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Executive functioning, adaptive skills, emotional and behavioral profile: A comparison between autism spectrum disorder and phenylketonuria

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ABSTRACT

Introduction: Influential theories maintain that some of Autism Spectrum Disorder (ASD) core symptoms may arise from deficits in executive functions (EF). EF deficits are also considered a neuropsychological marker of early treated individuals with phenylketonuria (PKU). Aims of this study were: to verify the occurrence and patterns of specific EF impairments in both clinical groups; to explore the coexistence of EF alterations with adaptive, behavioral and emotional problems in each clinical condition.

Material and methods: We assessed EF, adaptive, behavioral and emotional profile in 21 participants with ASD, 15 early treated PKU individuals, comparable for age and IQ, and 14 controls, comparable for age to the clinical groups (age range: 7–14 years).

Results: ASD and PKU participants presented two different, but partially overlapping patterns of EF impairment. While ASD participants showed a specific deficit in cognitive flexibility only, PKU individuals showed a more extensive impairment in EF with a weaker performance in two core EF domains (inhibition, cognitive flexibility) as compared to healthy controls. Psychological and adaptive profile was typical in PKU participants, while ASD participants experienced behavioral (externalizing symptoms), emotional (internalizing symptoms) and adaptive disorders (general, practical, social domains).

Conclusions: Present results support the view of a relative disengagement of adaptive and emotional-behavioral profile with respect to EF skills and suggest that other dysfunctions contribute to the multidimensional phenotype of ASD participants.

1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by persistent difficulties in social communication and interaction and restricted, repetitive patterns of behavior, interests or activities [1]. Levels of severity of the disorder can vary among individuals, especially as far as intellectual and language development are concerned.

Researchers have formulated several hypotheses on the nature of ASD cognitive profile. The theory of mind hypothesis suggests that ASD symptoms derive from a specific inability to attribute mental states to oneself and others [2]. Other researchers have proposed that ASD behavioral atypicalities are caused by more pervasive issues in central coherence (ability to derive overall meaning from a mass of details) [3]. Influential theories suggest that ASD symptoms, especially those belonging to the adaptive domain, may arise from deficits in EF [4,5]. Individuals with ASD indeed have difficulties in exerting control in novel or ambiguous situations, which require inhibiting responses, manipulating information during a task and changing their strategies.

EF include a set of cognitive control processes that manage lower functions to regulate goal-directed behaviors [6,7] and are responsible for guiding and managing cognitive, emotional and behavioral functions, especially during active problem solving [8]. There is general agreement about three core EF: inhibition (the ability to control one's

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attention, behavior, thoughts and emotions to complete the appropriate or necessary action, ignoring a strong internal impulse or an external stimulus), working memory (WM) (the ability to maintain and actively manipulate information) and cognitive flexibility (the ability to adapt to new demands, opportunities or needs, to switch from one set of responses to another -set-shifting- and to modify one's strategies according to the changed environmental conditions) [9–11]. Higher-order EF (i.e. problem solving and planning) are built from the core EF [12,13]. The ability to control attention can also be considered as part of EF [14]. EF emerge during the first years of life and continue to strengthen throughout childhood and adolescence, each component following its developmental trajectory [15,16].

EF in ASD have been extensively explored and a number of studies have focused specifically on school age children. Previous studies on inhibition in children with ASD found an impairment in inhibition of irrelevant distractors but not of prepotent responses [17,18], whereas other studies revealed significant impairments in the inhibition of prepotent responses [19]. Results on cognitive flexibility in children with ASD are not always consistent: some studies found an impairment [20–24], while others did not [24]. A domain of EF often found impaired in children with ASD is planning [19,20]. Verbal WM appears relatively intact in some studies [25,26], and deficient in others [23]. Finally, a number of studies found attention deficits in children with ASD [27,28] differently from others detecting typical levels of attention in ASD participants [29].

As well as EF, also adaptive behavior, frequently impaired in individuals with ASD [30], plays an important role in the achievement of positive functional outcomes. Adaptive behavior refers to the ability of a person to meet his or her personal needs and to deal with the demands in his or her environment [31], it includes a group of skills that allow individuals to function effectively in different life contexts (i.e. home, school, community etc) [32]. A number of studies suggested that EF might contribute to adaptive behavior by means of self-regulation of social and emotional processes [33,34].

Even though the number of people with ASD achieving independence as adults has increased over the years, they are far from being the majority yet [35,36]. Some authors maintain that EF might be one of the sources of heterogeneity in adaptive outcomes of people with ASD [37].

For instance, Panerai and coworkers [38] showed an association between cognitive flexibility and planning deficits and adaptive behavior problems, especially in socialization. Beyond cognitive difficulties, there is general agreement about emotional and behavioral difficulties in ASD [39–41]. A number of studies have investigated the relationship between EF and emotional symptoms: Cederlund and colleagues [42] found that depressive difficulties and EF impairments often co-occur in adolescents with ASD and Hollocks and colleagues [43] found a relationship between EF and anxiety symptoms. These authors hypothesize that anxiety in ASD may be driven by difficulties in executive, top-down control of attention, as reported in pediatric anxiety disorders [44,45]: poorer top-down control may lead to increased cognitive biases, associated with anxiety in the non-ASD adolescent population [46]. Reduced cognitive control in anxiety can be displayed through attention biases towards threatening stimuli [47]. Such biases may also be linked to difficulties in flexibly disengage from threat stimuli [48,49].

EF deficits have also been considered a specific neuropsychological marker of early treated Phenylketonuria (PKU) [50–56], starting from a very young age [57]. PKU (OMIM #261600) is caused by an inborn error of metabolism, in which early diagnosis and dietary treatment are fundamental to prevent intellectual disability [58]. By means of dietary restriction of phenylalanine, early treated PKU individuals show favorable clinical outcomes, compared with late or untreated ones, although there is still evidence of a lower Intelligence Quotient (IQ) and minor neuropsychological and psychiatric problems [50,59–64]. Children and adolescents with PKU (age range: 7–20 years) often show impairments in inhibition [52,65], WM [52], planning, problem-solving, attention [53,65,66], and cognitive flexibility [60,67]. Additionally, a higher incidence of anxiety, depressive symptoms, social isolation, physical complaints and hyperactivity has been reported in children and adolescents with PKU [68–70]. Conversely, results of other studies highlighted the absence of internalizing and externalizing difficulties in children and adolescents with PKU [71,72].

The possible co-occurrence of EF deficits and adaptive impairments has not been extensively investigated[73,74], while a concurrence of EF deficits and internalizing symptoms was found in children with PKU [75].

ASD and PKU, although very different clinical conditions, share a number of similarities, taking into account the neuropsychological profile. First of all, it should be noted that untreated PKU individuals usually show autistic features besides intellectual impairment [76–78]. Secondly, ASD and PKU, share a specific weakness in EF. If behavioral and emotional difficulties present in ASD originate, at least partially, from EF deficits, we would expect that clinical groups with comparable EF deficient profiles should present similar behavioral and emotional patterns.

The presence of differences in consistency, severity and profile of EF impairments in distinct disorders is linked to the so-called “discriminant validity” concept [5]: specific types of executive deficits may be associated with specific developmental disorders [20]. Comparing neurodevelopmental disorders with very different behavioral features, but similar neuropsychological deficits, can help to explore the nature of such deficits. For instance, Bisiacchi, Mento, Tarantino and Burlina [79] compared the neuropsychological profile of PKU participants with HIV-affected age-matched children and adolescents, two diseases with different etiologies and pathophysiological mechanisms, both resulting in direct and indirect effects on central nervous system. The authors reported that, although all participants had a normal global functioning, PKU and HIV groups showed lower performance in WM and attentional shifting than typically developing controls, with more widespread and severe impairments in children with HIV.

Stevenson and McNaughton [80] explored the phenotypic overlap between PKU and ADHD. By reviewing the existing literature, they hypothesize that the EF impairments (especially in WM, planning, and inhibition), found in PKU children as well as in children with ADHD, may result from two vastly different etiologies that converge on a specific core phenotype including similar dysfunctions of Gray's Behavioral Inhibition System [81], coupled with other disorder-specific dysfunctions. Comparisons of the commonalities and differences between EF deficits in different clinical conditions can allow greater understanding of the neuropsychology of the single disorders. EF deficits are indeed a correlate and possibly one of the causes of the disruptions in complex behavior detected in several developmental disorders [5]. The influence of high cognitive dysfunctions on the emotional-behavioral profile has yet to be clarified and could be disorder-specific.

In order to unravel the connection between neuropsychological impairment and behavioral disorders we compared EF, adaptive behavior and behavioral-emotional symptoms in children with ASD without accompanying intellectual impairment, children with early treated PKU and controls. Evidence for the presence of similar emotional and behavioral problems in PKU, as compared to ASD, is currently limited. Therefore, we compared these groups to investigate whether cognitive, emotional, behavioral and adaptive profiles of the two clinical conditions overlapped. We intended to explore if similar EF deficits in both groups corresponded to similar emotional, behavioral and adaptive problems.

Aims of this study were: to verify the occurrence and patterns of specific EF impairments (inhibition, cognitive flexibility, verbal WM, planning and attention) in both clinical groups and to explore the coexistence of EF alterations with adaptive, behavioral and emotional problems in each clinical condition.

Table 1
Demographic and biochemical characteristics of the PKU sample.

Patient ID	Age (years/months)	Sex	IDC (μmol/L)	Phe at the day of the examination (μmol/L)
1	13/2	M	370	268
2	8/5	F	278	116
3	13/4	F	390	420
4	8/2	F	315	308
5	8/9	F	252	356
6	14/0	M	397	207
7	8/11	M	339	167
8	10/11	F	260	345
9	10/3	M	355	350
10	10/7	F	315	397
11	10/2	M	330	265
12	8/4	F	320	255
13	7/8	M	275	282
14	13/8	M	385	326
15	8/1	M	298	273

Abbreviations: IDC = Index of Dietary Control, calculated as the mean Phe of all yearly medians.

2. Material and methods

2.1. Participants

Participants of both clinical groups (21 ASD and 15 PKU participants) were outpatients of the Department of Human Neuroscience, Child Neurology and Psychiatry Unit, Sapienza University of Rome. Inclusion criteria were: a) age ranging from 7 to 14 years; b) absence of intellectual disability, as explored by IQ measurement with Wechsler scales [82]. PKU participants were early diagnosed by neonatal screening program (first two weeks of life) and early and continuously treated (phenylalanine restricted diet only, see Table 1 for details).

ASD participants were diagnosed after a comprehensive multi-disciplinary assessment with a child psychiatrist and psychologist, in accordance with international diagnostic criteria (DSM-5) [1]. ASD symptoms were evaluated using ADOS-2 [83], gold standard test for autism spectrum assessment. The mean severity level of the disorder, calculated through ADOS-2 comparison score [83], was in the moderate range (mean = 7,19; sd = 1,63). The comparison score ranges from 1 to 10: 1 indicates minimal-to-no evidence of autism-related symptoms and 10 indicates a high level of impairment. Fourteen controls (age range 7–14) were recruited from city schools: they did not report neurodevelopmental, genetic or chronic diseases, or previous specialist consulting related to difficulties in neuropsychological or psychopathological areas, and had no school problems. To reduce the number of sessions, IQ was not assessed in control group (CG) participants (only Working Memory Index of WISC-IV was administered to CG participants to complete the executive functioning assessment).

The exclusion criteria were: a) a comorbid medical condition; b) clinical evidence of consumption of drugs or medicaments interfering with neurocognitive functions.

The local ethics committee approved the study protocol. Informed written consent was obtained from participants' parents before the enrollment in the study.

Table 2 shows the demographic features of all participants and full IQs of clinical groups. IQ was assessed with WISC-IV [82]. There were no significant differences in age among the three groups (Median test: $p = .677$), nor did we find significant differences in IQ between the clinical groups (Median test: $p = .735$).

2.2. Measures

2.2.1. Executive functions

2.2.1.1. Working memory. We measured verbal WM with Working Memory Index (WMI) from WISC-IV [82]. WMI comprises two subtests: Digit Span and Letter-Number Sequencing. The Digit Span subtest includes two sections: Digit Span Forward and Digit Span Backward. In the first section the examinee is required to recall a series of numbers presented by the examiner. In the backward section, the child has to repeat the numbers presented in reverse order. The Letter-Number Sequencing subtest requires the child to recall numbers in ascending order and letters in alphabetical order from a given number and letter sequence.

We assessed the other dimensions of EF with NEPSY–II Attention and Executive Functioning domain [84], which can be administered to children from 3 to 16 years. The subtests are the following (we describe them according to the specific function assessed):

2.2.1.2. Attention. The Visual Attention subtest measures speed and accuracy in focusing and maintaining attention on target visual stimuli among other visual stimuli, whereas the Auditory Attention subtest assesses selective auditory attention and the ability to sustain it (vigilance).

2.2.1.3. Inhibition. Inhibition assesses the ability to inhibit automatic responses in favor of novel responses. It provides an inhibition combined score which takes into account both speed and accuracy of the performance. Speed and accuracy can also be analyzed separately as the subtest provides an Inhibition-time score and an Inhibiton-error score.

2.2.1.4. Cognitive flexibility. Switching tests the ability to switch between response types. It provides a Switching-time score, a Switching-error score and a switching combined score.

Response Set subtest assesses the ability to shift and maintain a new and complex set. The child listens to a series of words and touches the appropriate circle (matching or contrasting) when he or she hears a target word.

Animal Sorting subtest assesses the ability to formulate basic concepts and to shift set from one concept to another. The child sorts cards into two groups using different self-initiated sorting criteria.

Finally, Design Fluency tests the child's ability to generate unique designs by connecting up to five dots, presented in two arrays: structured and random.

2.2.1.5. Planning-organization. Clocks subtest is designed to assess planning and organization, visuoperceptual and visuospatial skills and the concept of time in relation to analog clocks.

Table 2
Clinical and demographic characteristics of the sample groups.

Groups	N	Sex M	F	Age (months)					IQ				
				Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1. ASD	21	17	4	117.95	23.34	115	84	171	94.33	18.94	95	70	132
2. PKU	15	9	6	123.13	27.14	122	92	169	95.47	12.50	97	75	118
3. CG	14	6	8	122.36	23.90	118.50	91	166	–				

Abbreviations: ASD = autism spectrum disorder; PKU = phenylketonuria; CG = control group; IQ = intelligence quotient.

2.2.2. Emotional and behavioral profile

To evaluate emotional and behavioral symptoms, we used Child Behavior Checklist 6–18 (CBCL 6–18) [85], for parents of individuals between 6 and 18 years. The checklist includes 120 items. We used scores from the general scales (Internalizing Problems, Externalizing Problems and Total Problems) as indexes of emotional (internalizing) and behavioral (externalizing) problems. Validation studies of CBCL on the Italian population [86] highlighted satisfactory internal consistency and a good applicability of the instrument in the country.

2.2.3. Adaptive skills

To assess adaptive skills we used Adaptive Behavior Assessment System (ABAS-II) [32] (Parent Rating, Ages 5–21, 211 items). The questionnaire provides a comprehensive, norm-referenced assessment of the adaptive behavior of individuals from birth to age 89. It incorporates current American Association of Intellectual and Developmental Disabilities guidelines by providing composite norms for three general areas of adaptive behavior: Conceptual composite score (CCS), Social composite score (SCS) and Practical composite score (PCS). The questionnaire also provides a General Adaptive Composite score (GAC), which summarizes performance across all skill areas.

ABAS-II was standardized and validated for Italian population, showing high internal consistency, good levels of reliability and convergent and clinical validity.

Parents who completed checklists and questionnaires were 15 mothers and 6 fathers for ASD group, 11 mothers and 4 fathers for PKU group, 12 mothers and 2 fathers for CG.

2.3. Data analysis

We used SPSS 20.0 to analyze the data. We chose the Median Test [87–89], a non-parametric test useful with scale and ordinal data, for all comparisons among groups. SPSS provides pairwise comparisons when differences among groups are significant. We chose a non-parametric test because the distribution of the variables in the population is unknown.

Subtests Auditory Attention, Response Set, Clocks, Inhibition-error and Switching-error from NEPSY-II provide scores in percentile groups, which we transformed into ordinal ranks (rank 7 = above 75th percentile; rank 6: 51th - 75th percentile; rank 5: 26th - 50th percentile; rank 4: 11th - 25th percentile; rank 3: 6th - 10th percentile; rank 2: 2nd - 5th percentile; rank 1: below 2nd percentile). The other subtests from NEPSY-II provide scaled scores. The values we analyzed from CBCL and ABAS-II were respectively T scores and composite scores.

3. Results

In Table 3 we reported median, minimum and maximum scores of EF assessment in the three groups.

Median test detected significant differences ($p < .05$) in executive functioning among the groups for the following NEPSY subtests: Design Fluency (test statistic = 12.43; grand median = 8.00; $p = .002$), Response Set (test statistic = 10.69; grand median = 4.00; $p = .005$), Inhibition-error (test statistic = 6.40; grand median = 4.00; $p = .041$), Switching-error (test statistic = 8.51; grand median = 5.00; asymptotic $p = .014$), Switching-combined (test statistic = 10.59; grand median = 8.00; $p = .005$).

Individuals with PKU showed a weaker performance than controls in inhibition and cognitive flexibility, as pairwise comparisons revealed: the differences were significant in Design Fluency (adj. $p = .005$), Response Set (adj. $p = .014$), Inhibition-error (adj. $p = .048$), Switching-error (adj. $p = .010$), Switching-combined (adj. $p = .005$). Compared to the control group, also the performance of ASD children was impaired in some of the cognitive flexibility tasks: pairwise comparisons showed significant differences between ASD group and CG in Design Fluency (adj. $p = .004$) and Response Set (adj. $p = .011$).

There were no significant differences among groups in verbal WM (WMI: test statistic = 2.78; grand median = 97.00; $p = .249$), attention (Visual Attention: test statistic = 1.15; grand median = 10.00; $p = .563$; Auditory Attention: test statistic = 3.70; grand median = 5.00; $p = .157$) and planning-organization (Clocks: test statistic = 1.38; grand median = 5.00; $p = .503$). Also some aspects of inhibition and cognitive flexibility were comparable in CG, PKU and ASD groups: there were no significant differences in the speed component of inhibition and switching tasks (Inhibition-time: test statistic = 1.91; grand median = 10.00; $p = .384$; Switching-time: test statistic: 5.84; grand median = 10.00; $p = .054$), in the combined score (speed and accuracy) of inhibition (Inhibition-combined: test statistic = 4.93; grand median = 8.00; $p = .085$), nor in the ability of shifting among concepts and categories (Animal sorting: test statistic = 1.53; grand median = 10.00; $p = .465$).

Regarding the area of affective and behavioral symptoms, we analyzed general CBCL scales (internalizing, externalizing and total problem scales). Median, minimum and maximum T scores for the three groups are showed in Table 4.

Differences in internalizing (test statistic = 10.00; grand median = 58.50; $p = .007$), externalizing (test statistic = 8.50; grand median = 52.00; $p = .014$) and total problems (test statistic = 24.10; grand median = 53.00; $p < .0001$) were significant.

Pairwise comparisons showed that the ASD group's scores were significantly higher than the other groups' internalizing (CG-ASD adj. $p = .001$; PKU-ASD adj. $p = .017$) and total problems (CG-ASD adj. $p < .0001$; PKU-ASD adj. $p = .017$). Thus, children with ASD had more internalizing and total problems than controls and PKU. Differences in externalizing problems were only significant between ASD and controls (adj. $p = .004$).

Median, minimum and maximum composite scores in general and specific domains of adaptive behavior are showed in Table 5.

Children with ASD showed worse general and social adaptive skills than PKU children and controls: Median test showed significant differences among groups in GAC (test statistic = 13.68; grand median = 86.00; $p = .001$), CCS (test statistic = 10.97; grand median = 92.00; $p = .004$), SCS (test statistic = 27.94; grand median = 87.00; $p < .0001$), PCS (test statistic = 11.45; grand median = 81.00; $p = .003$). Pairwise comparisons revealed significant differences between ASD group and each of the other groups in GAC (CG-ASD adj. $p = .011$; PKU-ASD adj. $p = .001$) and SCS (CG-ASD adj. $p < .0001$; PKU-ASD adj. $p = .003$).

Pairwise comparisons detected significant differences between all pairs in PCS (CG-ASD adj. $p = .011$; PKU-ASD adj. $p = .001$; PKU-CG adj. $p = .043$): children with ASD's practical abilities were lower than children with PKU and controls, whereas children with PKU had better practical skills than controls. CCS pairwise comparisons showed no significant results ($p > .05$): the differences between pairs did not reach statistical significance for conceptual adaptation. All adjusted significance levels for pairwise comparisons are reported in Table 6.

4. Discussion

We compared EF, adaptive, emotional and behavioral functioning in participants with ASD without accompanying intellectual impairment, early treated PKU and controls.

Our results confirm the inhibition and cognitive flexibility impairment in children and adolescents with PKU [52,60,67] and the cognitive flexibility weakness in ASD [20–24], highlighting a common EF dysfunction in ASD and PKU. Verbal WM was intact in both clinical groups. This evidence supports the hypothesis that verbal WM is not impaired in these groups, consistent with previous results on ASD [25,26], but inconsistent with the conclusions of other studies on ASD [23] and PKU children [52]. Janos and colleagues [52] used different WM measures and PKU children's performance was impaired in the

Table 3
Clinical results of all samples across executive functioning domains and tests of significance among the three groups.

EF domain	Test	ASD (Median min-max)	PKU (Median min-max)	CG (Median min-max)	Median test sig.
Verbal working memory	Working memory index[a]	94 (61–151)	94 (79–130)	103 (79–136)	0.249
Inhibition	Inhibition combined[b]	7 (2–14)	7 (3 – 11)	10 (6–14)	0.085
	Inhibition total error[c]	4 [11th - 25th perc.] (1–7)	4 [11th - 25th perc.] (1–7)	5.50 [26th–50th – 51 th-75th perc.] (3–7)	0.041*
	Inhibition total completion time[b]	10 (1 – 13)	7 (1–13)	11.50 (6–15)	0.384
Cognitive flexibility	Design fluency[b]	7 (4–15)	8 (4–12)	11 (8–15)	0.002**
	Switching combined[b]	7 (2–15)	7 (1 – 10)	10 (6–15)	0.005**
	Switching total error[c]	4 [11th - 25th perc.] (1–7)	4 [11th - 25th perc.] (1–7)	6 [51 th-75th perc.] (3–7)	0.014*
	Switching total completion time[b]	10 (2–16)	9 (1–13)	11 (2–14)	0.054
	Response set[c]	3 [6th - 10th perc.] (1–7)	4 [11th - 25th perc.] (1–6)	6 [51 th-75th perc.] (3–7)	0.005**
	Animal sorting[b]	9 (5–19)	10 (5–19)	10 (7–14)	0.465
Planning	Clocks[c]	5 [26th–50th perc.] (2–7)	5 [26th–50th perc.] (3–7)	6 [51 th-75th perc.] (2–7)	0.503
Attention	Visual attention[b]	9 (1 – 12)	10 (2–14)	10.50 (3–14)	0.563
	Auditory attention[c]	5 [26th–50th perc.] (1–6)	5 [26th–50th perc.] (1–6)	5 [26th–50th perc.] (3–6)	0.157

Abbreviations: EF = executive functions; ASD = autism spectrum disorder; PKU = phenylketonuria; CG = control group; perc. = percentile.
[a] Composite scores: mean = 100, standard deviation = 15.
[b] Scaled scores: mean = 10, standard deviation = 3.
[c] Ordinal ranks from percentile groups (rank 7: above 75th percentile; rank 6: 51th - 75th percentile; rank 5: 26th - 50th percentile; rank 4: 11th - 25th percentile; rank 3: 6th - 10th percentile; rank 2: 2nd - 5th percentile; rank 1: below 2nd percentile): above average = rank 7; average scores = ranks 5 and 6; borderline scores = rank 4; below average = ranks 1,2,3.
* = $p < .05$
** = $p < .01$

Table 4
Clinical results of child behavior checklist general scales and tests of significance among the three groups.

CBCL scales (T score)	ASD (Median min-max)	PKU (Median min-max)	CG (Median min-max)	Median test sig.
Internalizing problems	67 (52–82)	52 (43–70)	50 (39–65)	0.007**
Externalizing problems	58 (33–70)	50 (41–74)	45 (33–60)	0.014*
Total problems	65 (50–77)	50 (38–76)	47.50 (36–55)	< 0.0001**

Abbreviations: ASD = autism spectrum disorder; PKU = phenylketonuria; CG = control group.
* = $p < .05$
** = $p < .01$

Table 5
ABAS-II composite scores and tests of significance among the three groups.

ABAS-II (domains)	ASD (Median min-max)	PKU (Median min-max)	CG (Median min-max)	Median test sig.
General adaptive composite	66 (54–93)	90 (53–114)	89 (75–120)	0.001**
Conceptual composite score	80 (48–101)	101 (55–114)	96.50 (81–117)	0.004**
Social composite score	70 (60–96)	98 (68–114)	97.50 (72–120)	< 0.0001**
Practical composite score	62 (44–96)	91 (48–111)	82 (70–116)	0.003**

Abbreviations: ASD = autism spectrum disorder; PKU = phenylketonuria; CG = control group.
** = $p < 01$

more demanding task (2-back task). Differently, we used WMI, a comprehensive score, based on digit span and letter-number sequencing tasks. This difference may imply that children with PKU show deficits in WM as the task becomes more complex, whereas their performance can appear typical in less demanding tasks.

This study did not confirm the deficit in planning and attention found by other researchers in ASD [19,20,27,28] and PKU [53,65,66]. Differences could be partially due to the heterogeneity of instruments used to evaluate EF: the test used in this study (Clocks) assesses not only the ability of organization and planning but also visuo-perceptual and visuospatial skills, whereas most studies used Tower of London or Tower of Hanoi, which require a more strategic type of planning involving also problem-solving skills, not evaluated in Clocks. Inhibition was also spared in our ASD sample. Previous data on this skill are not univocal: some authors found typical performance in inhibiting prepotent responses [17,18], while others detected deficits [19,23]. These discrepancies may be related to the different instruments used and to non-overlapping age ranges.

Children in ASD group showed significant difficulties in adaptive and emotional functioning: general, social and practical adaptive problems, internalizing and total number of difficulties of this group were significantly higher than those reported for participants with PKU and controls. ASD group also differed significantly from controls in externalizing problems. This result confirms the presence of adaptive behavior impairments in children with ASD, widely reported [30]. The occurrence of severe emotional problems in children with ASD has been well-established [39–41], as well as the coexistence of EF and

Table 6
Comparison of executive functioning, emotional, behavioral and adaptive profiles among participants with ASD, PKU and CG. Adjusted significance levels of pairwise comparisons between groups (pairwise comparisons were only calculated for the variables in which the median test showed a significant difference among the three groups of the sample).

Executive functions[a]	ASD-PKU	ASD-CG	PKU-CG
Design fluency	$p = 1.000$	$p = .004$**	$p = .005$**
Response set	$p = .273$	$p = .011$*	$p = .014$*
Inhibition-error	$p = 1.000$	$p = .596$	$p = .048$*
Switching-error	$p = 1.000$	$p = .490$	$p = .010$*
Switching-combined	$p = 1.000$	$p = .490$	$p = .005$**
Behavioral/emotional symptoms	ASD-PKU	ASD-CG	PKU-CG
Internalizing problems	$p = .017$*	$p = .001$**	$p = 1.000$
Externalizing problems	$P = .273$	$p = .004$**	$p = 1.000$
Total problems	$p = .017$*	$p < .0001$**	$p = 1.000$
Adaptive behavior	ASD-PKU	ASD-CG	PKU-CG
General adaptive composite	$p = .001$**	$p = .011$*	$p = 1.000$
Conceptual composite score	$P = .054$	$p = .082$	$p = 1.000$
Social composite score	$p = .003$**	$p < .0001$**	$p = 1.000$
Practical composite score	$p = .001$**	$p = .011$*	$p = .043$*

Abbreviations: ASD = autism spectrum disorder; PKU = phenylketonuria; CG = control group.
* = $p < .05$
** = $p < .01$
[a] In order to control the familywise type I error, adjusted *p*-values are calculated and used to make the decision for each pair. For pair (j, k), $H_{0,jk}$ was rejected at level α if $p_{adj,jk} < \alpha$. The adjusted *p*-values were calculated the following way: the *p*-value for each of the pairwise hypotheses was calculated and then the adjusted *p*-value was calculated as $p_{adj} = pK(K - 1)/2$.

emotional problems in older participants [42]. Previous studies reported concomitant EF deficits and internalizing symptoms in children and young adults with PKU [70,75], but internalizing symptoms were not found in our study. The absence of behavioral and emotional symptoms in PKU group is consistent with the results of a number of previous studies on children and adolescents with PKU [71,72]. These discrepancies may be due to the quality of dietary control in different samples, to the different age range of enrolled participants and to the use of different instruments.

EF play a pivotal role in the development of adaptive and emotional domains [37]. However, we did not detect impairments in the adaptive domains of PKU participants, notwithstanding a more widespread deficit in EF. These results suggest that ASD clinical profile rises from a complex interaction among multiple functions which cannot be reduced to EF deficits. The overlap of specific EF impairments between the two clinical groups is in line with the findings of previous research that compared different chronic disorders affecting individuals early in life [79,80]. This finding supports the hypothesis that EF deficits may be considered a common marker in developmental disorders [79].

The main limitations of this study are the cross-sectional design and the small sample size, which may affect the generalizability of the results. Future studies with larger sample size may plan age stratification, in order to analyze patterns of EF deficits in different age groups (i.e. children, adolescents, adults), or a longitudinal design with follow-ups at specific time points (from preschool until early adult age).

Another limitation is the absence of a measure of inhibition of irrelevant distractors: the inhibition task we used mainly evaluates inhibition of prepotent responses. The comparison between the results of both types of task may have added information on the cognitive profile of the two clinical groups.

Moreover, we did not evaluate controls' IQs assuming they were in the normal range. EF are indeed a subset of higher order cognitive functions and their domains only partially overlap with domains explored by conventional (multidimensional) IQ measurements [90]. General intelligence seems to show a strong relation with WM, but not with shifting and inhibition [91] and WM was not significantly different among groups in our study.

One of the major strengths is the use of a neuropsychological battery (NEPSY-II) designed for children, instead of being adapted from instruments for adults. Additionally, the comparison between ASD and PKU, yet to be explored, makes a contribution to the research field that investigates the nature of EF by comparing different neurodevelopmental disorders.

This work suggests two different patterns of impairments in ASD and PKU groups evaluated: both showed impairments on measures of EF (cognitive flexibility in ASD, inhibition and cognitive flexibility in PKU), but only the first group also showed emotional and adaptive difficulties, as compared to the CG group. More research is needed to confirm these findings, possibly with larger samples, multiple age groups, sensitive and varied neuropsychological instruments.

These results support a relative independence of adaptive and emotional behavioral difficulties from difficulties of executive functions and suggest that other dysfunctions might contribute to the multidimensional phenotype of individuals with ASD.

Compliance with Ethical Standards

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

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Declaration of Competing Interest

The authors report no conflict of interest.

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