Cognitive functioning in progressive myoclonus epilepsy type 1 (Unverricht-Lundborg Disease, EPM1)

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Abstract

Objective: The aim of this neuropsychological study of a large cohort of patients with progressive myoclonus epilepsy type 1 (Unverricht-Lundborg disease, EPM1) was to characterize the cognitive function of EPM1 patients and to explore the association between the disability caused by the disease and cognitive performance.

Method: Sixty-eight genetically verified EPM1 patients homozygous for the expansion mutation in the CSTB gene (37 males and 31 females aged 35 ± 11) participated in a neuropsychological assessment of intellectual ability, verbal memory, and executive and psychomotor function. The clinical evaluation comprised administering (and video-recording) the unified myoclonus rating scale (UMRS) to assess the severity of each patient’s myoclonus. Forty-six healthy volunteers (19 males and 27 females aged 32 ± 11) served as the control group for the neuropsychological tests.

Results: The cognitive performance of the EPM1 patient group was impaired. Verbal Intelligence Quotient (VIQ) was below the average range (VIQ < 85) in 49% of the patients; further, Performance Intelligence Quotient (PIQ) was below average in 75% of the patients. The patients performed worse than the controls in both immediate and delayed story recall (p = 0.001); however, in the word list learning task, the patients performed only slightly worse than the controls. The one-hour delayed recall of the learned words was similar in both groups, and the percentage of retained words and story contents did not differ between the patients and controls. The patients were impaired in all of the executive function tests as well as in the psychomotor speed tests (p < 0.001 for all). Also, the patients’ simple psychomotor speed in the tapping task was significantly slowed in comparison to controls (p < 0.001).

Conclusion: The patients had impaired performance in the majority of the cognitive measures; they showed the highest level of impairment in all the executive function tests and in the psychomotor speed tests. The measures of these cognitive domains are timed—therefore, it is clear that severe myoclonus limits patients’ performance. In contrast, verbal memory, especially delayed recall, was the least affected cognitive domain.

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1. Introduction

Progressive myoclonus epilepsy type 1 (Unverricht-Lundborg disease, EPM1, OMIM 254800) is an autosomal recessive disorder caused by mutations in the gene encoding cystatin B (CSTB), a cysteine protease inhibitor. Among the progressive myoclonus epilepsies, EPM1 has the highest worldwide incidence [1]. It is clustered in Finland, with an age-standardized prevalence of 1.53/100,000 [2]. It is also common in Western Mediterranean regions but has been diagnosed in populations around the globe since genetic testing became widely available [3,4].

EPM1 is characterized by stimulus-sensitive myoclonus and tonic-clonic epileptic seizures. Disease onset is in late childhood or adolescence (anywhere between the ages of 6–18 years). As EPM1 progresses, patients develop neurological symptoms including ataxia, incoordination, intention tremor, and dysarthria. Myoclonus causes major disability—all EPM1 patients have involuntary action-activated or stimulus-sensitive myoclonus, which may be induced by light, sound, touch, physical exertion, or stress. A recent study showed that on average, disabling myoclonus occurred 32 years after disease onset, and cognitive impairment occurred a little later than this [5]. Moreover, the severity
of EPM1 is variable, and the long-term outcome in adults ranges from an independent life with mild impairment to a severe handicap. Approximately one-third of EPM1 patients become wheelchair-bound due to progressive myoclonus and ataxia [1,3].

The first Finnish study of 65 EPM1 patients’ cognitive performance [6] evaluated their intellectual ability and performed a follow-up evaluation on 25 patients a mean of six years later. Their intelligence was relatively intact, but they were severely disabled. The estimated intellectual ability at the onset of the disease was in the low normal range; it had diminished by about 10 points in 10 years. It was suggested that the cognitive decline in Finnish patients with EPM1 was associated with the previously prevalent use of phenytoin treatment for the condition [7,8]. Later follow-up studies of EPM1 patients reported mild cognitive impairment as well as the slow progression of intellectual dysfunction [9,10]. More recently, Canafoglia et al. [5] found that younger age at onset, early severe myoclonus, and seizure persistence are predictors of a more severe outcome, including poorer cognition.

The present neuropsychological study is part of a nationwide Finnish study carried out at the Kuopio Epilepsy Center, Kuopio University Hospital in collaboration with the Folkhälsoan Institute of Genetics and Neuroscience Center, University of Helsinki. The aims of the current study were to characterize the cognitive function of Finnish EPM1 patients compared with healthy volunteers and to explore the association between the disability caused by the disease and patients’ cognitive performance.

2. Material and methods

2.1. Subjects

Sixty-eight genetically verified adult EPM1 patients (37 males, 31 females) homozygous for the expansion mutation in the CSTB gene participated in the study. The neuropsychological assessments were performed during patients’ two-day visit to Kuopio University Hospital for clinical, radiological, and neurophysiological evaluation [4]. Forty-six healthy volunteers (19 males, 27 females) of matching age and education were selected from a database of controls gathered for neuropsychological studies in Kuopio Epilepsy Center. The mean age of the patients (35 years, standard deviation [SD] = 11) and the controls (32 years; SD = 11) were comparable, as were their years of education (12 years, SD = 2 for both groups).

2.2. Clinical assessment

The patients’ medical histories including age at disease onset and medications used were collected retrospectively using Kuopio University Hospital’s or other health institutions’ medical records; additional information regarding the patients’ social situations and current medication regimens was obtained during the study visit. The unified myoclonus rating scale (UMRS) test panel consisting of eight sections was administered as part of the clinical patient evaluation. The tasks the patients were asked to do were video-recorded and evaluated using a standard UMRS protocol [11]. All the videos were reviewed and scored by the same study physician (J.H.) in order to reduce physician-to-physician variability in scoring; the main clinical results have already been published [4]. In the present study, Section 4 of the UMRS was used as a quantitative measure of action myoclonus. The patients were classified based on their myoclonus with action scores. (max. score = 160) into three disability groups: mild disability (score = 1–30), moderate disability (score = 31–59), and severe disability (score > 60).

2.3. Neuropsychological assessment

Neuropsychological assessments were performed by the same experienced neuropsychologist (M.A.). The test battery comprised tests for intellectual ability, verbal learning and memory, and psychomotor and executive function. Six subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [12]—Information, Similarities, Digit Span, Digit Symbol, Picture Completion, and Block Design—were used to calculate the patients’ Verbal Intelligence Quotients (VIQ) and Performance Intelligence Quotients (PIQ). Verbal memory was evaluated with a 15-word list learning test [13] and a story recall task from the Wechsler Memory Scale [14]. Immediate and one-hour delayed memory were assessed, and the percent retention score was calculated for both tests. Executive function was evaluated with the Trail Making Test (TMT) and the Stroop test [15]. Differences in time scores were calculated for parts of the TMT and Stroop tests in order to reduce the effect of the motor element in performance and to focus on the flexibility of processing. Psychomotor function was evaluated with the Digit Symbol test from the WAIS-R and with the Alternating S-task. In this task, the subject draws S-letters in alternating directions for two minutes; the score is the number of correctly drawn letters. Simple psychomotor speed was evaluated with the tapping task and the mean number of taps with both thumbs in ten seconds was analyzed.

2.4. Statistical analysis

Statistical analyses were performed using IBM SPSS version 21 (SPSS Inc., Chicago IL, USA). The chi-square test and the independent sample t-test were used for comparisons between the patients and the healthy controls. Pearson’s correlation test was carried out to investigate the relationship between the neuropsychological and clinical variables. To ensure the clinical utility of the findings, only correlations of moderate effect size (r of 0.30) or large effect size (r of 0.50) [16] were considered to be evidence of significant association between variables. Comparisons of neuropsychological test scores between the three disability groups of EPM1 patients (classified based on their myoclonus with action scores) were performed using a non-parametric Kruskal–Wallis test with a post hoc Mann–Whitney exact test. The significance level was set at p < 0.01; considering the number of comparisons made, this was to reduce the likelihood of making a type I error.

2.5. Ethical considerations

This study was carried out in accordance with the recommendations of the Declaration of Helsinki. The Ethical Committee of Kuopio University Hospital approved the study protocol. Finally, informed written consent was obtained from all of the study participants.

3. Results

3.1. Clinical characteristics

The mean age at onset of EPM1 was 10 years (varying from 6–25 years). The disease duration varied from 4–44 years (mean = 24 years, SD = 11). At the time of the neuropsychological assessment, all the patients were taking antiseizure medications (ASMs) with individually adjusted combinations and dosages (Table 1). The median number of ASMs per patient was three. One patient had monotherapy, and one patient was receiving combination of six ASMs, and the patients having more severe myoclonus had more ASMs. Nineteen patients had received phenytoin in
the early phase of their disease. In the clinical examination, 34 patients were able to walk, 13 occasionally needed a wheelchair, and 21 were wheelchair-bound.

3.2. Cognitive performance of EPM1 patients

The EPM1 patients showed impairment in cognitive function tests compared to healthy controls. The neuropsychological test scores of the patients and controls are presented in Table 2. The average cognitive ability of the patients (Table 2) was below the normal range. The VIQ was below the average range (VIQ < 85) in 49% of the patients; the PIQ was below the average range in 75% of the patients.

The patients’ memory performance was worse than the controls in both the immediate and delayed story recall tasks (p = 0.001); however, in the word list learning test, the patients performed only slightly worse than the controls. The scores for the delayed recall of the learned words and the percentages of retained words and retained story content were comparable between the patients and the controls.

The patients were impaired in all the executive function tests and in the tests measuring psychomotor speed (p < 0.001 for all patients). Further, the patients’ simple psychomotor speed in the tapping task was significantly slowed (p < 0.001).

Fig. 1 shows the performance of EPM1 patients in three cognitive domains—verbal memory, executive function, and psychomotor speed—normalized to the control group mean and SD (z-scores). The zero line represents the control mean. The most affected cognitive domain was psychomotor speed.

3.3. Relationship between clinical and neuropsychological variables in EPM1

In the correlation analysis of the clinical and neuropsychological variables, age at onset of EPM1 was moderately associated only with percent retention of the story (r = 0.35, p < 0.01). Longer disease duration and more severe myoclonus correlated significantly (r = 0.41, p < 0.001) and they were associated with impaired performance in many of the neuropsychological tests. Retention of the learned verbal material was not associated with these two clinical variables (Table 3). Longer disease duration was associated with lower PIQ, slower processing in the TMT, and poorer learning and delayed recall of the word list. More severe myoclonus and longer disease duration were both associated with impaired psychomotor functioning in the Alternating S-task, the Digit Symbol test, and the tapping task (Fig. 2). In addition, more severe myoclonus was associated with lower VIQ and PIQ as well as poorer learning of the wordlist and slowed processing speed in the Stroop test.

3.4. Cognitive performance of EPM1 patients according to clinical disability

Myoclonus causes major disability, and the patients were classified based on their myoclonus with action score into three disability groups: 22 patients had a mild disability, 22 had a moderate disability, and 24 had a severe disability. The demographic and clinical data of the patients in the three disability groups are presented in Table 4.

Table 5 shows the mean scores for each neuropsychological test by group and the main group effects. Significant differences

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**Table 1**

Antiseizure medication use at the time of neuropsychological assessment.

| Drug therapy          | Patients taking ASM combination therapy (n) | ASM | Patients taking specific ASM (n) | Mean dose (mg ± SD) | Range (mg, min–max) |
|-----------------------|--------------------------------------------|-----|---------------------------------|--------------------|---------------------|
| Monotherapy 1         | 1                                          | Valproate 67 | 1650 ± 730 | 300–4500 |
| Two ASMs 14           | 14                                         | Clonazepam 51 | 4 ± 3 | 0.3–12 |
| Three ASMs 24         | 24                                         | Levetiracetam 49 | 2290 ± 970 | 500–4000 |
| Four ASMs 19          | 19                                         | Topiramate 15 | 290 ± 240 | 75–1000 |
| Five ASMs 9           | 9                                          | Lamotrigine 13 | 200 ± 110 | 25–400 |
| Six ASMs 1            | 1                                          | Oxcarbazepine 10 | 13700 ± 8100 | 2400–24000 |
| Others ASM 17         |                                            | Clobazam 4 | 25 ± 13 | 10–40 |

* Phenobarbital, Primidone

**Table 2**

Cognitive performance of patients with EPM1 and controls.

| Neuropsychological variable | EPM1 patients (n = 68) | Controls (n = 46) | P-value |
|-----------------------------|------------------------|------------------|---------|
|                             | M          | SD    | M        | SD    |         |
| Intellectual ability        |            |       |          |       |         |
| VIQ                         | 84.5       | 14.7  | 34.1     | 6.2   | 0.04    |
| PIQ                         | 75.0       | 14.4  | 7.1      | 2.5   | 0.07    |
| Verbal memory               |            |       |          |       |         |
| List learning               | 31.2       | 7.9   | 34.1     | 6.2   |         |
| List delayed recall         | 6.1        | 2.9   | 7.1      | 2.5   |         |
| Percent retention           | 61.3       | 25.3  | 67.8     | 19.9  | 0.15    |
| Immediate story recall      | 10.7       | 4.0   | 13.7     | 4.0   | 0.001   |
| Story delayed recall        | 8.5        | 4.0   | 11.3     | 4.7   | 0.001   |
| Percent retention           | 76.5       | 20.3  | 82.6     | 19.7  | 0.12    |
| Executive function          |            |       |          |       |         |
| Trail Making test           | 100.9      | 68.3  | 51.2     | 33.4  | <0.001  |
| Stroop test                 | 41.8       | 27.6  | 24.2     | 12.8  | <0.001  |
| Psychomotor function        |            |       |          |       |         |
| Alternating-S               | 36.2       | 27.3  | 111.7    | 35.0  | <0.001  |
| Digit Symbol                | 24.0       | 12.6  | 58.2     | 14.3  | <0.001  |
| Tapping                     | 32.0       | 7.9   | 47.1     | 5.6   | <0.001  |

VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient. Values significant at p < 0.01 are shown in bold. Mean = M; standard deviation = SD.
between the disability groups were found in VIQ and PIQ as well as in all the psychomotor function tests but not in the verbal memory measures. Post hoc tests showed that the patients with severe disability had lower VIQ ($p = 0.001$) and PIQ ($p < 0.001$). In the psychomotor function tests—the Alternating S-task, the Digit Symbol test, and the tapping task—the patients with severe disability were significantly slower than the patients with mild disability ($p < 0.001$ for all tests). The simple tapping speed of patients with severe disability was also slower compared to patients with moderate disability ($p = 0.002$).

Patients with severe disability had difficulty performing the executive function tests due to fatigue and increasing myoclonus at the end of the neuropsychological assessment. Nine patients with severe disability completed the Stroop test; however, the lack of power due to the small group size may have affected the result. Only two patients with severe disability completed the TMT; thus,
comparison of the three groups was not performed. However, the performance of patients with mild and moderate disability did not differ in the TMT. Fig. 3 contains the cognitive data for EPM1 patients with mild, moderate, and severe disability across the three cognitive domains of verbal memory, executive function, and psychomotor speed relative to healthy controls.

4. Discussion

This cross-sectional study evaluated the cognitive functioning of genetically confirmed EPM1 patients and its relationship to disease-related clinical characteristics. To date, this is the largest EPM1 patient population to be evaluated using a comprehensive neuropsychological test battery at the same study center and by the same experienced neuropsychologist. The patients with EPM1 had impaired performance in the majority of the cognitive functions; however, even EPM1 patients with severe myoclonus showed only mild impairment in the verbal memory tasks. Long-term verbal memory in particular seemed to be preserved.

Two previous studies [17,18] investigated the cognitive profile of patients with genetically confirmed EPM1 using a comprehensive neuropsychological test battery. Both studies included 20–21 EPM1 patients and reported that the patients’ cognitive performance was impaired compared to the healthy controls [17,18]. Giovagnoli et al. [18] concluded that the cognitive profile of patients with EPM1 was characterized by impaired processing and executive functions with the preservation of verbal memory, praxis, and theory of mind. Ferlazzo et al. [17] revealed that the patients had widely impaired cognitive functioning with below-average VIQ, PIQ, and Full Scale IQ scores. However, there was high variability in their level of intellectual functioning, and action myoclonus seemed to interfere with performance on tasks featuring time limits and precision demands. In the present study below-average intellectual ability of EPM1 patients was shown mostly in PIQ, and to a lesser extent, in VIQ. The patients’ cognitive functioning varied substantially, from significantly impaired to high average.

Verbal memory was the least-affected cognitive domain in the present study. Verbal memory performance was poorer and ineffective in the immediate and delayed recall of the story, which was read only once, but this was not the case in learning the word list with four repetitions and delayed recall of the learned words. In addition, the patients’ ability to retain the learned verbal material...
in both memory tests after a delay was comparable to the controls’ performance. This finding is in accordance with earlier studies of patients with EPM1, which did not report finding any major memory disorder. Preservation of verbal memory despite impaired executive functions has been reported [18], and only deficits in short-term memory have been found [17].

This study observed impairment in all the executive function tests as well as in the tests of psychomotor speed. Executive dysfunction has been suggested as being characteristic of EPM1, with patients demonstrating decreased processing speed and impaired flexibility of executive function [17,18]. The tests of executive function and psychomotor function are timed and require speedy and precise motor coordination as well as flexible processing. Therefore, severe myoclonus clearly restricts performance in the tests. Neuropsychological assessment can be strenuous and stressful for patients and mental struggling during tests may even trigger myoclonus, thus worsening performance.

Severe action myoclonus causes major disability in EPM1 and complicates everyday activities [4,19]. Because it also affects cognitive performance, the present study examined neuropsychological test performance in three groups with different degrees of disability caused by myoclonus. Immediate and delayed verbal memory was comparable in all three disability groups; thus, memory performance was not related to the severity of myoclonus and degree of disability. Especially, psychomotor function and performance in executive tests diverged according to myoclonus severity (Fig. 3).

The simple motor speed in thumb tapping was most impaired in patients with severe disability. The patients with severe disability were impaired in all the psychomotor function tests and in PIQ

### Table 5

| Cognitive test scores for EPM1 disability groups and group comparisons. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Neuropsychological measure      | Mild disability | Moderate disability | Severe disability |
|       | Mean  | SD    | Mean  | SD   | Mean  | SD     |
| Intellectual ability            |                 |       |       |       |       |       |
| VIQ                             | 92.2  | 11.2  | 84.6  | 16.5 | 77.4  | 12.4  |
| PIQ                             | 85.5  | 13.7  | 75.6  | 11.1 | 64.7  | 9.9   |
| Verbal memory                   |                 |       |       |       |       |       |
| List learning                   | 34.6  | 6.8   | 30.8  | 6.7  | 28.7  | 8.9   |
| List delayed recall             | 6.5   | 2.7   | 6.1   | 2.6  | 5.8   | 3.4   |
| Percent retention               | 57.7  | 20.5  | 62.0  | 24.7 | 63.8  | 29.9  |
| Story recall                    | 11.8  | 3.9   | 10.9  | 4.2  | 9.5   | 3.9   |
| Story delayed recall            | 9.9   | 3.7   | 8.1   | 3.7  | 7.6   | 4.4   |
| Percent retention               | 82.4  | 16.6  | 73.8  | 17.7 | 73.8  | 24.8  |
| Executive function              |                 |       |       |       |       |       |
| Trail Making test               | 90.7  | 82.0  | 115.6 | 50.8 | -     |       |
| Stroop test                     | 30.7  | 14.6  | 43.0  | 22.1 | 64.0  | 43.9  |
| Psychomotor function            |                 |       |       |       |       |       |
| Alternating S                   | 60.1  | 28.9  | 30.9  | 16.5 | 14.4  | 7.0   |
| Digit Symbol                    | 33.0  | 12.8  | 21.9  | 8.9  | 13.1  | 6.0   |
| Tapping                         | 38.5  | 5.8   | 32.4  | 5.4  | 24.1  | 4.7   |

* Missing data (only two patients performed the test). Values are expressed as means and SDs. Values significant at p < 0.01 are shown in bold. VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; SD = standard deviation.
compared to the patients with mild disability. PIQ is calculated from tests that are timed and require visuomotor coordination—like the tests of psychomotor function. The present study could not evaluate the executive function of patients with severe disability because most of the patients with severe myoclonus could not perform the tests adequately. Severe myoclonus hampered the speed of visuomotor coordination as well as speaking in timed tests.

The brain networks implicated in the executive functions are complex. They include prefrontal cortex regions’ connections with parietal and sensorimotor areas as well as connections with visual and auditory areas and subcortical structures such as thalamic nuclei [20–24]. Previous imaging studies of EPM1 patients have shown widespread thinning of the cortex, especially in the sensorimotor, primary, associative visual, associative parietal, and temporal areas [25,26]. Gray matter volume loss was also observed in the frontal areas and the central, parietal, and thalamus areas [27]. One study reported a trend in the association of cortical thinning in the parietal, prefrontal, and prefrontal areas with myoclonus severity [25]. In addition, fMRI studies showed reduced activation of the inferior frontal junction [28], which correlated with disease duration and patients’ age. This study confirms that Finnish EPM1 patients show significant psychomotor speed reduction, which progressively correlates with action myoclonus severity. This finding is well in accordance with fMRI study results. It is typical for EPM1 patients to have difficulty initiating or halting a motor action; this can be observed in patients with different levels of myoclonus severity. This clinical feature and previous fMRI results may at least partly explain the decline in psychomotor speed observed in this study population.

Disturbances in sensorimotor integration have been found in numerous neurophysiological studies of EPM1 patients, including changes in cortical excitability measured with transcranial magnetic stimulation and giant SEP responses [26,29–31]. These changes and previously observed cortical thinning in sensorimotor areas and associative parietal and prefrontal areas might partially explain the deficits observed in the executive tests. That said, no significant atrophy of the temporal or parietal structures have been reported in EPM1 patients, possibly explaining the preserved verbal memory functions observed previously and in this study.

In a previous study, the present authors confirmed findings that an earlier disease onset is associated with a more severe phenotype, including more disabling myoclonus and poorer intellectual performance, especially a lower PIQ [4]. Similar results of below-average cognitive functioning have been reported [10,17]. Severe myoclonus is associated with disease duration and reflects the progression and variability of the disease [4,5]. It also affects the reliability of cognitive function assessment with traditional neuropsychological tests.

Although age of EPM1 onset has previously been associated with myoclonus severity and cognitive outcomes [4,5], the current study did not confirm the relationship between age at onset and poorer cognitive performance. However, it is clear in this study population that the severity of myoclonus itself plays a role in performance on the psychomotor and executive function tests. Long duration of the disease and severity of myoclonus correlated with poorer performance. The limitation of the current study is its cross-sectional nature, which limits it from directly addressing the possible progression of cognitive impairment.

All but one patient were receiving treatment with multiple ASMs. These medications can cause drowsiness and slowing. The majority of patients were taking clonazepam; 15 out of 68 were receiving topiramate, which can also influence performance on executive tests. It has been speculated [7,8] that the extensive use of phenytoin has a major impact on EPM1 patients’ cognitive performance. However, in the present study, only a minority of the patients had used phenytoin, and only for short periods; therefore, phenytoin usage does not explain the cognitive problems described above. EPM1 patients suffering from more severe myoclonus were more likely to have multiple ASMs therapy. Due to logical cross correlations between the severity of the disease and ASMs’ load and considering the cross-sectional design of the study, it is impossible to evaluate the impact of the individual ASM or combined polytherapy on the cognitive impairment observed in the study. Overall, although medication regimens for EPM1 patients were complex and the drug load could have partly influenced patients’ cognitive performance, the medications alone or in combinations are unlikely to explain the impairment in executive or psychomotor functions observed in this study. Moreover, the long-term verbal memory was preserved also in EPM1 patients with more severe myoclonus and, thus, having higher ASM load. This finding further supports the notion, that the findings of the impairment in the executive function tests as well as in tests of psychomotor speed cannot be attributed or explained by the drug load used by the patient.

In conclusion, the EPM1 patients displayed impaired performance in the majority of the cognitive functions evaluated in this study. Verbal memory, especially delayed recall, was the least affected cognitive domain. Therefore, EPM1 should not be regarded as a progressive memory disorder, a feature of the disease, which should be taken into account when communicating with the patients and when planning their living arrangements. The patients were most impaired in executive function tests as well as in tests of psychomotor speed. Long duration of the disease and severity of myoclonus correlated with poorer psychomotor performance.

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Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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