Cross-Sectional study

Assessing chronic fatigue syndrome: Self-reported physical functioning and correlations with physical testing

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A R T I C L E   I N F O

Article history:
Received 13 March 2019
Accepted 13 March 2019

Keywords:
Fatigue
Self-reporting
Physical assessment
Physical endurance
Gait
Posture
Walking

A B S T R A C T

The pathophysiology of chronic fatigue syndrome (CFS) remains unclear; no biomarkers have thus far been identified or physical tests designed to underpin its diagnosis. Assessment mainly uses Fukuda’s criteria and is based on the exclusion of symptoms related to other diseases/syndromes, subjective self-reporting, and outcomes of self-report questionnaires. In order to improve the baseline assessment and progress evaluation of individuals suspected of CFS and using an association-oriented research strategy and a cross-correlational design, this study investigates possible associations between the performance on two physical tests, i.e. ‘Timed Loaded Standing’ (TLS), assessing trunk-arm endurance, and the ‘Stops Walking with Eyes Closed while performing a secondary Cognitive Task’ (SWE CCT), measuring impaired automaticity of gait, and the results of two self-report questionnaires, the Checklist Individual Strength (CIS, total score and fatigue subscale score) and the physical functioning and vitality subscales of the Short Form Health Survey (SF-36) to gauge the participants’ subjective feelings of fatigue and beliefs regarding their abilities to perform daily-life activities. Comparisons of the outcomes obtained in 27 female patients with a confirmed diagnosis of CFS revealed that trunk-arm endurance as measured with the TLS correlated with the SF-36 physical functioning subscale only (raw p value: 0.004). None of the other correlations were statistically significant. It is concluded that the TLS may have potential as an objective assessment tool to support the diagnosis and monitoring of treatment effects in CFS.

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1. Introduction

1.1. In search of biomarkers for chronic fatigue syndrome (CFS)

As a chronic complaint, fatigue has been studied for many decades (Muscio, 1921), but scientific research of the syndrome requires the use of well-defined inclusion criteria (Rimbaut et al., 2016). Although contrasting case definitions exist for patients presenting with persistent or pervasive fatigue as their primary complaint (Jason et al., 2012) and more recent criteria have been proposed (Carruthers, 2007), the scientific community tends to adhere to the 1994 criteria of Fukuda et al. (1994). Since no specific biomarker or any objective (bio)physical and reliable, validated, CFS-specific psychological tests are as yet available to confirm the diagnosis (Fukuda et al., 1994), this poses problems both at intake and during the follow-up of patients with suspected CFS.

Despite this lack of robust diagnostic or monitoring measures, over the years research has yielded useful as well as conflicting findings. Patients with CFS have, for instance, been shown to have normal to near-normal aerobic capacities compared to a sedentary population (Riley et al., 1990), while another study reported their power output, in terms of watts per kilogram and oxygen uptake, to be inferior to that of a healthy control group (Wallman et al., 2004).
Using a cardiopulmonary exercise test, Keller et al. (2014) found patients with CFS to be unable to attain the maximal and ventilatory threshold intensities they had achieved 24 h earlier during a first maximal exercise test. To determine patients’ global physical functioning, accelerometers recording their activity levels during 24 h can also be used (Tryon, 2005). Recently, the first results obtained with a heart-rate variability biofeedback therapy (HRV-BF) showed significant reductions in general fatigue similar to those recorded during and after graded exercise therapy (GET), with cognitive components of fatigue, i.e. mental quality of life and depression, improving significantly more in the patients having received HRV-BF (Windhorst et al., 2017). A recent review concludes that the causes for muscle dysfunction and exercise intolerance may vary in CFS as the diagnosis does not represent a single illness (Gerwyn and Maes, 2017), which constitutes a major problem for its assessment. Finally, the findings of several studies suggest that the perception of fatigue does not necessarily run parallel with the results of physical tests (Riley et al., 1990; Weinstein et al., 2009; Ratter et al., 2014; Meeus et al., 2015; Nijs et al., 2004).

1.2. Self-report questionnaires to assess CFS

Chronic fatigue as a subjective phenomenon is usually assessed in a clinical setting through validated self-report questionnaires (Hardt et al., 2001). Multiple such inventories to delineate a patient’s baseline cognitive, somatic and other health-related complaints and their perception of their daily physical activity levels have been proposed and tested (Krupp et al., 1989; Lee et al., 1991; Verroulen et al., 1997; Prince et al., 2008; Meeus et al., 2011), of which the Chalder Fatigue Questionnaire (Morriss et al., 1998; White et al., 2007), the Short Form Health Survey (SF-36), and the Checklist Individual Strength (CIS; Verroulen et al., 1994) are amongst those most commonly used.

With regard to the subjective and objective measurement of cognitive functioning as a sub-topic of CFS-related complaints, Cockshell and Mathias (2014) state that there is little evidence of a direct difference between patients suffering from CFS and healthy controls. Although Cvejic et al. (2016) posed that any such differences might reflect differences in the personal experiences of patients with CFS and unaffected peers, the group recently also failed to find any clear associations between the objective performance improvements in neurocognitive functioning and the patients’ subjective ratings (Cvejic et al., 2016), while another CFS study generated mixed results comparing self-reported attention problems with information processing speed and objective measures of sustained attention (Ickmans et al., 2013). Yet another study also found no significant associations between self-reported impaired memory, attention deficits, and objective cognitive performance measurements in their patients with CFS (White et al., 2007).

Nevertheless, the fear of imminent catastrophes, depression, anxiety, and momentary negative affectability have been shown to be significantly associated with momentary feelings of fatigue (Sohl and Friedberg, 2008; Jason et al., 1999). An important limitation in relation to self-report questionnaires for patients with CFS in particular concerns the fluctuations in cognitive performance over time, which will influence their physical performance and thus their responses to questionnaires (Ray et al., 1993; McDonald et al., 1993; Wearden and Appleby, 1997). What is more, one should be aware of possible over-estimations (Friedberg and Jason, 1998; Austin et al., 1998; Wilcox, 2005). The results on some questionnaires may, for example, be influenced by weather conditions (Messner and Wanke, 2011), while this may also be the case with the location and the context in which the questionnaires have to be filled in (e.g. travel distance, waiting-room and seating conditions, waiting times, and lighting) (Cvejic et al., 2016). The respondents’ scores may then be biased (either lowered or elevated), for which the data should be corrected, with threshold and ceiling effects being taken into account (Friedberg and Sohl, 2008; Elbers et al., 2012). Anonymity seems to be another important variable (Fan et al., 2006). All the above factors can affect responses, potentially cloaking patient feedback.

In their systematic review analysing 18 self-report fatigue questionnaires, Mota and Pimenta (2006) outlined the many differences in the number of items and targeted populations (mental, physical, cancer), and questioned their validity. The authors accordingly plead for improvements on the strength of these differences. Since 2004, self-report questionnaires are being adapted and compiled worldwide by PROMIS, the Patient-Reported Outcomes Measurement Information System initiative originally launched by the NIH (US National Institutes of Health). It is the group’s target to provide measures that meet four criteria: comparability, reliability and validity, flexibility, and inclusiveness. An important aspect of their method is the inclusion of both positively and negatively oriented dimensions of a health concept in the same database. Relevant to our context, the group specifically mentioned ‘fatigue’ and ‘energy’ (Cella et al., 2010) and, since then, a new, concise, online fatigue scale has been developed that appears to accurately assess daily fatigue in various clinical and general populations, with a high reliability in the ‘average’ to ‘severe’ fatigue range (Christodoulou et al., 2014).

1.3. Performance tests to gauge symptoms indicative of CFS

Arguably, physical characteristics assessed by a trained health professional would provide more objective data that could be used to support or further define self-reported symptoms of chronic fatigue. In this light, our group evaluated the performance outcomes on two low-tech physical tests in patients fulfilling Fukuda et al.’s criteria of CFS: the Timed Loaded Standing test (TLS) measuring trunk-arm endurance (Shipp et al., 2000; Eyskens et al., 2015) and the Stops Walking Eyes Closed with a Cognitive Task (SWECT), developed by our group, gauging the presence/absence of automaticity of gait (Eyskens et al., 2015). Compared to a carefully matched control group of healthy volunteers, we found the patients with CFS to perform in the pathological range on both tests. Their trunk-arm endurance was also statistically significantly lower than the values recorded for a control group of participants residing in The Gambia and India and even lower than those obtained in osteoporotic patients that were on average 25 years older (Eyskens et al., 2015). The SWECT showed the CFS sample to have significantly less automaticity of gait compared to healthy peers (Eyskens et al., 2015). To date, evidence supporting the clinical importance of linking subjective perceptions of fatigue and functional impairment to...
objective, physical outcomes such as reduced trunk-arm endurance and impaired gait automaticity is lacking for the CFS population.

1.4. Investigating the relationship between self-reported symptoms and physical performance outcomes

Still, even when strict diagnostic or inclusion criteria are used (Afari and Buchwald, 2003; Cella et al., 2011), divergences between outcomes on physical tests and self-report indices will occur in people coping with CFS (Weinstein et al., 2009) as they may differ due to age, comorbidities, familial and social backgrounds, socioeconomic status, and living and working conditions. A well-defined cohort of patients with CFS may then rather consist of different subgroups that do not necessarily share the same pathogenesis and pathophysiology (Maes, 2013).

To contribute to the assessment, and ultimately the diagnosis and monitoring of CFS, in the present study we evaluate possible parallels between the data obtained with the two physical performance tests (TLS and SWECCT) in female patients with CFS and their scores on selected scales of two widely-used self-report questionnaires using an association-oriented research strategy and a cross-correlational design, hypothesising that the performance data of both tests will reflect the severity of the self-rated symptoms of fatigue and functional impairment.

2. Methods

2.1. Patient recruitment

Recruitment of study participants was conducted at the Clinic of General Internal Medicine of Antwerp’s University Hospital, Belgium, as part of the university’s wider research project on CFS.

Patients had all been referred by their GPs with a suspicion of CFS and were evaluated by a medical specialist (G.M.) with extensive experience in diagnosing CFS to confirm the diagnosis, with eligible participants being provided both oral and written information about the wider research and the current study.

The Antwerp University Ethics Committee approved the study protocol and written, informed consent was obtained from all participants. In order to prevent gender bias, only women were invited to perform both the TLS and SWECCT (Nigs et al., 2011).

2.1.1. Medical assessment

All patients were screened for other possible medical causes, signs, and symptoms in accordance with the criteria described by Fukuda et al. (1994) also comprising standard blood testing and hormonal, cardiac, pulmonary, and psychiatric screening.

2.1.2. Inclusion and exclusion criteria

Only patients meeting the 1994 CDC diagnostic criteria (Fukuda et al., 1994) were included. It should be noted that all patients participating in our study also satisfied the more recent Canadian criteria as defined by Carruthers (2007; also see: Meeus et al., 2016). To avoid gender bias, male patients were excluded.

2.2. Study methods

2.2.1. Self-report assessment

As part of the recruitment procedure, prior to the TLS and SWECCT or any treatment, the participants had completed two self-report questionnaires at the Clinic of General Internal Medicine of Antwerp’s University Hospital under the supervision a clinical psychologist (J.J.) who also calculated the raw and norm scores. Since our participants were part of a larger CFS study, there was some delay between the self-report and physical performance assessments. The mean time gap was 62.4 days (range 30–95 days).

Since the primary goal of our research was to look for objective parameters that could confirm the self-reported symptoms and help tailor the rehabilitation of individual patients, for our study we specifically selected subjective scales that would reflect the patient’s complaints best in terms of perceived fatigue severity and functional ability.

We first opted for the Checklist Individual Strength (CIS) (Vercoulen et al., 1999; Bültmann et al., 2000). The scale’s total score has been shown to be a valid measure of perceived fatigue during the last two weeks (Vercoulen et al., 1999) and the respondent’s ability to function in relation to his/her fatigue and work ability according to a large-scale prospective cohort study on prolonged fatigue in the working population (Bültmann et al., 2000). The CIS allows subtle changes in fatigue levels and fluctuations over time to be identified (Vercoulen et al., 1997). The scale comprises 20 items that are rated on 7-point Likert scales and generates a total score and four subscale scores: ‘subjective experience of fatigue’ (8 items), ‘attention’ (5 items), ‘motivation’ (4 items), and ‘physical activity level’ (3 items). The checklist has good reliability (Cronbach’s alphas ranging from 0.83 to 0.92) and discriminative validity. Higher scores are more problematic. A total score of >76 or a score of >35 on the ‘subjective fatigue’ subscale suggests severe fatigue. We were particularly interested in the fatigue subscale as it provides a good index of the major complaint of patients with CFS and used both the CIS total score and the fatigue subscale scores for our analyses.

Since we expected their outcomes to specifically reflect the patients’ perceived functional impairments (see Table 1), we also selected the ‘physical functioning’ and ‘vitality’ subscales of the Short Form Health Survey (SF-36) (Ware and Sherbourne, 1992; Ware et al., 1993): the latter because it gauges the opposite of ‘being fatigued’. The full SF-36 is widely used to assess various dimensions of health and functional limitations or health-related quality of life (Ware and Sherbourne, 1992; Ware et al., 1993; Aaronson et al., 1998) and is recommended by Van Hoof et al. (2003) in their study on self-report measures for the research of CFS. Its 36 items are clustered in nine subscales that are rated on a nominal or ordinal level and transformed to scores ranging from 0 to 100, with higher scores indicating better health (Ware and Sherbourne, 1992; Ware et al., 1993; Aaronson et al., 1998). The scale’s psychometric properties have been thoroughly studied, revealing a high reliability and validity in different populations, including patients with CFS (McHorney et al., 1994; Hardt et al., 2001). The mean Cronbach’s alpha for the subscales is 0.84 (Hardt et al., 2001) and for adults with CFS the values range from 0.74 to 0.93 (Aaronson et al., 1998).

2.2.2. Physical assessment

Both physical performance tests were also administered at the Clinic of General Internal Medicine of Antwerp’s University Hospital, and rated by the same physiotherapist (J.E.).

During the Timed Loaded Standing test (TLS) (Shipp et al., 2000) the time is recorded during which a person can stand upright, holding a one-kilogram dumbbell in each hand with arms raised to 90° shoulder flexion and elbows extended and wrists in a neutral pronation/supination position. The TLS has been shown to generate reliable data, with good intra-class correlation coefficients for the ‘same’ and ‘six-to-ten days’ test-retest (Shipp et al., 2000). High scores represent a better performance (Shipp et al., 2000).

The Stops Walking Eyes Closed with a Cognitive Task (SWECCT; Eyskens et al., 2015) is based on the classic Stops Walking While Talking test developed by Lundin-Olsson et al. (1997) and consists of three phases: A. the participant is invited to initiate gait with eyes open, walking in a straight line; B. after having walked 7 m (s)
he is instructed to close his/her eyes and asked to continue walking, where it is noted whether gait is sustained or halts; and C, after another 7 m of walking with eyes still closed a simple question is asked (e.g. "How much is 100 minus 7") and it is again noted whether gait is maintained or stops. Scores from 0 to −3 are awarded: 0 when no deterioration in gait pattern is observed throughout the test, −1 when the eyes were aimed at the floor or the feet during phase A and for slight variations in gait (e.g. wavering, slowing down) during phases B and C, −2 for deviations from the straight line, and −3 for stopping. With scores added, higher negative scores reflect poorer performance indicating less automaticity.

2.2.3. Statistical analysis

Descriptive statistics such as means and standard deviations (SDs) were computed for all variables and the distribution of the variables was investigated using histograms and the Shapiro-Wilk test for normality. Since the analysis edged towards non-parametric methods, medians were calculated for the descriptive statistics and for the correlation analysis between variables, Kendall’s tau correlation coefficient was used, with higher correlation coefficients indicating a stronger relationship between the variables. The significance of correlation coefficients was set at 5% controlling for capitalisation on chance using the Bonferroni-Holms method (Holms, 1979). All analyses were performed using IBM SPSS Statistics 21.

3. Results

In total, 33 non-pregnant women were enrolled in the study, with 31 completing all tests; the data of 27 were subsequently included in the final analysis since in four the time gap (> 95 days) between the physical and self-report assessments was considered too long. The participants in the analysis sample (n = 27) were between 21 and 51 years old (mean age: 36.5 years), with all being of Belgian descent and Dutch-speaking; the mean body mass index between 21 and 51 years old (mean age: 36.5 years), with all being too long. The participants in the analysis sample (n

In Table 2, correlations are presented between the physical outcome variables (TLS and SWECCT) and the data obtained through self-reporting (SF-36 and CIS). The TLS performance scores were exclusively statistically significantly associated (p = 0.004) with the SF-36 physical functioning subscale score. The SWECCT showed no statistically significant associations with any of the self-reported scale scores.

4. Discussion

Fatigue and lack of energy to function adequately during the day are core complaints of individuals reportedly suffering from chronic fatigue. In the absence of biomarkers underpinning these subjective complaints, we evaluated two physical performance tests in women diagnosed with CFS, the outcomes of which could serve to improve both the diagnosis and monitoring of the syndrome - or at least supply useful data to help quantify the perceived symptoms.

In two previous studies of our group, we found trunk-arm endurance, as measured with the TLS (Eyskens et al., 2015), and automaticity of gait, as assessed with the SWECCT (Eyskens et al., 2015), to be impaired in female patients coping with CFS compared to the performance of non-disabled peers. In this study, again including female patients only, we contrasted the outcomes on both tests with the outcomes on selected items of two self-report questionnaires, the CIS total scale and its fatigue subscale, and the vitality and physical functioning subscales of the SF-36, finding that lower TLS values indeed coincided with lower scores on SF-36’s physical functioning subscale, both indicative of CFS. However, no other correlations were found.

To the best of our knowledge, with our study we were the first to focus on the possibility and validity of a link between self-reported symptoms and the ability to stand or walk in a CFS population (White et al., 2007, 2015). Our findings pertaining to the TLS may be of relevance for the treatment of CFS given that the guideline treatment of graded exercise therapy is based on a progressive loading of the patient’s aerobic capacities. Also in view of the contrasting results reported in the medical literature concerning the aerobic capacities of patients with CFS (Weinstein et al., 2009; Sargent et al., 2002), trunk-arm endurance might then be used as

Table 1

<table>
<thead>
<tr>
<th>Scale</th>
<th>Mean</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS_total score</td>
<td>115.5</td>
<td>116</td>
<td>88</td>
<td>140</td>
<td>13.1</td>
</tr>
<tr>
<td>CIS_fatigue subscale</td>
<td>51.9</td>
<td>53</td>
<td>40</td>
<td>26</td>
<td>3.8</td>
</tr>
<tr>
<td>SF-36, physical functioning subscale</td>
<td>43.0</td>
<td>45</td>
<td>0</td>
<td>75</td>
<td>20.9</td>
</tr>
<tr>
<td>SF-36, vitality subscale</td>
<td>25.7</td>
<td>25</td>
<td>0</td>
<td>55</td>
<td>12.4</td>
</tr>
</tbody>
</table>

CIS = Checklist Individual Strength; SF-36 = 36-item Short Form Health Survey.

Table 2

<table>
<thead>
<tr>
<th>Test</th>
<th>Self-report scale</th>
<th>Kendall’s Tau Correlation</th>
<th>Ranking</th>
<th>Raw p-value</th>
<th>Adjusted significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLS</td>
<td>SF-36_PHF</td>
<td>0.401</td>
<td>8</td>
<td>0.004</td>
<td>0.006*</td>
</tr>
<tr>
<td>SWECCT</td>
<td>SF-36_PHF</td>
<td>−0.309</td>
<td>7</td>
<td>0.04</td>
<td>0.007</td>
</tr>
<tr>
<td>TLS</td>
<td>SF-36_Vit</td>
<td>0.267</td>
<td>6</td>
<td>0.063</td>
<td>0.008</td>
</tr>
<tr>
<td>SWECCT</td>
<td>CIS_Total</td>
<td>0.190</td>
<td>5</td>
<td>0.199</td>
<td>0.01</td>
</tr>
<tr>
<td>TLS</td>
<td>CIS_Total</td>
<td>−0.124</td>
<td>4</td>
<td>0.369</td>
<td>0.013</td>
</tr>
<tr>
<td>SWECCT</td>
<td>SF-36_Vit</td>
<td>−0.118</td>
<td>3</td>
<td>0.441</td>
<td>0.017</td>
</tr>
<tr>
<td>TLS</td>
<td>CIS_Fatigue</td>
<td>0.079</td>
<td>2</td>
<td>0.590</td>
<td>0.025</td>
</tr>
<tr>
<td>SWECCT</td>
<td>CIS_Fatigue</td>
<td>0.057</td>
<td>1</td>
<td>0.708</td>
<td>0.05</td>
</tr>
</tbody>
</table>

TLS = Times Loaded Standing; SWECCT = Stops Walking Eyes Closed with a Cognitive Task; SF-36_PHF = the Short Form Health Survey, physical functioning subscale; SF-36_Vit = Short Form Health Survey, vitality subscale; CIS_Total = Checklist Individual Strength, total score; CIS_Fatigue = Checklist Individual Strength, fatigue subscale.

* Correlations are ranked in increasing order of raw p-values. The adjusted significance levels tested against the data obtained using the Bonferroni-Holms method are listed in the last column.
an indicator for personalised rehabilitation.

The same can be said of patients lacking automaticity of gait. Implementing a GET program could take into account the means patients use to move and change their position in space, since the way patients with CFS anticipate physically demanding daily life tasks could be related to their complaints (Nijs et al., 2012).

5. Conclusions

Exploring possible parallels between physical performance outcomes as gauged with the TLS and SWECCT and self-reported symptoms of CFS (CIS and SF-36 scores), we found TLS- and SWECCT-assessed trunk-arm endurance to correlate to the SF-36 physical functioning subscale scores despite the fairly large time interval (up to 62 days) between the psychological assessment and performance tests, suggesting that this task has the potential to serve as an objective baseline assessment tool for CFS and to quantify subsequent treatment results.

6. Limitations

In this exploratory study, only female patients diagnosed with CFS were evaluated, limiting the external validity of the findings to this population. A major shortcoming of our study is that it lacks a healthy control group. Inclusion of controls and retests may reveal larger differences in and more significant correlations between the physical and subjective indicators, reflecting both ends of the spectrum. Future studies are needed to replicate the current findings in larger samples and explore associations between physical functioning measurements and self-reported symptom severity in male peers and in children reporting complaints indicative of CFS, preferably in a comparative design with an unaffected control group.

It is also important to note that, since patients were referred by their primary care physicians to our university clinic with a suspicion of CFS, there is a selection bias in our study population, with the differences in patients — with extreme and longstanding fatigue — having been too small to find more than the one correlation.

Finally, the timing of the assessments warrants discussion. The patients were asked to not only rate their condition at the time of the self-report assessment but also regarding the previous two days (CIS) and four weeks (SF 36). In some cases, the interval (30–95 days) between the subjective and performance assessments may have been too long. Since fluctuations in perceived and actual physical abilities are characteristic for patients with persistent, pervasive fatigue, this could have affected the results either way.

Conflicts of interest

None.

Declaration

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

Informed consent

Informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects were always observed.

Funding

Our research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Financial disclosures

The authors have declared that no competing interests exist.

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Analysis and interpretation of the data: Jan b Eyskens, Jela Illegems, Luc De Nil.
Drafting of the manuscript: Jan b Eyskens, Luc De Nil, Jo Nijs.
Critical revision of the manuscript for important intellectual content: Jela Illegems, Greta Moorkens, Jo Nijs.
Statistical analysis: Jarl Kampen, Jela Illegems.
Administrative, technical, or material support: the Staff of the Academic Hospital Antwerp.
Study supervision: Professor Greta Moorkens.

Additional contributions: not applicable

Institutional review: The Ethics Committee of the University Hospital Antwerp approved the study protocol. Written informed consent was gained from all participants.

Participant follow-up: The authors intend to inform the participants, of whom contact information is available, of the publication of this study.

Acknowledgments

We thank all for their help, with special thanks to Hugo Stuer, MD for the many hours discussing chronic fatigue as a trans-disciplinary phenomenon.

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