Subtle visuomotor deficits and reduced benefit from practice in early treated phenylketonuria

Claudia Caprile, Jaume Campistol, Laura Puigcerver, Alfonso-Pablo Gutiérrez-Mata, Itziar Alonso-Colmenero, Roser Colomé and Jordi Navarra

ABSTRACT

Introduction: Phenylketonuria (PKU) is a rare metabolic disease that causes slight-to-severe neurological symptoms. Slow performance has been observed in PKU but the influence of high-order (i.e., not purely motor) deficits and of temporary variations of the phenylalanine (Phe) level on this slowness has not been fully corroborated as yet. Response speed and the effect of motor practice during the performance of a visuomotor coordination task were measured, in a group of patients with early-treated phenylketonuria (ET PKU).

Method: We compared the performance of a group of early-treated PKU patients with ages ranging from 11 to 25 years and a control group of healthy volunteers on a computerized visuomotor task. Participants performed rapid movements towards one of five response buttons, as indicated by a visual stimulus that could appear in five different positions on a computer screen. The results of our visuomotor task were correlated with neurobiological data (Phe levels) and with neuropsychological measures of motor (finger tapping) and executive functions (Stroop task).

Results: The ET PKU group showed slower responses than the control group. Furthermore, an absence of a practice effect (i.e., faster response times at the end of the study) was found in the PKU group but not in the control group. Our results also revealed that this absence of practice effect correlated with higher Phe levels on the testing day with respect to the average Phe level of the previous 12 months and, although weakly, with performance on the Stroop task. Conclusions: This pattern of results indicates slower visuomotor performance and a less beneficial effect of practice in ET PKU. The correlations found among our visuomotor measures, the same-day Phe level, and the Stroop test may reflect the negative effects of dopamine reduction in brain areas involved in motor control, selective attention, and learning.

1. Introduction

Phenylketonuria (PKU) is a hereditary metabolic disease characterized by a deficiency of the hepatic enzyme phenylalanine 4-hydroxylase (PAH), the presence of high levels of phenylalanine (Phe), and low levels of dopamine (see Hoeksma et al., 2009). The impact of this disease is observed at both the neural and behavioral levels. Severe neurological disabilities can be prevented by a strict reduced Phe diet from early infancy (Pietz et al., 1998). Despite such treatment, patients with early-treated (ET) PKU (i.e., patients diagnosed with PKU at birth who have had strict and uninterrupted diet restrictions from birth) can still present relatively low scores on intelligence tests (Huijbregts, De Sonneville, Licht, Van Spronsen, & Sergeant, 2002; Smith, Beasley, & Ades, 1990), as well as both neuropsychological (Anderson et al., 2007; Brumm et al., 2004; Diamond & Baddeley, 1996) and neurological anomalies (see Butler, O’Flynn, Seifert, & Howell, 1981; Gassió et al., 2010).

General slowness has been reported in the literature on PKU (see Janos, Grange, Steiner, & White, 2012; Moyle, Fox, Arthur, Bynevelt, & Burnett, 2007), but the data are not conclusive regarding its possible cause. According to an
select one of 2 different response options seems to be slower in early-treated PKU patients than in control individuals (Albrecht, Garbade, & Burgard, 2009). Regarding reaction times (RTs) in simpler tasks (e.g., stimulus detection), previous studies reported somewhat contradictory results, showing both slow (see Huijbregts et al., 2003; Moyle et al., 2007) and normal RTs in PKU patients (see Channon, Mockler, & Lee, 2005; Henderson, McCulloch, Herbert, Robinson, & Taylor, 2000). Henderson and colleagues (2000) did not find slower responses in PKU patients than in control participants in a visual detection task. According to these authors, this lack of effect might be due to the fact that the PKU sample had very low phenylalanine levels in blood and also the fact that the task employed in this study was too simple. In line with this earlier study, Channon et al. (2005) did not report any significant RT increase in a group of PKU patients when performing tasks that did not recruit any high-order (i.e., not purely motor) or executive function such as performing certain rapid perceptual judgments. In contrast, slow responses are robustly observed in more complex tasks that require visuomotor coordination and involve some sort of action control, monitoring various response options, or even taking a decision (Arnold et al., 1998; Pietz et al., 1998). Dawson and collaborators (2011) assessed reaction times in PKU by investigating saccadic latencies. These authors found that the latencies of eye movements were significantly slower, when trying to follow a visual stimulus, in patients who were off-diet than in patients who were on-diet and a control group of healthy volunteers. Furthermore, this study also revealed that saccadic latencies became shorter in a group of women with PKU under prenatal strict diet. The results showed significant improvement in reaction time with stricter control of Phe, perhaps indicating that the negative effects of Phe levels seem to be somewhat reversible (Dawson et al., 2011). Noteworthy, the task employed in this previous study (i.e., following a visual stimulus with the eyes) involve complex decisional and action control processes to some extent.

Although alterations in both fine and gross motor skills have been reported in PKU (see Anderson et al., 2007; Gassió et al., 2010; Huijbregts et al., 2003), the most commonly reported cognitive deficits in ET PKU involve the so-called executive functions (see Christ, Huijbregts, de Sonneville, & White, 2010). The neuropsychological evaluation of these functions using several tests (e.g., see Araujo et al., 2009; Leuzzi et al., 2004) often reveals anomalous performance in PKU. This anomalous performance could easily explain some of the results found in relatively complex motor and manipulative tasks used in studies investigating motor functions in PKU. If this is the case, we should be able to see, in a group of patients with PKU, a relation between specific measures of executive functions and their performance in a (relatively complex) motor task. In order to address this possibility experimentally, we used a visuomotor coordination task in which the participants had to press one of five different buttons, each of them located at different spatial positions (see Mollica et al., 2015; see also Figure 1). In each experimental trial, a stimulus provided the participants with the location (among 5 different alternatives) of the button that they had to press (see Figure 1). The position of the target on the screen had to be translated into motor commands in order to press the targeted button. Therefore, the task employed in the present study was not a detection task (i.e., pressing a button as fast as possible when detecting a visual target). The task was not a choice task either, because the participants were already provided with a “choice among 5 different alternatives” in each trial, so they did not have to decide among these response alternatives by themselves. In contrast, the selected task required the conscious control of specific actions and selective attention to one specific location (among others), allowing us to address the possible relation between the previously reported motor slowness, in a group of patients with ET PKU, and their performance in a classic measure of executive functions (the Stroop test; see Golden & Freshwater, 1978).

Crucially for the purpose of the present study, the use of this particular computer-based, and relatively complex (in terms of action control), visuomotor task also allowed us to examine, for the first time in a group of patients with ET PKU, whether these patients present alterations in the ability to take advantage of practice with the task. Since the level of dopamine is compromised in...
PKU, it is plausible that the nigrostriatal pathway, which contributes extensively to motor control and, even more importantly, to learning new motor skills (see Malenka, Nestler, & Hyman, 2009; Molina-Luna, 2009), would show functional deficits in these patients. Behaviorally, these deficits would imply a poor ability to learn (or automate) specific motor actions by means of practice. Therefore, a lessened practice effect with our visuomotor coordination task was expected in the group of ET PKU compared to a control group of participants with no neurological or psychiatric pathology.

In order to fully elucidate the possible origin of the slowness observed in PKU, the two different measures obtained in our task (mainly response times and the effect of practice) were correlated, in the patient group, with data from another two neuropsychological tests: the Finger Tapping Test (FTT; Spreen, 1991) and the Kaufman Brief Intelligence Test (K-BIT; Kaufman & Kaufman, 1990).

Finally, a possible relation between performance in our visuomotor task and Phe levels in blood could also be expected in the present study. Concerning this matter, we were particularly interested in investigating whether a temporary increase in Phe level in blood was associated with worse visuomotor performance. This result would also suggest the negative effects of dopamine descent on motor control and/or motor learning in these patients. Previous studies using RT data have already shown positive correlations between response speed and phenylalanine concentrations in blood at test time, in ET PKU (Diamond, Prevor, Callender, & Druin, 1997; Huijbregts et al., 2002). However, the possible relation between Phe level and the ability to take advantage of motor practice has not yet been addressed in the literature.

2. Method

2.1. Participants

Nineteen patients (57.89% female) diagnosed with PKU from birth (with age ranging from 10 to 25 years; \( x = 18.15, SD = 4.47 \)) and 13 healthy controls, similar in age (\( x = 18.85, SD = 4.34 \) years) and gender distribution (61.5% female), participated in the study. All of the patients had shown, in a genetic study, a mutation in the PAH gene, had normal IQ (>80; \( x = 101.68, SD = 10.8 \)), and received low-Phe dietary control (with protein restrictions). Please see Table 1 for details on Phe levels of the patient group.

None of the patients received tetrahydrobiopterin (BH₄) treatment or docosahexaenoic acid (DHA) supplement. All of them were recruited at our center, underwent metabolic control (including tyrosine levels and phenylalanine from dried blood) on a 2-month basis, and had a complete blood test annually. The treatment required following a controlled diet, with medical supervision twice a month at the hospital.
Table 1. Patients' biological data.

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<th>Phe_12 month (µmol)</th>
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Note. Phe_day = phenylalanine levels at day of test; Phe_recm = phenylalanine levels recommended for the participants’ age range in Spain; Phe_12 month = medium of phenylalanine levels in the previous year; VEP right = visual evoked potentials at right eye; VEP left = visual evoked potentials at left eye.

The control group included participants with no history of psychiatric, neurological, or motor disorders. They had received normal formal education, and showed no learning disabilities. They were recruited through relatives and acquaintances of employees at our center. Written informed consent was obtained from all participants or from guardians/relatives of the participants under 18 years of age, before participating in the study. The experimental testing was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki.

2.2. Apparatus and stimuli

The visual stimulus that oriented the participants towards one of the five different buttons consisted of a green square (3.63° of visual angle) appearing on a black background on a 17” CRT computer screen (Asus A55 V; refresh rate = 60 Hz). This green square appeared in a particular location that corresponded to the button that the participant had to press, on a modified computer keyboard, in that particular trial. The distribution of each of these visual stimuli represented the location of each of the five different response buttons on the modified computer keyboard (see Figure 1). Only one visual stimulus appeared in each trial to indicate the position of the target button to participants (see Figure 1). The response keys were made of hard foam and were also green on a black background. A “starting-point” rectangle (also made of foam) was attached to the lower-central part of the keyboard (see Figure 1) to indicate the initial resting position of the finger to participants. DMDX presentation software (Forster & Forster, 1999), running on an Intel Core computer, was used to present the stimuli and record the participants’ RT.

2.3. Procedure

Participants sat in a dimly lit sound-proofed room, at a distance of approximately 55 cm from the computer screen. They were instructed to perform a goal-directed visuomotor task in which they had to press, as quickly and accurately as possible and with the index finger of their dominant hand, one of five buttons that corresponded to the visual stimulus presented on the screen (see Figure 1a). In each trial, participants had first to put their finger in the starting rectangle (resting position) and fix their gaze in a central cross of 1.05° of visual angle. After 500 ms of fixation, the target stimulus was presented, and the participants responded. The participants were instructed to move their hand back to the resting position during a 2000-ms intertrial interval in which a black screen was presented after the participant’s response (see Figure 1b). The experimental session contained two identical blocks and lasted a maximum of 5 min. Each block included 40 experimental trials. The participants had the possibility to rest between blocks.

Response times (i.e., the time between the visual target “go” signal appearance and the response made by each participant) were collected for the dominant hand in each group. The experimenters made sure, from a window outside the sound-attenuated booth, that the participants were not executing any anticipatory movement or placing their hand near the response buttons instead of on the starting platform before the appearance of the target. The participants were explicitly instructed to avoid such strategies.

2.4. Other measures

Data from the visuomotor task were correlated with other neuropsychological measures: the standard version of the Stroop test (Golden & Freshwater, 1978). The results were corrected by age, as specified in the test (see Stroop, 1935).
Basic motor skills (which did not require visuomotor coordination or action control) were obtained from the Finger Tapping Test (FTT; see Spreen, 1991), which participants performed with the index finger of their dominant hand. A counting device was used to register the participants’ taps in five consecutive 10-s intervals. The Kaufman Brief Intelligence Test (K-BIT; Kaufman & Kaufman, 1990) was also administered to the patients with ET PKU to obtain a general measure of intelligence.

The P1 visual evoked potential (VEP), obtained from electrodes O1 and O2 (in occipital regions) using a Viking Select Nicolet system (Vyasis Healthcare), was available for ET PKU patients. The typical stimulation used in routine clinical examination of the visual system was delivered by a Nicolet Biomedical Nic 2015 visual stimulator (Vyasis Healthcare). The patients’ phenylalanine levels were obtained as part of the regular clinical monitoring of PKU patients, conducted every 2 months at the hospital.

### 2.5. Data analysis

Only RTs from trials with a correct response were considered for statistical analysis. The participants’ average of RTs (in the whole experimental session, as well as in the first and last 30 trials of the experiment) was the main dependent variable. The possible effect of practice with the task was obtained by subtracting the mean RT in the first 30 trials from the mean RT in the last 30 trials. Reaction times that were 3 standard deviations (SDs) above or below the participant’s average RT were not included in the statistical analyses. The software SPSS 17.0 (Chicago: SPSS Inc.) was used for statistical analyses. Data met the normality criteria, and parametric tests were performed in the statistical analyses (analysis of covariance, ANCOVA; independent-samples t test, paired-samples t test) to find possible differences between the ET PKU and the control group.

Parametric correlation analyses (only conducted in the patient group) were carried out to address possible associations between the measures obtained in our visuomotor task and both the Phe levels and the neuropsychological data. The behavioral measures obtained in our study were correlated with Phe levels on the day of testing, the average of monthly Phe levels from the last 12 months previous to the test, and the same-day improvement/worsening in Phe level. This last measure represented the difference between the Phe level obtained on the day of testing and the average Phe level in the 12 months prior to the test.

Significance level was established at \( p = .05 \).

### 3. Results

#### 3.1. Response times (RTs)

As expected, the participants’ accuracy in pressing the foam button indicated by the visual stimulus approached 100% correct in both groups. A box plot analysis conducted with the participants’ RT averages did not reveal the presence of any outlier participants. To examine the effects of group and age on processing speed, we conducted an ANCOVA with the mean of RTs as dependent variable, and group as independent variable. We also introduced age and the effect of practice (first 30 trials minus last 30 trials) as covariates to see whether or not these variables modulated the participants’ performance. The results revealed a significant effect of group, \( F(1, 31) = 6.30, p = .018 \), \( \eta^2 = .184 \) (observed power = .679), but no influence of the participants’ age, \( F(1, 31) = 0.262, p = .613 \), \( \eta^2 = .009 \) (observed power = .078) or “effect of practice” on their RTs, \( F(1, 31) = 0.090, p = .766 \), \( \eta^2 = .003 \) (observed power = .060).

In order to investigate the possible effect of practice with the task on each group’s RTs, the average of each participant’s RTs in the first and the last 30 trials was used for further analyses. An ANCOVA was carried out, including the within-subjects factor “practice” (i.e., the first 30 vs. the last 30 trials), the between-subjects factors “group,” and the participants’ “age” as covariate. The analysis showed a significant effect of practice, \( F(1, 31) = 5.34, p = .038 \), \( \eta^2 = .291 \) (observed power = .571), and a significant interaction between this factor and group, \( F(1, 31) = 4.97, p = .044 \), \( \eta^2 = .277 \) (observed power = .542), but no effect of age, \( F(1, 31) = 1.02, p = .347 \), \( \eta^2 = .050 \) (observed power = .334). The interaction between practice and both age and group was not significant, \( F(1, 31) = 1.24, p = .276 \), \( \eta^2 = .040 \) (observed power = .284). Further analyses run in each group separately showed an effect of practice only in the control group, \( F(216) = 3.51, p = .004 \), but not in the ET PKU group, \( F(18) = 0.512, p = .615 \) (see Figure 2b)).
In summary, ET PKU patients showed slower responses overall when performing the visuomotor task, and the velocity of their responses did not improve with practice with the task. In contrast, participants in the control group were faster and showed clear benefits from practice (see Figure 2).

3.2. Correlations with phenylalanine levels

Correlation analyses were performed using the Pearson coefficient. These included the following variables: RTs in the visuomotor task, practice effect (first 30 trials RTs minus last 30 trials RTs), and metabolic Phe data (same-day Phe level, Phe level for the last 12 months, and same-day Phe level improvement/worsening—that is, same-day Phe level minus Phe level for the last 12 months). The results of these analyses revealed a significant negative correlation between RTs and the improvement/worsening of Phe level ($r = -0.436, p = .031$), indicating that higher Phe levels with respect to the average Phe level during the previous 12 months were associated with lessened ability to benefit from experience with the task.

3.3. Correlations with neuropsychological tests and visual-evoked potentials (PKU group)

The individual scores of ET PKU patients in the neuropsychological tests appear in Table 2. The correlation analysis performed with data from neuropsychological tests (Stroop and FTT), VEPs, IQ (K-BIT), and data from our visuomotor task (RTs and practice effect) only showed a significant negative correlation between practice effect and the overall IQ ($r = -0.528, p = .01$) indicating that less total IQ was associated with the absence of practice effect (i.e., no decrease of RTs in the last 30 trials). Our analyses also revealed nearly significant negative correlation between the word–color interference measure in Stroop test and practice effect ($r = -0.379, p = .055$). This correlation became significant ($r = -0.436, p = .031$) when using a nonparametric test (Spearman’s rank correlation coefficient). None of the other correlation analyses reached statistical significance.

4. Discussion

We investigated the presence of slowness in a visuomotor task in patients with ET PKU. Our results revealed larger RTs in the ET PKU group than in the control group. Keeping in mind that the most of patients tested ($n = 17$) did not show altered results in the finger tapping test with respect to normative data and also that no correlation was found between this test and our visuomotor measures, a plausible explanation for our results may be that patients with ET PKU show visuomotor anomalies especially when the task (a) requires higher order (i.e., not purely motor) processes such as visuomotor coordination and action control, and (b) allows for multiple responses, requiring selective attention to execute the appropriate action/movements. No influence of age or
practice was observed in these effects. The mild correlation found, in the ET PKU group, between the practice effect with the task and the color–word interference measure in the Stroop test may perhaps reflect the fact that both tasks recruit selective attention and cognitive control to some extent. An appropriate allocation of attention to the responses and the inhibition of distractors that are not appropriate responses (i.e., the nontargeted locations, in our study) are needed in both cases.

In our study, a negative correlation was found between the participants’ same-day improvement/worsening in Phe level and the effect of practice. This result indicated that the increase in Phe levels with respect to the year’s Phe level average is associated with lesserened ability to take advantage of practice with a given visuomotor task. We believe that this result provides further support for the use of the effect of practice with a visuomotor task as a possible measure to analyze the negative effects of a temporary increase in Phe levels (and, arguably, a reduction in dopamine levels), in PKU. Indeed, it has already been suggested that Phe variability over time may be a powerful predictor of several cognitive deficits (e.g., in executive functions) in PKU (see Hood, Grange, Christ, Steiner, & White, 2014). Our results may represent a first attempt to extend these previous results to the case of the difference between the Phe level at a particular discrete point in time and the average Phe level across a longer period of time (e.g., the last 12 months). Taken together, the results of previous studies and our pattern of results suggest that any increase or decrease in Phe level (and the associated change in dopamine) can potentially have a relatively short-term impact on certain brain functions. In a recent study, Dawson and collaborators (2011) studied saccadic latencies, in ET PKU patients, while following a visual stimulus. The results of this study revealed longer saccadic latencies in patients with ET PKU that did not follow a strict diet. Moreover, stricter control of Phe levels seemed to improve the participants’ saccadic latencies (Dawson et al., 2011).

Although the possible effect of fatigue cannot be completely ruled out, it is doubtful that this variable had a strong effect on the results if we take into account the short duration of the visuomotor test (5 min at most) and the fact that the participants were allowed to rest for a while between the first and the second blocks. Besides, the presence of correlations between practice effect and both the IQ and the worsening/improve of Phe levels may also contradict the “fatigue” account of this result. Keeping in mind that the dopamine pathways are compromised in PKU, the poor ability to improve the execution of certain actions involved in a particular task (arguably, by means of motor learning) seems to be the most likely explanation for the pattern of results found. The possible origin of such difficulties (and perhaps the slowness itself and other symptoms such as tremor; see Pérez-Dueñas et al., 2005) may lie in functional anomalies in movement-related areas in the cortico-basal ganglia motor loop, including the nigrostriatal dopamine pathway and both motor and premotor areas. The dopamine-based nigrostriatal pathway plays a crucial role in the control of motor function and, even more importantly, in learning new motor skills by means of practice (Molina-Luna et al., 2009). The involvement of premotor cortex in the early stages of motor sequence learning is also worth highlighting (see Jueptner, 1997a). Therefore any subtle and/or temporary anomaly in these highly interconnected areas may interfere negatively with the ability to perform and automate motor tasks. More conclusive evidence, perhaps correlating neuroimaging and behavioral data, is needed to elucidate whether possible structural and/or functional dysfunctions of the dopaminergic nigrostriatal pathway give rise to motor deficits in PKU.

Table 2. Patients’ neuropsychological data.

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Note. K-BIT = Kaufman Brief Intelligence Test; K-BIT_vb = participants’ score on verbal intelligence of K-BIT test; K-BIT_m = participants’ score on nonverbal intelligence of K-BIT test; K-BIT_overall = general coefficient of intelligence of K-BIT test; W/C Stroop = word–color interference measure in Stroop test; tapping dh = scores in the Finger Tapping Test (FTT) with the dominant hand.
Previous neuroimaging studies have reported gray matter anomalies, in a somewhat heterogeneous group of PKU patients, in motor-related brain structures such as motor and premotor cortex, which have also been associated with specific deficits found and behavioral levels in neuropsychological tests (e.g., Gassió et al., 2010; Pérez-Dueñas et al., 2006). Considering also the well-documented presence of structural anomalies in the white matter, further research correlating behavioral data with diffusion tensor imaging (DTI) would also help to clarify a possible relation between the motor slowness and motor automating deficits observed here and the presence of abnormal cortico-cortical and/or cortico-spinal connectivity.

At a speculative level, the significant correlation found between practice and the Stroop test may perhaps reflect a dysfunction in the dopamine-based dorsolateral prefrontal cortex (DLPFC; see Tarn & Roth, 1997). Interestingly, motor learning has been associated functionally with the DLPFC in a number of previous studies (see Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Jueptner & Weiller, 1998; Middleton & Strick, 2000; Pascual-Leone, Wassermann, Grafman, & Hallett, 1996; Sakai et al., 1998). Another possible explanation for this pattern of results is a deficit in sustained attention. Indeed, previous studies have already found an association between high phenylalanine levels and reduced sustained attention in PKU (e.g., Ten Hoedt et al., 2011).

Previous studies have reported an interrelation between deficits in executive functions and slow RTs in PKU (e.g., Janos et al., 2012). The executive functions have previously been related with dopamine mechanisms that are compromised in the presence of high Phe levels (see Huijbregts et al., 2002). Although a weak relation between one of our measures (practice effect) and the color-word interference in Stroop was observed, perhaps reflecting the presence of common processes in the two tasks, further examination conducted with other (perhaps more appropriate) tests of executive functions is certainly needed to fully elucidate the exact implication of these functions in the task used in the present study.

In our study, the practice effect also correlated with the overall IQ in the group of patients. This result fits well with previous evidence suggesting lower intelligence, even in ET PKU patients under continuous dietary control, and an association between general IQ and deficits in different aspects of cognition (e.g., executive functioning and processing speed; see Albrecht et al., 2009; Christ et al., 2010). Although caution is needed when interpreting nonsignificant correlations in relatively small samples, the absence of correlation between the RTs in our visuomotor task and the latency of the P1 VEP indicates that the slowness observed at a behavioral level may not be associated with slowness in processing the visual stimuli that guided the participants’ responses.

The results of the present study also suggest that the response slowness observed in the ET PKU group does not correlate with the performance in a simple neuropsychological test for motor function (i.e., the FTT). Taken together, the slower RTs observed in the visuomotor task, and the fact that most of the participants with ET PKU (89%) did not present altered results in the FTT, may perhaps suggest that the motor slowness is more prevalent, in ET PKU, in tasks that involve more than one response option and action control to some extent.

A limitation of our study is the fact that several measures included in our study (Stroop interference, FTT, K-BIT, VEPs) were only available for the ET PKU group. This prevented us from performing full between-group and covariate analyses for all of the variables included in our study. It is therefore necessary to be cautious in interpreting some of the results that we obtained. More research is needed to further understand the nature of the subtle deficits in visuomotor coordination and their possible relation with the presence of unbalanced levels of phenylalanine and dopamine in certain areas of the brain. Another limitation of the study is the fact that the hypotheses regarding the possible brain structures (and their functions) that we propose to explain our results are necessarily speculative and need to be further tested in other studies, perhaps using neuroimaging.

In conclusion, a novel task was employed, in the present study, to assess possible visuomotor alterations in ET PKU patients. Our results confirm the presence of movement slowness and also reveal difficulties in improving performance in a visuomotor task by means of immediate practice. These difficulties seem to be (a) associated with temporary increases in Phe level and (b) partially mediated by high-order (not purely motor) mechanisms, as the mild correlation observed between one of our measures and a particular measure of the Stroop test suggests.
Disclosure statement
No potential conflict of interest was reported by the authors.

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