
Responsabilidades Éticas

Conflicts of Interest: Os autores declaram não possuir conflitos de interesse.

Suporte Financeiro: O presente trabalho não foi suportado por nenhum subsídio, bolsa ou bolsa de estudo.

Provenance: Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financial Support: This work has not received any contribution grant or scholarship.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências