A lifetime with Phenylketonuria
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Is BRIEF a useful instrument in day to day care of patients with Phenylketonuria?

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ABSTRACT

Objectives. Despite early and continuous treatment many patients with phenylketonuria (PKU) still experience neurocognitive problems. Most problems have been observed in the domain of executive functioning (EF). For regular monitoring of EF, the use of the Behavior Rating Inventory of Executive Function (BRIEF) has been proposed. The aim of this study was to investigate whether the BRIEF is indeed a useful screening instrument in monitoring of adults with PKU.

Study design. Adult PKU patients (n = 55; mean age 28.3 ± 6.2 years) filled out the BRIEF-A (higher scores = poorer EF) and performed computerized tasks measuring executive functions (inhibition, cognitive flexibility, and working memory). The outcome of the BRIEF-A questionnaire was compared with neurocognitive outcome as measured by three tasks from the Amsterdam Neuropsychological Tasks (ANT).

Results. Forty-two percent of the PKU patients scored in the borderline/clinical range of the BRIEF-A. Six of the 55 patients (11%) scored >1 SD above the normative mean, mostly on the Metacognition Index. With respect to ANT measurements, patients mainly showed deficits in inhibitory control (34-36%) and cognitive flexibility (31-40%) as compared to the general Dutch population. No significant correlations between the two methods were found, which was confirmed with the Bland-Altman approach where no agreement between the two methods was observed. Only with respect to inhibitory control, patients scored significantly worse on both BRIEF-A and ANT classifications. No other associations between classification according to the BRIEF-A and classifications according to the ANT tasks were found.

Conclusions. Patients reporting EF problems in daily life are not necessarily those that present with core EF deficits. The results of this study suggest that regular self-administration of the BRIEF-A is not a sufficient way to monitor EF in adult PKU patients.
1. INTRODUCTION

Phenylketonuria (PKU; OMIM 261600) is an inborn error of phenylalanine metabolism (Blau, van Spronsen, & Levy, 2010; van Spronsen, 2010), affecting about 1 in 18,000 newborns in The Netherlands (Verkerk, 1995). PKU is caused by a mutation within the gene encoding the hepatic enzyme phenylalanine hydroxylase (PAH), normally converting phenylalanine (Phe) into tyrosine (Tyr). Biochemically, the defect is characterized by increased blood and tissue concentrations of Phe and normal to decreased Tyr concentrations.

Untreated PKU is characterized by neurological and behavioural problems, such as severe mental retardation, epilepsy, developmental delays, and anxiety disorders (de Groot, Hoeksma, Blau, Reijngoud, & van Spronsen, 2010; Smith & Knowles, 2000). Outcome is clearly related to blood Phe concentrations (Koch et al., 2002; Waisbren et al., 2007). Since the introduction of the neonatal screening for PKU in 1974 in The Netherlands, early diagnosis and treatment are feasible and have reduced most of the neurological problems (Blau et al., 2010).

Current treatment mainly consists of a Phe-restricted diet reducing the intake of natural protein with, in addition, a synthetic amino acid mixture devoid of Phe and enriched with Tyr. Some patients benefit from large doses of the natural cofactor of PAH by treatment with tetrahydrobiopterin (BH$_4$) (Blau et al., 2010). Even with early and continuous treatment and Phe levels within the target range, PKU patients still score 4-8 IQ points lower and present with neurocognitive, social, and emotional problems compared to the general population (Anastasoaie, Kurzius, Forbes, & Waisbren, 2008; Christ, Huijbregts, de Sonneville, & White, 2010; DeRoche & Welsh, 2008). Most problems in PKU patients have been observed in the domain of executive functions (EF) (van Spronsen, Huijbregts, Bosch, & Leuzzi, 2011).

EF encompasses complex brain processes responsible for the management of neurocognitive functions, which control goal-oriented behaviour and problem solving abilities. Problems with EF can express themselves in decreased concentration, learning problems, impulsivity, and inappropriate behaviour due to alterations in the prefrontal cortex and associated brain regions (Anderson et al., 2007; Antenor-Dorsey et al., 2013; van Spronsen et al., 2011). An article of Waisbren and White in this journal [MGM] suggested the Behavior Rating Inventory of Executive Function (BRIEF) as a reliable screening method to identify and monitor aspects of daily executive dysfunctioning in patients with PKU (Waisbren & White, 2010). The BRIEF is an easy and frequently used standardized questionnaire to assess executive functioning and can also be administered by non-psychologists. However, there is little agreement about the domains of impairment in studies with early-treated PKU patients using the BRIEF (Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002;
Antshel & Waisbren, 2003; Sharman, Sullivan, Young, & McGill, 2009), while there is also only one known study that has compared the BRIEF with neuropsychological measurements of EF in PKU (Anderson et al., 2002). In that study four different EF measures (i.e. Contingency Naming Test, Rey Complex Figure, Tower of London, and Controlled Oral Word Association Test) were compared with scales of the BRIEF. Only very modest correlations between the BRIEF and scores on these paper-and-pencil tasks were shown, indicating that different constructs within EF were measured.

Therefore, in the current study we compared the BRIEF-A questionnaire with neurocognitive outcome as measured by the Amsterdam Neuropsychological Tasks (ANT; De Sonneville, 2014), a computerized test battery that has been used in a series of studies examining neurocognitive functioning in early and continuously treated PKU patients of different ages (De Sonneville, L. M. J., 1999; De Sonneville, Schmidt, Michel, & Batzler, 1990; Huijbregts, de Sonneville, Licht, Sergeant, & van Spronsen, 2002; Huijbregts, de Sonneville, Licht, van Spronsen, & Sergeant, 2002; Huijbregts et al., 2002; Huijbregts, de Sonneville, van Spronsen, Licht, & Sergeant, 2002; Huijbregts et al., 2003; Jahja et al., 2013; Jahja, Huijbregts, de Sonneville, van der Meere, & van Spronsen, 2014; ten Hoedt et al., 2011). The ANT has consistently shown Phe-related EF problems in PKU. However, performing the ANT is time consuming and the test battery can only be administered by trained professionals. This, in turn, may be particularly problematic for adults with PKU, who generally visit the clinic less frequently than children. Therefore, a questionnaire such as the BRIEF, which is relatively easy and quick to fill out, and which is able to signal EF problems, could indicate whether more intensive and specific neuropsychological testing is required. The central, underlying question of this study is whether the BRIEF-A is a useful screening or monitoring instrument in day to day care of adults with PKU.

2. MATERIAL AND METHODS

2.1 Participants
Fifty-five Dutch adult PKU patients (25 male, 30 female) participated in this study. All patients were born after introduction of the neonatal screening in The Netherlands in 1974 and were screened for PKU within one week after birth. Patients were treated early (< 1 month after birth) and continuously, at least up to 12 years of age. In The Netherlands, target Phe concentrations between 120 and 360 µmol/L are recommended for the first 12 years of life, however during adolescence and adulthood most patients exceeded the recommended upper target Phe concentrations. The average age of the patients was 28.3 years (SD 6.2 years, range 18.7 to 40.0 years).
Concurrent Phe (658 ± 347, range 66-1550 µmol/L) and Tyr (50 ± 18, range 24-94 µmol/L) concentrations on the day of testing were available for 53 out of 55 patients. All patients met the National Institutes for Health (NIH) diagnostic criteria for hyperphenylalaninemia (HPA) or PKU. Treatment consisted of a Phe-restricted diet and/or BH₄ administration. Patients with IQ below 80, medical conditions other than PKU with known effects on neurocognitive and social functioning or usage of medication that could influence neurocognitive functioning were excluded from participation in this study.

Patients from six university medical centres in The Netherlands were included: University Medical Centre Groningen, Academic Medical Centre Amsterdam, Maastricht University Medical Centre, Radboud University Medical Centre Nijmegen, Erasmus University Medical Centre Rotterdam and University Medical Centre Utrecht. This study is part of the PKU-COBESO study, which examines COgnitive functions, BEhavioural problems and SOcial functioning in early and continuously treated PKU patients in relation to metabolic control (Jahja et al., 2013). National approval has been given by the medical ethics committee of the University Medical Centre Groningen in The Netherlands and the study has been registered in the CCMO Register (NL38932.042.11). Participants gave written informed consent to participate in the study after procedures had been fully explained. All procedures were performed according to standardized protocols.

2.2 Measurements
The Behavior Rating Inventory of Executive Function - Adult version (BRIEF-A) was used to measure executive functioning in daily life of the adult PKU patients (Roth, Isquith, & Gioia, 2005). The questionnaire consists of 75 questions, assessing nine subdomains of executive functioning: Inhibit, Shift (Cognitive Flexibility), Emotional Control, Self-Regulation, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor. The four subdomains Inhibit, Shift, Emotional Control and Self-Regulation together determine the Behavioural Regulation Index (BRI). Furthermore, the combined scores of the other five mentioned executive functions represent the Metacognition Index (MI). The Global Executive Composite (GEC) is the total score of all nine subdomains and represents the overall executive functioning in daily life.

Individuals with a T-score ≤ 50 are considered to have normal executive functions based on a healthy Dutch and Flemish population between 18 and 65 years old. A T-score between 50 and 65 is regarded as increased or borderline, and a T-score above 65 indicates clinical significance (clinical range). In this study 23 out of the 55 patients (42%) had a score in the borderline/clinical range (T-score > 50). However, in order to be able to optimally compare the BRIEF-A and the ANT, a score of 1 SD
above the normative mean was used for both tests in our main analyses. Thus, for these analyses a T-score ≥ 60 was used to make a distinction between patients with normal EF and patients with problems in executive functioning.

For the present study, three tasks from the computerized test battery ANT were included to measure the executive functioning of the participants in a ‘laboratory’ setting. The following tasks were included in this study: Shifting Attentional Set Visual (SSV), Sustained Attention Dots (SAD), and Feature Identification (FI). These tasks assessed the three core EF: inhibition (SSV, SAD), cognitive flexibility (SSV), and working memory (FI) (van Spronsen et al., 2011).

The Shifting Attentional Set Visual (SSV) measured inhibition of prepotent responses and cognitive flexibility. On the screen appeared a horizontal bar in which a coloured square moved from left to right or vice versa. In the first part a compatible response should be made, in the second part an incompatible response should be given, and in part three both conditions were randomly combined.

In the Sustained Attention Dots (SAD) task, 600 patterns of 3, 4 or 5 dots (each 200 times) were presented on the computer screen in a random sequence. Participants had to recognize the 4-dot pattern while the 3- and 5-dot patterns had to be rejected. Incorrect responses were followed by a beep signal as feedback.

In the Feature Identification (FI), participants had to recognize a target pattern consisting of 3 x 3 white and red squares in a display consisting of four stimulus patterns. The visuo-spatial working memory was examined by varying the degree to which the separate features constituting the target and distracter patterns had to be conjoined to reach a decision.

A more detailed description of the tasks can be found in Jahja et al. (2013) and Huijbregts et al. (2002).

The mean reaction time and number of errors were determined for each ANT task separately, and were expressed as Z-scores based on the mean of the healthy population. To better interpret the study findings regarding associations between the BRIEF-A and the ANT, the ANT Z-scores were converted into T-scores. Also two groups were composed for the ANT assessment, where again (as in BRIEF) a T-score ≥ 60 (1 SD above mean) was considered as an increased (i.e. poorer) score on executive functioning (De Sonneville, 2014).

2.3 Statistical analysis

Four different approaches were adopted to establish the degree of agreement between the BRIEF-A and the ANT tasks. Patients were divided into two groups based on a T-score ≥ 60 for both the BRIEF-A and for each ANT task. The Z-scores of the ANT tasks were converted into T-scores by using an arithmetic transformation T = 10(Z) + 50, where a T-score of 60 is 1 SD above the mean.
The SSV consists of three parts, for each part the mean reaction time and number of errors were recorded. Inhibition was represented by the difference in mean reaction time and number of errors between task parts 2 and 1, and cognitive flexibility by the difference in reaction time and error rate between parts 3 and 1 (Jahja et al., 2014). For the SAD and FI the mean reaction time and total number of errors were used as measures for speed and accuracy of task performance (inhibitory control and working memory, respectively). Next, the following analyses were performed:

1) Correlations between the BRIEF-A and neurocognitive outcomes of the ANT were studied with Spearman’s Rank Order correlation analysis.

2) Comparisons of ANT outcome between patients within the BRIEF-A normal range and patients with increased scores on the questionnaire were, in case of normal distribution, made using Independent Samples T-test. In case of non-normal distributions the Mann-Whitney U-test was performed.

3) In order to investigate overlap between classification according to the BRIEF-A and classification according to the ANT tasks, Chi-square tests were performed. If the assumptions of the Chi-square test concerning the minimum expected cell frequency were violated, the Fisher’s Exact Test was used.

4) Finally, the Bland-Altman approach was chosen to assess the level of agreement between the two methods by using T-scores. The mean differences between the two methods of measurement and 95% limits of agreement (1.96 SD) were calculated. The one-sample T-test was used to test the null-hypothesis and see whether the difference between the variables was equal to 0. In case of a significant result, there was no agreement between the methods (null hypothesis rejected). How well the two methods of measurement agree depends on the range between the two limits: the smaller the range the better the agreement (Bland & Altman, 1986). To control for proportional bias linear regression was performed.

A threshold of $\alpha < 0.05$ was considered to be statistically significant. Data are expressed as mean ± SD and range, unless stated otherwise. Statistics were performed with IBM SPSS Statistics 20.

3. RESULTS

Twenty-three of the 55 patients (42%) scored in the borderline/clinical range of the BRIEF-A with a T-score > 50, of whom three reached the clinical range. Twenty-two (40%) patients reached the borderline/clinical range on the BRI and 29 (53%) patients on the MI. As measured by the ANT, patients showed mainly problems on the domains inhibitory control (SAD) and cognitive flexibility (SSV) compared to the healthy population (see Table 1). For subsequent statistical analyses, groups based
on BRIEF-A GEC scores were formed using a cut-off T-score of ≥ 60 (>1 SD above normative mean) in order to obtain comparable distributions for BRIEF-A and ANT-scores. Six of the 55 (11%) patients had an increased score on the GEC of the BRIEF-A, 10 on the MI and 6 on the BRI. No significant differences for age, gender, and IQ were found between the two groups.

Historical and concurrent Phe concentrations did not significantly differ between the two groups either. Demographical and clinical characteristics of the PKU patients for each group are shown in Table 2.

<table>
<thead>
<tr>
<th>Table 1. Amsterdam Neuropsychological Tasks (ANT) classifications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANT tasks</strong></td>
</tr>
<tr>
<td>FI</td>
</tr>
<tr>
<td>Mean reaction time</td>
</tr>
<tr>
<td>Number of errors</td>
</tr>
<tr>
<td>SAD</td>
</tr>
<tr>
<td>Mean reaction time</td>
</tr>
<tr>
<td>Number of errors</td>
</tr>
<tr>
<td>SSV Inhibition</td>
</tr>
<tr>
<td>Mean reaction time</td>
</tr>
<tr>
<td>Number of errors</td>
</tr>
<tr>
<td>SSV Cognitive Flexibility</td>
</tr>
<tr>
<td>Mean reaction time</td>
</tr>
<tr>
<td>Number of errors</td>
</tr>
</tbody>
</table>

When data analyses were performed within the continuous scores on ANT and BRIEF-A, no significant correlations between GEC, MI, and BRI scores, and performance of the three ANT tasks were found.

Comparing ANT performance between the two BRIEF-A groups, showed that the group with higher (i.e. poorer) BRIEF-A scores had a significantly slower mean reaction time on the SAD ($p = 0.040$). No significant differences were observed on the other ANT tasks. The outcomes of the three ANT tasks for BRIEF-A groups are presented in Table 3. Note that ANT scores (median + range) are also presented for when a cut-off of T > 50 was used to form groups based on BRIEF: no significant group differences were observed when this cut-off was used either.

In order to find out whether patients in the “problem group” of the BRIEF-A (GEC, MI, and BRI) were also the patients who showed EF deficits on the ANT, the Chi-square test and Fisher’s Exact Test were performed. Patients in the problem
group based on GEC score also had significantly increased T-scores (≥ 60) on the mean reaction time of the SAD \( (p = 0.015) \). No significant overlap in classifications was found with ANT working memory, ANT inhibitory control as measured by SSV, and ANT cognitive flexibility. No significant results were found either when looking at the clinical/borderline range of the BRIEF-A with T > 50.

**Table 2. Overview of demographical and clinical characteristics of the PKU patients, groups based on T-scores of on Global Executive Composite (GEC) of BRIEF-A**

<table>
<thead>
<tr>
<th></th>
<th>T&lt;60</th>
<th>T≥60</th>
<th>( p^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>n = 49</td>
<td>n = 6</td>
<td></td>
</tr>
<tr>
<td>Mean Age in years</td>
<td>28.4 ± 6.2</td>
<td>28.2 ± 6.7</td>
<td>0.944</td>
</tr>
<tr>
<td></td>
<td>(18.7-40.0)</td>
<td>(20.6-39.1)</td>
<td></td>
</tr>
<tr>
<td>Gender M/F</td>
<td>23/26</td>
<td>2/4</td>
<td>0.427</td>
</tr>
<tr>
<td>IQ(^1)</td>
<td>101.3 ± 11.0</td>
<td>98.3 ± 15.5</td>
<td>0.554</td>
</tr>
<tr>
<td></td>
<td>(80-125)</td>
<td>(80-118)</td>
<td></td>
</tr>
<tr>
<td>Phe at diagnosis (μmol/L)</td>
<td>1549 ± 1003</td>
<td>1502 ± 1088</td>
<td>0.935</td>
</tr>
<tr>
<td></td>
<td>(120-3900)</td>
<td>(520-2462)</td>
<td></td>
</tr>
<tr>
<td>Phe at testing day (μmol/L) (blood spot)</td>
<td>662 ± 355</td>
<td>628 ± 313</td>
<td>0.822</td>
</tr>
<tr>
<td></td>
<td>(66-1550)</td>
<td>(262-1010)</td>
<td></td>
</tr>
<tr>
<td>Tyr at testing day (μmol/L) (blood spot)</td>
<td>51 ± 18</td>
<td>50 ± 14</td>
<td>0.897</td>
</tr>
<tr>
<td></td>
<td>(25-94)</td>
<td>(24-65)</td>
<td></td>
</tr>
<tr>
<td>Phe lifetime (μmol/L)</td>
<td>445 ± 149</td>
<td>479 ± 186</td>
<td>0.788</td>
</tr>
<tr>
<td></td>
<td>(221-882)</td>
<td>(321-684)</td>
<td></td>
</tr>
</tbody>
</table>

\(^{1}\)Wechsler Adult Intelligence Scale (WAIS III)
\(^{2}\)Independent Samples T-test or Mann-Whitney U-test were used depending on the distribution

The Bland-Altman approach was used to assess the level of agreement between the two measurements. The mean differences between the BRIEF-A and ANT did not significantly differ from 0 for four of the eight variables (number of errors for FI, SAD, SSV inhibition and cognitive flexibility), which indicates that that the null-hypothesis could not be rejected and that there is possibly some agreement between BRIEF and these three ANT tasks. However, no evident agreement between the two methods could be observed with the Bland-Altman, because the ranges of the 95% limits of agreement were broad. In addition, all three tasks showed proportional bias, which also indicates that no agreement between the BRIEF-A and different ANT tasks was observed.
Table 3. ANT outcome in groups based on Global Executive Composite of BRIEF-A outcome

<table>
<thead>
<tr>
<th></th>
<th>Normal range T≤50 BRIEF-A n = 32</th>
<th>Borderline / Clinical range T&gt;50 BRIEF-A n = 22</th>
<th>Normal range T&lt;60 BRIEF-A n = 49</th>
<th>Increased scores T≥60 BRIEF-A n = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRIEF-A GEC</td>
<td>91.5 (31.0)</td>
<td>114.0 (63.0)</td>
<td>100.0 (50.0)</td>
<td>139.0 (40.0)</td>
</tr>
<tr>
<td>BRIEF-A MI</td>
<td>38.5 (23.0)</td>
<td>49.0 (35.0)</td>
<td>58.0 (32.0)</td>
<td>82.0 (23.0)</td>
</tr>
<tr>
<td>BRIEF-A BRI</td>
<td>51.0 (24.0)</td>
<td>68.0 (37.0)</td>
<td>41.0 (26.0)</td>
<td>57.5 (20.0)</td>
</tr>
<tr>
<td>FI</td>
<td>Mean reaction time (ms) 1193 (1134)</td>
<td>1212 (1113)</td>
<td>1186 (1134)</td>
<td>1497 (1010)</td>
</tr>
<tr>
<td>Number of errors</td>
<td>5.0 (19.0)</td>
<td>6.0 (22.0)</td>
<td>5.0 (22.0)</td>
<td>6.5 (8.0)</td>
</tr>
<tr>
<td>SAD</td>
<td>Mean reaction time (ms) 709 (625)</td>
<td>794 (486)</td>
<td>717 (625)</td>
<td>828 (168)</td>
</tr>
<tr>
<td>Number of errors</td>
<td>25.5 (65.0)</td>
<td>21.0 (46.0)</td>
<td>22.0 (68.0)</td>
<td>20.0 (40.0)</td>
</tr>
<tr>
<td>SSV Inhibition</td>
<td>Mean reaction time (ms) 260 (956)</td>
<td>240 (1207)</td>
<td>259 (956)</td>
<td>142 (1207)</td>
</tr>
<tr>
<td>Number of errors</td>
<td>0.5 (22.0)</td>
<td>1.0 (24.0)</td>
<td>1.0 (24.0)</td>
<td>0.5 (9.0)</td>
</tr>
<tr>
<td>SSV Cognitive Flexibility</td>
<td>Mean reaction time (ms) 537 (1225)</td>
<td>552 (819)</td>
<td>538 (1225)</td>
<td>685 (598)</td>
</tr>
<tr>
<td>Number of errors</td>
<td>3.5 (39.0)</td>
<td>2.0 (23.0)</td>
<td>3.0 (39.0)</td>
<td>4.0 (10.0)</td>
</tr>
</tbody>
</table>

ANT: Amsterdam Neuropsychological Tasks; BRIEF-A: Behavior Rating Inventory of Executive Function Adults; FI: Feature Identification; SAD: Sustained Attention Dots; SSV: Shifting Attentional Set Visual. Data expressed as median (range)

4. DISCUSSION

As problems with EF such as decreased attention and learning problems are still present in treated PKU patients, we investigated whether the BRIEF-A is a useful screening instrument in monitoring PKU patients with respect to EF deficits. The outcome of the BRIEF-A questionnaire was compared with neurocognitive outcome as measured by the computerized test battery ANT. Three main findings can be determined. Firstly, on the BRIEF-A 42% of the patients scored in the borderline/clinical range (T-score > 50), however only 11% of the PKU patients showed scores ≥ 1 SD. Most of the deficits were observed in the Metacognition Index. In the ANT, in the same population, PKU patients showed mainly problems in inhibitory control (34-36%) and cognitive flexibility (31-40%) compared to the average healthy Dutch population.

When comparing ANT and BRIEF outcomes, no significant correlations were found. This was confirmed with the Bland-Altman approach. Moreover, patients in the “problem group” of the BRIEF-A only had a significantly increased score on the
ANT task SAD (which measures inhibitory control). This was also the only ANT task for which group classification ((T < 60 vs. T ≥ 60) showed significant overlap with classification according to BRIEF scores (T < 60 vs T > 60). No significant overlap was found with the other ANT tasks. We will first address some methodological issues before discussing the results in more detail.

First, only adult patients between 18 and 40 years old were included in this study, therefore only the BRIEF-A was taken into account. In general, the prefrontal cortex and associated brain regions responsible for the executive functions reach adult levels around the age of 20 years (Tau & Peterson, 2010). It would therefore be interesting to also include children and adolescents, as the associations between questionnaire scores and neuropsychological tasks measuring EF may be different at different maturational stages. Second, in this study we used only self-report from the BRIEF-A, however individuals with PKU, and particularly those with EF problems, may have difficulty monitoring their own performance. It would be interesting to also include informant reports of the BRIEF-A. A strength of the current study is that we used both categorical and continuous approaches for our statistical analyses. A disadvantage of the sole use of the categorical approach would have been that it reduces variance in the data, thereby limiting the possibility of finding significant associations between BRIEF and ANT scores. Therefore, continuous and semi-continuous approaches were also used. An advantage of the categorical approach compared to a continuous approach is that conclusions can be drawn with respect to actual borderline or clinical range EF problems in PKU.

As noted, a relatively high number of PKU patients scored in the borderline/clinical range, however a small group scored more than 1 SD above the mean of the BRIEF-A, where most deficits were observed in the Metacognition Index (initiate, working memory, plan/organize, organization of materials, and monitor). Studies to date show little consistency with respect to the domains of impairment, as revealed by the BRIEF, in early treated PKU patients. Sharman et al. (2009) found similar results: the study identified problems in the subdomains of working memory, planning and organizing, monitoring, and initiation. A study of Antshel & Waisbren (2003) reported significantly lower scores on the Metacognition Index in children with PKU compared to healthy controls, while (Anderson et al., 2002) only found impairments in subdomains of shifting and monitoring.

Despite the lack of consistency among (specific) results of the different studies, the BRIEF-A appears to pick up some form of executive dysfunction on each occasion. One could argue that more specific assessment would be required subsequently. Although, in order to find more evidence for this way to proceed (i.e. in order to draw such a conclusion), larger studies with more patients would be required showing a significant level of agreement between questionnaire and test outcomes.
The next question would be which instruments are appropriate to be used to this end. ANT tasks seem to be a good choice in this respect, as they are able to pick up very specific, core EF deficits, as they have consistently done in groups of PKU patients in the past (De Sonneville, 1999; De Sonneville et al., 1990; Huijbregts et al., 2002; Huijbregts et al., 2002; Huijbregts et al., 2002; Huijbregts et al., 2002; Huijbregts et al., 2003; Jahja et al., 2013; Jahja et al., 2014; ten Hoedt et al., 2011). In the present study, the ANT showed that a significant proportion of adult patients presented with core EF deficits. However, the lack of significant associations between BRIEF-A and ANT categorizations indicated that patients reporting EF problems in daily life are not necessarily the ones that present with core EF deficits. Earlier studies examining the overlap between questionnaire measures of EF in daily life and core EF tasks in PKU (not using the specific combination BRIEF-ANT) also found no or only very modest correlations (Anderson et al., 2002; Channon, Mockler, & Lee, 2005). Thus, it seems doubtful whether the BRIEF-A (and possibly other questionnaires) can be used as the sole screening instrument to pick up core EF deficits in PKU. At the very least there should be different informants, as patients with core EF deficits might be unable to accurately fill out such questionnaires because of a lack of insight in their functioning. Self-administration of such questionnaires could also lead to clinicians missing patients who should actually be monitored more intensively. As EF in daily life is also important and has been shown to be related to Phe levels (Anderson et al., 2002; Antshel & Waisbren, 2003; Sharman et al., 2009), a new method for regular screening and monitoring should not necessarily discard the use of questionnaires. These should however be filled out by for example partners, family members, or friends (perhaps even colleagues, supervisors, etc.), and could very well be shortened (as the separate dimensions do not seem sufficiently informative, at least not in PKU patients). Such questionnaires could be supplemented with short (widely accessible) neuropsychological tasks tapping into core executive abilities. Many different tasks reliably measuring core EF are available, and it is possibly necessary to administer different tasks at different time points as well. From the present data it is concluded that regular self-administration of the BRIEF-A is not a sufficient way to monitor all aspects of EF in adult PKU patients.
Is BRIEF a useful instrument in day to day care of patients with PKU?

REFERENCES


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