

**Speed of processing and executive functions in adults with phenylketonuria (PKU):
Quick in finding the word, but not the ladybird**

Cristina Romani¹, Anita MacDonald², Sara De Felice¹ and Liana Palermo^{1,3,4*}

1. School of Life and Health Sciences, Aston University, Birmingham, UK

2. Birmingham Children's Hospital, Birmingham, UK

3. Queen Elizabeth Hospital, Birmingham, UK

4. Department of Medical and Surgical Sciences, Magna Graecia University of Catanzaro,
Catanzaro, Italy

*Address correspondence to:

Liana Palermo, Ph.D.

Department of Medical and Surgical Sciences,

Magna Graecia University of Catanzaro, Catanzaro, Italy

Email: Liana.palermo@unicz.it

Tel: 0039-0961-3695902

A reduction in processing speed is widely reported in the inherited metabolic disease phenylketonuria (PKU) possibly as a consequence of white matter lesions. We investigated possible deficits and their relationship with executive functions in a sample of 37 early-treated adults with PKU (AwPKU). AwPKU were not characterized by a generalized speed deficit but instead, their performance could be explained by two more specific impairments: a) a deficit in the allocation of visuo-spatial attention which reduced speed of processing in visual search tasks, and, possibly, in some reading conditions and ~~in~~ visuo-motor coordination tasks and b) a more conservative decision mechanism which slowed down returning an answer across domains and which, for language tasks, explained a fixed delay in responding compared to controls, independently of difficulty of condition. These results suggest that the impairments in executive functions-~~EF~~ seen in AwPKU are not the consequence of a generalized speed deficit. They also suggest that speed of processing is linked to the efficiency of a particular cognitive component and cannot be considered a general function spanning domains. Instead, at least in AwPKU, a reduced speed in returning answers may be linked to the fact that, because of their history, a cautious style is adopted and accuracy is prioritised over speed. Similarities with patterns in aging are discussed.

Keywords: Phenylketonuria; speed of processing; executive functions; aging; serial vs. parallel search; feature vs conjunction search

Phenylketonuria (PKU) is an ~~inherited-genetic~~ metabolic disorder characterized by mutations in the gene coding for the enzyme phenylalanine hydroxylase (PHA) which is necessary to metabolize the amino acid phenylalanine (Phe) into tyrosine (Scriver & Kaufman, 2001). A loss or reduction in PHA activity causes ~~accumulation-of-blood~~ Phe ~~accumulation-in-the blood~~, toxic ~~Phe~~ concentrations in the brain, and ~~a lack of the amino acid~~ tyrosine ~~deficiency~~. When ~~left~~-untreated, PKU ~~causes-results-in~~ severe mental disability, microcephaly, seizures and behavioural problems (Blau, van Spronsen, & Levy, 2010). ~~A combination~~ ~~combination~~ of newborn screening programs and early treatment with a low-phenylalanine diet prevents severe neurological damage and mental disability, but mild cognitive impairments are still present even in early-treated ~~patientsepopulations~~ (for a review see Christ, Huijbregts, de Sonneville, & White, 2010; Janzen & Nguyen, 2010; Moyle, Fox, Arthur, Bynevelt, & Burnett, 2007).

The ~~most commonly reported~~ deficits ~~reported-most-often~~ in children involve executive functions (for a review see Christ et al., 2010; DeRoche & Welsh, 2008) and a reduction in ~~speed of processing-speed~~ (for a review see Albrecht, Garbade, & Burgard, 2009). Some studies have suggested that adults with PKU (from now on AwPKU) are mainly affected by a reduction in ~~speed processingspeed-of-processing~~ (Channon, Mockler, & Lee, 2005; Channon, Goodman, Zlotowitz, Mockler, & Lee, 2007; Feldmann, Denecke, Grenzebach, & Weglage, 2005; Moyle, Fox, Bynevelt et al., 2007) with spared executive functions. Channon et al. (2005), for example, showed that AwPKU were slower, but not less accurate, in tasks tapping executive functions (*n*-back task and Flanker inhibitory task). Moyle, Fox, Bynevelt et al. (2007) reported that AwPKU were impaired in the Processing Speed Index (PSI) of the Wechsler Adult Intelligence Scale and in a visuo-motor coordination task ~~which are time constrained~~ ~~which-involved speed~~ (Trail Making Test part A), but not in executive function tests tapping shifting, such as the trail Making Test Part B and the verbal fluency task. Feldmann et al. (2005) assessed 35 adolescents and young adults with PKU (age range 13-21) with tasks tapping speed of processing (i.e., Number Combination Test which involves visual-motor tracking and basic sequencing skills), inhibitory control (Stroop) and sustained attention (Test d-2; a test in which 'd' letters should be crossed out ignoring distractors) and only found a speed reduction across tests.

Other studies, however, have ~~also~~ reported what appear to be independent deficits in tasks involving EF, especially, for functions involving planning and flexibility (e.g., Brumm, Azen, & Moats, 2004; Nardecchia et al., 2015; Smith, Klim, Mallozzi, & Hanley, 1996). ~~In~~ ~~With~~ the same sample of AwPKU investigated here (Palermo et al., 2017), we found reduced

speed in tasks tapping visuo-spatial attention (e.g. choice reaction time, visual search tasks), language (e.g. reading of word and nonword) and visuo-motor coordination (Digit symbol coding and Grooved Pegboard), but also deficits in complex executive functions related to planning, reasoning and cognitive flexibility (Wisconsin Card Sorting Test, Tower of Hanoi, Semantic Fluency, Similarity and Vocabulary of the WASI). These deficits were found even with untimed tasks or tasks in which the need for processing speed was minimal. Instead, we found no deficit in a core executive function such as inhibitory control (i.e. no deficit in the inhibitory component of the Stroop test, and no increased semantic interference in picture naming), consistent with previous studies (Brumm et al., 2004; Channon, German, Cassina, & Lee, 2004; Channon et al., 2005; 2007; Feldmann et al., 2005). Moreover, across a range of tasks, speed measures did not ~~demonstrate return~~ larger impairments than accuracy measures for some executive functions.

Disentangling the relative contribution of speed of processing and executive functions to performance is ~~generally~~ difficult. –Both skills contribute to IQ in healthy participants (Ardila, Pineda, & Rosselli, 2000; Friedman et al., 2006; Sheppard & Vernon, 2008). In normal development, they appear to improve and decline together. Speed of processing increases from childhood to adulthood, but then declines after midlife (Cerella & Hale, 1994; Kail, 1991a,b; Jenkins, Myerson, Joerding, & Hale, 2000; Nettelbeck & Burns, 2010). Similarly, executive functions develop up to adulthood and decline in ~~later life~~ ~~older adults~~ (e.g., Anderson, 2002; Best & Miller, 2010; Romine & Reynolds, 2005). Moreover, age-related improvements in one skill contribute to age-related improvements in the other (e.g., Christ, White, Mandernach, & Keys, 2001; Fry & Hale, 1996). –EF and processing speed are likely to be closely interlinked and establishing ~~if whether~~ deficits are independent or ~~one~~ the consequence of ~~each~~ the other is as ~~challenging~~ ~~difficult~~ in PKU as in other populations. The issue has been extensively debated in the ‘aging’ literature, where both types of deficits are present.

According to “**the processing speed**” hypothesis, cognitive age-related decline is due to a generalized slowing of cognitive processing caused by a diffuse deterioration of white matter (Salthouse, 1996). Consistent with this hypothesis, studies have shown correlations between speed of processing and white matter integrity in older adults (e.g., negative correlations with fractional anisotropy; see Kerchner et al., 2012). In turn, slowed processing will cause impairments in higher functions involving executive control because not all the relevant information ~~needed~~ ~~ecessary~~ to complete a cognitive operation will be available when ~~necessary~~ ~~required~~ (Salthouse, 1996). If each cognitive operation is delayed,

this will have widespread consequences so that not only tasks may be completed later than expected, but a correct answer may not be reached at all. Therefore, a reduction in processing speed may account for the poor performance shown by PKU participants in complex tasks, even if performance is measured in terms of accuracy rather than speed of processing.

The neurophysiological impairment which underlies the cognitive deficits seen in PKU is certainly consistent with the hypothesis of a primary speed deficit. High levels of Phe are toxic for the oligodendroglia cells which form the myelin sheaths in the central nervous system (Dyer, 2000) and myelin is crucial to speed of processing. However, studies which have looked at an association between white matter deterioration and speed of processing in PKU have generally failed to find positive results (see Brumm et al., 2004) with positive associations generally ~~be~~-limited to measures of IQ (see Anderson et al., 2004; 2007).

According to the "**prefrontal-executive" hypothesis** of age decline (West, 1996) ~~changes~~, ~~changes~~ in frontal areas lead to specific deficits in executive functions, which, in turn, lead to more general deficits including deficits in speed of processing (see Albinet, Boucard, Bouquet, & Audiffren, 2012). A similar hypothesis can be ~~considered~~~~entertained~~ in ~~the case of~~ individuals with PKU. For example, longer reaction times (RTs) may be due to occasional lapses in sustained attention which will cause some unusually long RTs and increase the overall average. Deficits in planning and inhibitory control may also reduce performance in a variety of tasks. Specifically, they may reduce performance in verbal fluency tasks and visual search which are impaired in both older adults (Jurado & Rosselli, 2007; Hommel et al., 2004; Rodriguez-Aranda & Martinussen, 2006) and in individuals with PKU (Banerjee et al., 2010; Brumm et al., 2004; Channon et al., 2004; Palermo et al., 2017). Both tasks require an ~~effective~~~~icient~~ search (of the mental lexicon and of visual displays, respectively) with efficient mechanisms of inhibitory control so that time is not ~~lost~~~~wasted~~ searching locations that have already been explored. Thus, specific impairments of EF, combined with the fact that speed may be more sensitive than accuracy for ~~revealing~~ ~~identifying~~ ~~de~~deficits, may give the ~~misleading~~ ~~false~~-impression that a reduction in speed of processing is the main ~~problem~~~~difficulty~~ in AwPKU (and in older adults) when, in fact, difficulties have a different source.

~~Clearly~~~~The fact that~~ deficits of EF and speed of processing co-occur across populations, (see also traumatic brain injury: Azouvi, Vallat-Azouvi, & Belmont, 2009; Ciaramelli, Serino, Di Santantonio, & Ládavas, 2006; Ponsford & Kinsella 1992; and

diabetes: Brands et al., 2005), ~~but this~~ does not demonstrate, ~~however,~~ that they are causally related to one other, nor that they depend on the same neurophysiological mechanisms. It is ~~also possible, instead,~~ that they are damaged independently. Studies assessing the nature of speed of processing impairments in PKU are very limited. Janos, Grange, Steiner and White (2012) showed ~~that,~~ in children with PKU, ~~that~~ processing speed contributed to performance on most, but not all, executive tasks, but that executive impairments in working memory and inhibitory control were still significant after controlling for processing speed. These results, ~~together with those we have already cited-cited above about -of~~ impairments in executive tasks where speed is not a premium, suggest partial independence of EF from speed of processing. Similarly, deficits of speed of processing appear to be independent from at least some EF deficits. In the sample of AwPKU, we found that reduced speed of processing was present even in tasks involving minimal planning abilities, like reading and manual dexterity tasks (see Palermo et al., 2017).

Finally, some studies within the aging literature have suggested that older adults' speed impairment is particularly evident in the visuo-attentional domain when assessed with search tasks (Hommel, Li, & Li, 2004). Performance in language tasks is more preserved, even when assessed with speed measures (Hale & Myerson, 1996; Lawrence, Myerson, & Hale, 1998; see also Shafto & Tyler, 2014). If the same results were replicated with AwPKU, ~~they would argue against~~ an overarching speed deficit ~~would not be supported.~~

~~In~~ ~~the~~ ~~paper~~ ~~investigate,~~ ~~we~~ ~~ask~~ if there is ~~a~~ reduced speed of processing in AwPKU compared to matched controls, across different domains, tasks and conditions', ~~considering and consider~~ distributions of RTs across trials. These analyses will provide ~~essential crucial~~ information ~~about on~~ the nature of a potential speed impairment in this population, and inform interpretation of similar difficulties in other neurologically impaired populations. A comparison with older adults will be particularly important because PKU disrupts neurophysiological substrates in a ~~manner way that~~ that is similar to what occurs in ~~older~~ age. PKU both reduces the availability of the neuro-transmitter dopamine (Landvøgt et al., 2008; Lykkeldund et al., 1988; Puglisi-Allegra et al., 2000), which is important for EF, and disrupts the integrity of white matter tracts (see Anderson & Leuzzi, 2010), which is important for speed of processing. Comparable disruptions occur in old age (for a review on age-related reduction of white matter integrity see Gunning-Dixon et al., 2009; Madden, Bennett, & Song, 2009; for age-related change in the dopamine system see Erixon-Lindroth et al., 2005; Kaasinen & Rinne, 2002).

Plan of Study and Predictions

Our experimental report will be subdivided into three main sections. In the first section, we ~~will~~ report the cognitive performance of the PKU group and assess speed of processing across domains and accuracy in tasks related to executive functions (EF). As expected, deficits will be shown. However, spared performance in some tasks and relationship with dietary control will provide some early indications of underlying deficits. In the second section, we ~~will~~ assess correlations between speed ~~performance~~ in various domains and accuracy in different types of EF. As expected, correlations ~~are~~~~will be~~ significant, but, in itself, ~~this does~~~~this does~~ not explain the nature of these relations. Finally, in the third section, we ~~will~~ carry out specific analyses of RTs distributions across domains, tasks and conditions. These analyses ~~will~~ help ~~elucidate~~~~clarify~~ the primary deficit/s underlying cognitive difficulties in AwPKU and, also, more generally, ~~inform~~~~illuminate~~ the relationship between speed and executive functions in normal as well as pathological cognition.

The hypothesis that deficits of EF are the consequence of a reduction in speed of processing predicts that this reduction should be generalized and not specific to certain domains. This hypothesis is particularly plausible for ~~what we will call the~~ higher-order EF involving planning and reasoning. In tasks involving planning a semantic search (semantic fluency), solving a puzzle (Tower of Hanoi) or understanding the rules of a game (WCST), it is ~~possible~~~~probable~~ that processing delays ~~will~~ accumulate to a catastrophic point which prevents returning the right answer. Perhaps it is more difficult to imagine that processing delays will affect the ability to suppress unwanted answers (inhibitory control), maintain attention or retain information in STM. Certainly, finding that speed deficits are specific for certain domains (e.g., visuo-spatial attention) will argue against the hypothesis that deficits of EF are the consequence of a reduced speed of processing. The mirror-reverse hypothesis -- that deficits of speed of processing are the consequence of deficits of EF—also makes specific predictions regarding ~~of~~ the pattern of RTs to see in various tasks. Problems with sustained attention predict occasionally long RTs, difficulties with inhibition predict strong effects of distractors and a difficulty in making decisions may predict no difficulty when the tasks ~~does~~ not require a binary decision, but only detection. Different predictions are outlined in more detail below. To help the reader, different patterns of speed reduction in relation to different deficit hypotheses ~~of deficit~~ are outlined in Table 1. Outcomes are also indicated so that they can be referred to, later, in the General Discussion.

Insert Table 1 about here

AwPKU may suffer from an overarching speed deficit which affects all cognitive processing. This predicts similar patterns of speed reduction across tasks of visual target detection, visual search, picture naming and reading. Importantly, the hypothesis of a generalized speed deficit also predicts that differences from controls will progressively increase with difficulty. Here, we assume that more difficult conditions are those with slower response times in healthy controls. We further assume that more difficult/slower conditions will be those which require more processing steps (we use the term 'processing step' in a loose way to indicate any cognitive operation; thus, searching an area of the lexicon or inhibiting distractors could be considered a processing step). An individual with a speed deficit will show a larger difference from controls in a more difficult condition because an initial difference in speed will be multiplied by the larger number of steps needed by the more difficult condition. Other hypotheses (e.g., the hypothesis of a delay in making decisions), in contrast, may predict a fixed delay across conditions.

Alternatively, AwPKU may have speed deficits only in particular domains. A reduction in speed may be limited to or stronger in the visuo-spatial domain, as has been reported for older adults (Lawrence et al., 1998). This hypothesis predicts that the hallmark of a speed deficit (increased differences in speed with increased difficulty) will be seen only, or mainly, in conditions which involve visuo-spatial attention, thus, in visual search tasks and, in reading, in conditions which tax visual attention (nonword reading; conditions contrasting word length in number of letters). Instead, this hallmark will not be seen in conditions which tax lexical access (e.g., in picture naming and, in reading, in conditions contrasting frequency and regularity).

Still a third alternative is that a reduction in speed of processing is not a primary deficit but, instead, is the consequences of a deficit in executive functions. Here, we will take into consideration potential deficits in a) sustained attention, b) inhibitory control and c) decision making.

According to the sustained attention hypothesis, longer average response times are due to occasionally long RTs, which occur when sustained attention has been relaxed. This predicts that the PKU distribution of RTs will overlap with that of the controls, but with a longer tail of slow RTs. Differences with the controls will only be present at the extreme end

of the distribution. In contrast, a 'real' speed deficit predicts that differences will be found even when RTs are relatively fast.

According to the inhibitory control hypothesis, a reduction in speed is mainly mediated by a difficulty in inhibiting distractors. Both in visuo-attentional and language domains we will use tasks which allow us to modulate the effect of distractors and assess effects on speed of processing. In visual search tasks, a target must be found among other visual items. In picture naming, the right name must be found in the mental lexicon. In visual search tasks, we will manipulate number of distractor items. In picture naming, we will manipulate the number of semantically related pictures preceding a target. It has been shown that interference builds up across a sequence of semantically related pictures even when they are intermixed with fillers, with each related item taking progressively longer to name (see Howard, Nickels, Coltheart, & Cole-Virtue, 2006; Oppenheim, Dell, & Schwartz, 2007). This task, therefore, allows us to establish whether differences between AwPKU and controls increase with the need to suppress semantic distractors, in the same way as differences should increase with number of visual distractors in search tasks.

Finally, a reduction in speed may be due to a delay in decision making. AwPKU may be more careful than control participants at the time of returning an answer, for example, taking extra time to check their answers. This hypothesis makes the specific prediction that AwPKU will have difficulty when the task requires a decision between binary alternatives (as in yes/no tasks), but no/less difficulty when the task only requires a response when the target is detected (go-no-go tasks). It also predicts that responses should be particularly slow in search tasks when the target is absent. Uncertainty is high during an absent trial because more careful checking *could* reveal that the target is actually there. Lastly, difficulties in making decisions could predict a stable delay across conditions if participants increase their deadline for making a response by a fixed amount.

2. METHODS

2.1 Participants and Procedure

Thirty-seven early-treated individuals with classical PKU were recruited from a pool of patients currently followed by the Department of Inherited Metabolic Disorders at the University Hospitals Birmingham and who had been continuously treated with a low-phenylalanine diet since birth. At the time of testing, 7 participants were on an unrestricted diet and 30 still on a low-phenylalanine diet. We invited all early treated PKU individuals attending the clinic to participate, plus a few who were still contactable, but not attending

clinic follow-up appointments. All individuals who responded to the invitation were tested. The PKU participants were compared to a group of 30 healthy controls matched for age, gender, and educational status. Healthy volunteers were recruited through the Aston University volunteering website. The same participants were tested in Palermo et al. (2017).

Data on historical Phe levels were obtained from the PKU database at The Clinical Chemistry Department at Birmingham Children's Hospital. Diagnosis was through newborn screening conducted at 5-7 days after birth.

Participants were tested in a quiet room in two separate testing sessions, each lasting about 3 hours. Blood Phe concentrations were measured prior to each testing session to determine current Phe levels. The research was approved by the NHS and Aston University Ethics committees. All participants gave voluntary informed consent to take part. All efforts were made to administer all tasks to all participants, but some data points are missing because not everybody returned for the second session.

2.2 Tasks

IQ was measured using the Wechsler abbreviated scale of intelligence (WASI; Wechsler, 1999). Since we are interested in measures of speed of processing, we analyse RTs in a number of tasks where accuracy was high with no analyses at a corresponding level of detail on error rates. Only correct RTs were included in these analyses. Outlier RTs which were 3 SD above the participant mean or below 250 ms were also excluded. Conversely, to minimize confounding with speed, we report performance in executive tasks only in terms of accuracy (but see Palermo et al., 2017 for complete results). These measures should provide an indication of EF, excluding difficulties with speed (but, again, see Palermo et al., 2017 for complete results). Whenever possible, accuracy has been scored in terms of error rates. This makes it easier to compare speed and accuracy measures. Higher scores indicate worse performance in both cases.

2.2.1 Speed of Processing Measures

1. Visuo-spatial attention

Simple Detection (go-no-go). Participants were asked to press the response button as soon as a ladybird appeared on the screen. The task included 20 trials. Presentation of the stimulus was preceded by a fixation cross displayed for 1000ms. The interval between fixation point and presentation of the ladybird was variable (1-3 seconds).

Detection with distractors (go-no-go). Participants had to respond to a ladybird as soon as it appeared on the screen by pressing a response key. As before, the stimulus appeared at a random interval after fixation (1-3 seconds) and was displayed until a response was made. Ladybirds, however, were interspersed with green bugs and they could appear either alone or together or with a green bug. Participants were asked to press a button whenever the ladybird appeared on the screen alone or with a green bug. There were 64 trials; 32 with the ladybird and 32 without. Of the trials with the ladybird, 16 only contained the ladybird, 8 had 2 ladybirds and 8 a single distractor. Of the trials without the ladybird, 16 had one distractor and 16 had 2 distractors. Failures to respond were counted as errors, as were responses to the wrong stimulus (maximum number of errors 64). After the task was run once, it was repeated by reversing the required response (i.e. the target was now the green bug).

Choice RT (from Cambridge Neuropsychological Test Automated Battery, CANTAB). In this task, an arrow-shaped stimulus appeared either on the left or the right hand-side of the computer screen. Participants were asked to press the button on the left of the response box, if the arrow pointed to the left and the button on the right, if the arrow pointed to the right. The side of presentation and the direction of pointing were always congruent with each other. The stimulus appeared at a random interval after fixation (1-750 ms) and was displayed for a maximum of 3100ms. If no response was made during this time, an error was recorded.

Visual search. Here, the task was to identify if a red ladybird (target) was present among distractors by pressing the 'yes' or 'no' button. As in previous studies (see Hommel, et al., 2004), our stimulus arrays consisted of 4, 8, or 14 distractor items in target-absent trials (no trials) with one distractor replaced by the target in target-present trials (yes trials). In the *feature search* condition, distractors were only green bugs, which differed from the target in both colour (green vs. red) and shape (bug vs. ladybird). In the *conjunction search* condition, there were also red bugs that differed from the target in shape, but not colour. A fixation cross was displayed for 1 second and the stimuli were presented immediately afterwards. Stimuli were displayed until a response was made. Feature and conjunction conditions included 36 trials each. They were presented in alternating blocks of 12 trials.

2. Language Processing

Word/nonword reading. Participants were asked to read aloud as fast and accurately as possible 140 words and 40 nonwords, presented in two separate blocks. The words included 80 regular words which contrasted frequency (40 of high frequency and 40 of low

frequency) and letter length: within each frequency category, there were 10 very short words (4 letters), 10 short words (5 letters), 10 medium-length words (6 letters) and 10 very long words (7-8-9 letters). In addition, 60 words contrasted orthographic regularity with 30 words being regular and 30 words being irregular (contained at least one very uncommon grapheme-phoneme correspondence; e.g., harbour, autumn). The 40 nonwords were obtained by changing one or two letters in corresponding high frequency words. Length was contrasted with 10 nonwords in each length category (very short, short, medium and long).

Stimuli appeared one at a time at the centre of a computer screen. Each word was preceded by a fixation cross for 1000 ms and disappeared 500 ms after a response was made. RTs were recorded via a voice-key.

Picture naming. We used a task similar to that originally used by Howard et al. (2006), which measures general speed in lexical access, but also an effect of semantic interference that arises when pictures belonging to the same semantic category are named in succession one after the other (see below Executive Functions method section). 165 pictures were presented one at a time on a computer screen. Participants were instructed to say the name as soon as possible. All pictures were black and white line drawings of common objects. 120 pictures belonged to 24 different semantic categories (5 items in each category) and the remaining 45 were fillers. They were presented in a randomized order. The number of pictures between successive members of the same category varied from two to eight. RTs were recorded via a voice-key. Previous results have shown that RTs progressively increase with the ordinal position in the set of semantically related pictures (Howard et al., 2006; Oppenheim et al., 2007). Overall mean RT was taken as a measure of speed in lexical access. The accuracy difference between items early and late in each semantic set was taken as a separate measure of inhibitory control (see later).

The Stroop Test- Colour Naming. Participants were asked to report the ink colour of three types of stimuli showed on the computer screen: a sequence of 'X' letters ('XXXX', *neutral condition*), coloured words where the colour of the ink matched the meaning of the word ('red' written with red ink; *congruent condition*), coloured words where the colour of the ink was incongruent with the meaning of the word (e.g. 'red' written with yellow ink; *incongruent condition*). There were 24 trials for each condition. RTs were recorded via a voice-key. Only RTs for congruent and neutral conditions were included in the language speed measure. Accuracy differences between congruent and incongruent conditions were included as a measure of inhibitory control (see later).

2.2.2.. Visuo-motor coordination

Trail Making Test A (Reitan, & Wolfson, 1985). This task requires drawing a trail with a pencil to join several circles. In version A, the circles only contain numbers. Participants had to connect the circles in ascending order as quickly as possible. Performance was scored in terms of the number of seconds required to complete the task. Version B, which requires alternation between numbers and letters, was not included because it measures both speed of processing and inhibitory control.

Digit symbol (Wechsler, 1981). Participants were given a key grid of numbers and matching symbols and a test grid with series of numbers and empty boxes below them. The task consisted of filling as many empty boxes as possible with the corresponding symbols in 90 seconds. Each incorrectly matched number–symbol and each empty box counted as an error (maximum number of errors= 93).

Grooved Pegboard Test (Trites, 1977). This test requires both visual-motor coordination and fine motor control. The apparatus consisted of a pegboard with 25 holes and 25 pegs. The participants had to put the pegs into the holes using only one hand as quickly as possible. Two trials were carried out with the dominant hand and two trials with the non-dominant hand. Performance was scored as the number of seconds required to complete the task.

2.2.3. Higher-order Executive Functions: Planning and Reasoning

Semantic Fluency condition (Rosen, 1980), participants were required to generate as many words as possible belonging to a specific category (i.e. animals) in 1 min of time. Scoring was based on the number of acceptable words produced. We used animal rather than letter fluency since here performance depends more on an organized search where animals are grouped by type (see Troyer, Moscovitch, Winocur, Alexander and Stuss, 1998).

The Tower of Hanoi puzzle (ToH, Shallice, 1982) assesses the ability to plan to solve a problem. Participants were asked to move rings (i.e., 3, 4 or 5 rings) of different sizes across three pegs to form a tower of large to small discs on the last peg. This is a challenge because a larger ring can never be placed on top of a smaller ring and only one ring can be moved at a time. Problems of increasing complexity were presented, from a version that could be solved in 7-moves to one that required 31 moves (number of trials =9). A trial was ended if after 6 minutes the participant was not able to reach the goal configuration. Since many PKU participants were not able to achieve a solution before the deadline, performance

was scored in terms of total number of unresolved trials and not in terms of the number of movements necessary to solve each trial (maximum number of errors = 9)-

The Wisconsin Card Sorting Test – 64 Card Version (WCST-64; Kongs, Thompson, Iverson, & Heaton, 2000) is an abbreviated form of the standard 128-card version. This test assesses the ability to derive rules and use feedback to shift cognitive set. Participants were presented with four place-holding cards depicting symbols differing in colour (green, red, blue, and yellow), number (1-4), and shape (circles, triangles, crosses and stars). The participants were then given a deck of 64 cards and asked to match each card with the corresponding place-holding card. Participants were not told what stimulus dimension (colour, number or shape) to use to match the cards, but feedback was provided after each choice. Once the participant made 10 consecutive correct matches for a predetermined sorting category (e.g., colour), the sorting rule was changed (e.g., shape), without telling the participants, and he/she had to discover the new sorting rule. Each incorrectly matched card was counted as an error (maximum number of errors= 64).

2.2.4. Other Executive functions: Inhibitory control, Sustained Attention and STM

1. Inhibitory control

The Stroop Colour-Word Test- Interference (Stroop, 1935). The difference in accuracy between the incongruent and congruent condition of the stroop test (described above) was taken as a measure of inhibitory control. To succeed in the incongruent condition, participants had to suppress the tendency to *read* the word.

Picture Naming - Semantic Interference. The difference in naming accuracy between the first and last exemplar of a series of semantically related nouns from the picture naming test (described above) was taken as an index of the difficulty in controlling lexical semantic interference.

2. Sustained Attention

Rapid Visual Information Processing (RVP; adapted from Sahakian, Jones, Levy, Gray, & Warburton, 1989). This task assesses the ability to maintain attention over time. Digits ranging from 2 to 9 appeared on the screen, one at a time, at a rate of 100 digits per minute. Participants had to detect three target sequences of 3 digits (i.e., 2-4-6, 3-5-7, 4-6-8) by pressing the response key when the last number of the sequence appeared on the screen. There were four blocks of 19 trials each (76 trials in total); 9 trials contained the sequence and 10 did not. Each trial contained a variable number of digits (from 3 to 10). For each block, an error was scored for each incorrect answer (e.g. pressing the response key at the

wrong time) or omission within a time window including the 2 digits following the last digit of a target sequence (1800 ms). Maximum number of errors = 76.

3. Short term memory (STM)

Digit span. Participants were asked to repeat a sequence of digits spoken by the examiner at the rate of approximately one per second. The sequences ranged from four to eight digits ($N = 10$ for each length). The task ended when the participants could not recall more than half of the sequences of a given length. To calculate the span, a value of 0.1 was assigned to each sequence repeated correctly. Each length, therefore, was scored one point if all the sequences were correct and 3 points were added as a baseline.

Nonword repetition. Participants were asked to repeat a sequence of nonwords spoken by the examiner. There were 10 sequences of 2 nonwords, 10 of 3 nonwords, and 10 of 4 nonwords. Nonwords respected the phonotactic constraints of the English language. The task ended when fewer than half of the sequences of a given length were repeated correctly and all subsequent items were counted as incorrect. One error was counted for each sequence repeated incorrectly (maximum number of errors = 30).

Corsi Block Span (Corsi, 1972). The examiner tapped a sequence of blocks at the rate of one per second and immediately afterwards participants attempted to reproduce the sequence in the same order. Sequences of increasing length (from 1 to 9) were presented, with three trials for each length. The task was stopped when the participant failed to reproduce all three sequences of a given length. For each length, one point was given if all three sequences were reproduced correctly, 0.66 if two were correct and 0.33 points if only one sequence was correct.

3. RESULTS

3.1. Demographics, cognitive performance and relationship with blood Phe levels

Results for control and PKU groups are reported in Table 2. The two groups are matched for age, gender and education. Blood Phe concentrations are reported in three age bands: Childhood: 0-10 years old, Adolescence: 11-16 years old and adulthood: 17 years to present, as well as at testing time. The Phe level in each band was calculated by averaging the mean annual Phe levels in the time band. Across the group, Phe levels were well controlled in childhood, but diet was progressively relaxed after early childhood with corresponding increasing blood Phe levels. Overall, AwPKU had a full-scale IQ in the control range (only one impaired participant), but significantly lower than matched controls (see also De Roche & Welsh, 2008; Moyle, Fox, Arthur, & Burnett, 2007 for a meta-

analysis). One should note that differences in IQ are likely to reflect primary differences in cognitive abilities rather than demographic differences. AwPKU and controls were matched for age, education and gender. Moreover, the AwPKU's performance on a spelling task, which is strongly influenced by socio-economic background (Hartas, 2011) was very similar to the controls and, in fact, slightly better (AwPKU: average % errors = 3.9%, SD= 4.6; Controls: average % errors= 4.8%, SD= 5.7; $t=-.6$, $p=.52$).

 Insert Table 2 about here

Table 3 shows the performance of the PKU group in tasks tapping: 1. processing speed in the visuo-attentional and language domains, 2. visuo-motor coordination and different types of EF. The visuo-motor coordination tasks have a speed component because they ask for task completion in a set time, but they do not measure speed of processing with the same precision of tasks requiring RTs and do not allow comparisons of speed across trials and conditions.

Accuracy in the tasks measuring speed of processing is not reported since it was not the focus of our study and was generally high and not significantly different from controls (z scores: detection with distractors =0.2; choice RT=0.1; feature search=-0.2; conjunction search=-0.2; picture naming=0.3; colour naming =0.0; word reading=0.1, nonword reading=0.4; see Palermo et al., 2017 for more complete results). This rules out speed-accuracy trade-offs. Since we wanted to assess the impact of reduced speed of processing on EF it was also important that measures of EF minimized a speed component. Thus, the measures included do not measure RTs, but number of items/responses correct except for the tasks tapping inhibitory control. Here to minimize a speed component we considered only differences in accuracy between high and low interference conditions.

To allow comparison, results are presented in standardized z scores based on the control group. For each type of function, we also report an aggregate score which averages z scores across tasks. Table 3 also reports correlations with Phe values. In a previous study (Romani et al., 2017), we showed that both median and standard deviations are important predictors of performance. Here, we report correlations with average Phe, because, if a single measure is used, averages may be better predictors encompassing both typical values and variations.

Insert Table 3 about here

AwPKU were significantly slower than controls across tasks and were impaired in executive functions. This replicates what has been found in previous studies. Results, however, are not homogeneous within and between functions. There are some significant exceptions:

1. There are no significant differences in detection tasks with or without distractors. A lack of difference in simple detection may be due to this task tapping mainly peripheral/motor speed. However, performance was normal even when the task included distractors, in the face of abnormal performance on the “Choice RT” task. This suggests that AwPKU are less impaired when the task does not require a choice between responses (as in go-no-go tasks).
2. Performance is normal in tasks requiring inhibitory control abilities. This is an early indication that a speed reduction in more complex tasks may not be the result of a difficulty in inhibiting unwanted information.
3. Within language tasks, processing speed is normal in picture naming, mildly impaired in word reading and severely impaired in nonword reading. This provides an early indication that speed in lexical access is not ~~affected. a problem-~~ Instead, longer RTs in reading could arise at the level of orthographic analysis where visual processing may be slower and/or reliant on smaller processing units.
4. The patterns of association with Phe levels differ across domains. Consistent with previous studies, visuo-attentional speed is influenced by quality of metabolic control early in life ~~but it is less influenced by control later in life and less by later metabolic control-~~(see also, Albrecht, et al., 2009). In contrast, visuo-motor coordination and sustained attention are more influenced by quality of metabolic control in adolescence and adulthood. Finally, there are no significant associations with language speed (see also Romani et al., in press). These results provide an early indication of differences between domains and, in particular, of difference in processing speed between language and visuo-spatial tasks, which will be explored in the following sections.

3.2 Correlations between EF and Speed of Processing

In this section, we ~~will want to~~ assess ~~the~~ degree of association between speed of processing and EF. First, we calculated Pearson's correlations between speed scores (visuo-spatial attention and language), visuo-motor coordination and executive function scores (complex EF, sustained attention, short term memory and inhibitory control) separately for the control and AwPKU groups. Results are shown in Table 4.

 Insert Table 4 about here

The PKU group ~~demonstrates~~ ~~shows~~ stronger correlations among tasks than the control group. Language speed correlated significantly with visuo-attentional speed and with visuo-motor coordination in AwPKU, but not in the controls (Pearson r with visuo-attentional speed: AwPKU=.46 vs. Controls=.11; visuo-motor speed: AwPKU=.45 vs. Controls=.07). Also, visuo-motor speed correlated significantly with EF in AwPKU, but not in the control ~~groups~~ (Pearson r with Complex EF: AwPKU=.66 vs. Controls=.11; Sustained attention: AwPKU=.50 vs. Controls=.08; STM: AwPKU=.57 vs. Controls=.21; for AwPKU, p always $<.015$; for controls p always $\geq .27$). Stronger correlations in the PKU group are consistent with a common factor (level of Phe) increasing the strength of the association in AwPKU, but not in controls.

We also carried out univariate ANCOVAs to ~~examine if see whether~~ AwPKU and controls continued to differ in processing speed after controlling for EF and, conversely, ~~if whether~~ impairments in EF remained significant when differences in speed measures were considered. Since we were concerned about the overlap between executive functions and our index of visuo-motor coordination, we only considered measures of language speed and visuo-spatial speed for this analysis. Differences in processing speed disappeared when EF (complex EF, STM and sustained attention) were covaried (language speed $F_{1,56}=2.7$; $p=.11$; visuo-attentional speed $F_{1,62}=0.96$; $p=.33$). Differences in complex executive functions remained significant when language and visual-attentional speed were covaried ($F_{1,57}=5.7$; $p=.02$), but differences in STM ($F_{1,57}=1.6$; $p=.22$) and sustained attention ($F_{1,57}=0.01$; $p=.94$) did not. These results partly replicate ~~the findings of what was found by~~ Janos et al. (2012) with PKU children.

The fact that most differences disappear when performance in other functions is covaried is not surprising given the high degree of correlation seen in the PKU group. This ~~makes~~ it difficult ~~to disentangle/unravelling~~ deficits of speed of processing and executive

functions by [only simply](#) considering the degree of association across participants. Other approaches described in the following sections will be more productive.

3.3 Analyses of [Speed-Performance Speed](#)

Here, we concentrate on language and visuo-spatial tasks where speed of processing was measured by RTs to visual stimuli.

3.3.1. RT Distribution within tasks: Quartile analyses

-Slower speed of processing in PKU could be mediated by lapses in attention. Our reported speed measures were corrected for outliers (RTs >3 SD from the subject mean were eliminated), making this unlikely. However, as a further [evaluation/assessment of this possibility](#), we carried out a quartile analysis considering all RTs (including outliers) from each task and subdividing the RTs of each participant into four quartiles, with the 1st quartile the fastest and the 4th quartile the slowest. Results for language and visuo-spatial tasks are shown in Figure 1.

 Insert Figure 1 about here

Results were analysed statistically with a number of ANOVAs (one for each task) with *Group* as a between-subjects factor, and *Quartile* as a within-subjects factor. The interaction *Group x Quartile* was of particular interest. There was no significant interaction, for Simple Detection [$F_{3,177} = .3$, $p = .83$; partial eta-squared = .01], Detection with Distractors [$F_{3,177} = 0.2$, $p = .91$; partial eta-squared = .003], Picture Naming [$F_{3,177} = .3$, $p = .80$; partial eta-squared = .01], and Colour naming [$F_{3,174} = 1.4$, $p = .23$; partial eta-squared = .02], but there was a significant interaction for Choice Reaction Time [$F_{3,195} = 4.8$, $p < .01$; partial eta-squared = .1], Feature search [$F_{3,177} = 6.1$, $p < .01$; partial eta-squared = .1], Conjunction search [$F_{3,177} = 8.9$, $p < .01$; partial eta-squared = .1], Word Reading [$F_{3,174} = 3.8$, $p < .05$; partial eta-squared = .1], and Nonword Reading [$F_{3,177} = 6.7$, $p < .01$; partial eta-squared = .1] in all of these cases the profile was steeper in the PKU group, with RTs increasing more sharply across quartiles. Importantly, however, planned post hoc comparisons on the significant interactions showed significant differences between PKU and Controls for all quartiles, in all tasks (see asterisks in figure 1).

We confirmed differences in slope across quartiles by considering the linear regression coefficient for each participant and then comparing PKU and control groups. There was no significant difference between AwPKU and Controls in the slopes for Simple Detection [$t_{1,59} = -.6, p = .56$], Detection with Distractors [$t_{1,59} = -.4, p = .67$], Picture Naming [$t_{1,57} = -.5, p = .60$], and Colour Naming [$t_{1,58} = -.6, p = .56$], and only a marginal difference for Word Reading [$t_{1,59} = -1.8, p = .08$]. Instead there was a significant difference for Choice Reaction Time [$t_{1,65} = -2.4, p = .02$], Feature Search [$t_{1,59} = -2.6, p = .01$], Conjunction Search [$t_{1,59} = -3.1, p = .003$], and Nonword Reading [$t_{1,59} = -2.6, p = .01$].

Conclusions. Firstly, our results ~~indicateshow~~ that, at least for some tasks, differences ~~between AwPKU and controls were~~ ~~became progressively greaterlarger~~ for trials which were slower. This is consistent with a speed deficit. Difficult trials will involve more processing steps, with each step contributing to increased differences between ~~the two groups. AwPKU and controls.~~ Results are less consistent with a deficit of sustained attention. This should produce some very long responses (and therefore differences for the slowest quartiles), but no differences in speed for the fast quartiles. Instead, significant differences between the two groups were present across *all* quartiles, including, importantly, the fastest quartile.

Secondly, an increased difference with controls across quartiles (a fanning out pattern) was ~~observed seen~~ only in certain tasks: visual search tasks, word reading and nonword reading. Other tasks (~~—detection tasks, picture naming and color naming~~) showed stable differences from controls across quartiles (a parallel pattern). This suggests that a reduction in speed of processing affects tasks which require systematic use of visual-attention to identify items in position (mainly visual search and nonword reading), but not tasks where sequential processing of positions is not crucial (as in picture naming, colour naming and, to a lesser extent, word reading). As will be discussed more later, in a sequential task AwPKU may either need more time for each processing step or need to break the task into more processing units/steps. Either way, more difficult trials will see an increased difference with controls.

3.3.2 RT Distribution across Tasks: Brinley Plots

Here, we assess ~~if whether~~ differences between PKU and control groups become ~~greaterlarger~~ when conditions are more difficult. To do so, we plotted the mean performance of AwPKU for different task conditions against the mean performance of the controls in the same conditions (so called Brinley plots; for applications see Cerella, Poon, & Williams,

1980; Ferraro, 1996; Puopolo, Martelli, & Zoccolotti, 2013). In addition, we plotted the RTs of fast vs. slow PKU participants against the controls. There is variability in the performance of AwPKU, partly due to their present and past [quality of](#) metabolic control. If a contrast between PKU and controls is reliable, ~~it we should~~ [be see it](#) enhanced when slow and fast PKU participants are distinguished. Fast and slow participants in visuo-spatial and language tasks, were identified by averaging the z scores of each participant for each type of task, and then considering the participants in the fastest and slowest quartile (see also Hale & Jansen, 1994; Myerson, Hale, Zheng, Jenkins & Widaman, 2003). The language and visuo-attentional conditions used for the plots are listed in the Appendix with corresponding RTs. To allow a stronger contrast between visuo-attentional and language tasks, only conditions manipulating lexical variables (word frequency and regularity) were included for reading. Results are shown in Figure 2.

 Insert Figure 2 about here

Panels A and B show results for the visuo-attentional tasks and panels C and D for the language tasks. For the visuo-attentional tasks the slope of the linear regression is 1.3 indicating that for each unit of time increase in the controls, there is 30% larger increase in AwPKU (panel A). - This is consistent with differences in speed between the PKU and the control group: the harder (more visually complex) the task, the [greater/larger](#) the difference with controls. Language tasks, instead, show a constant difference across difficulty levels (panel C). AwPKU show a fixed delay, regardless of the difficulty of the condition. The slopes in the two types of tasks are statistically different from each other (visuo-spatial tasks: $y = 1.30$; $R^2 = 0.99$; language tasks: $y = 0.93$; $R^2 = 0.91$; $t_{1,29}=4.0$; $p < .001$).

When fast and slow PKU are contrasted (panels B and D), the same patterns emerge, but in a stronger form. With the visuo-attentional tasks, the fast PKU participants behaved similarly to the controls. Their regression line is almost overlapping with the reference line (dotted line in the figure). Instead, the slow PKU group showed differences which become progressively [greater/larger](#) the harder the condition. With the language tasks, the regression lines of the fast and slow PKU are parallel and, the regression line of the fast PKU is negative compared to controls, indicating that the AwPKU performed better than controls with difficult conditions. The slopes of the slow PKU in the visuo-attentional and language tasks

are significantly different from one another (for the visuo-spatial tasks, $y = 1.70$; $R^2 = 0.95$; for language tasks, $y = .90$; $R^2 = 0.63$; $t_{1,29}=4.0$; $p < .001$). The difference between fast and slow PKU increases significantly with difficulty in the visuo-spatial tasks (slow PKU: $y = 1.70$; $R^2 = 0.95$; fast PKU: $y = .99$; $R^2 = 0.99$; $t_{1,36}=7.4$; $p < .001$) but not in the language tasks (slow PKU: $y = .90$; $R^2 = 0.63$; fast PKU: $y = .68$; $R^2 = 0.96$; $t_{1,22}=1.0$; $p = .32$).

Conclusions. AwPKU ~~demonstrate show~~ increasing differences from controls with increasing levels of task difficulty in visuo-attentional tasks, but not in language tasks. This result reinforces results from previous sections showing that AwPKU do not suffer from uniform cognitive slowing. Instead, more pronounced difficulties arise when scanning a visual input compared to searching the mental lexicon. The conditions included in the language tasks involve accessing the right representation in the lexicon (regular and irregular words of high and low frequency) and inhibiting competitors in conditions with increased semantic interference (positions in a series of related items). Our results indicate that the extra processing needed to activate the target in these more difficult conditions is the same in controls and AwPKU.

3.3.3. Patterns in Visual Search

Here, we explore further the performance of AwPKU in visual search tasks. In a *feature search*, targets differ from distractors within a *single* feature dimension (e.g., a *red* lady bird among *green* bugs in our task). In this case, targets appear to 'pop out' and only a parallel search is needed to perform the task. This makes RTs independent of the number of distractors in the display (display size) and reduces the difference between present/absent trials. Instead, in a *conjunction search*, targets and distractors differ by a combination of features (e.g., displays include red and green items and bugs and ladybirds; the target is a combination of red and ladybird). This requires more attention to be deployed to the distractors so that locations need to be serially searched to find the target. This makes RTs dependent on the number of items in the display, and on whether the target is present or absent. When the target is absent, all locations need to be exhaustively searched before a 'no' answer can be returned. Instead, when the target is present, on average, a smaller sample of locations will need to be searched before the target is found (Wolfe, 1994; Hommel et al., 2004, Treisman & Gelade, 1980).

Slower performance in visual search tasks may be due to difficulties with EF. An efficient search requires planning/inhibitory control/STM. Locations must be systematically searched and locations that have already been searched should not be searched again (see

Hommel et al., 2004, for a discussion of these possibilities in older adults). Executive function deficits will result in increased effects of number of distractors and even worse performance when a target is absent because already searched positions may be searched again. Efficient search, however, also depends on specific visuo-attentional skills. A deficit of visual-attention also predicts an exaggerated effect of the number of distractors, especially when the target is absent, because each processing step will take longer (if attention moves more slowly) and/or more processing steps will be needed (if the visuo-attentional window is smaller).

PKU vs controls. Results in Figure 3 show the average RTs of AwPKU and controls as a function of display size and present/absent trials in Feature and Conjunction search. For each group (PKU and controls) and type of task (Feature and Conjunction search) participants were identified as fast or slow by ranking them according to their average RT and then selecting participants in the slowest and fastest quartiles. Panel A shows differences between the control and PKU group overall. Panels B and C show differences between fast and slow participants within each group.

 Insert Figure 3 about here

Results were analysed with mixed ANOVA with *Group* as a between-subjects factor (AwPKU, Controls) and *Task* (Feature vs. Conjunction search), *Display Size* (4, 8, 12) and *Condition* (yes/no trials) as within-subject factors. There were main effects of *Group*: AwPKU were slower ($F_{1,59} = 12.4, p = .01$; partial eta-squared = .22); *Task*: RTs were slower in conjunction search ($F_{1,59} = 601, p < .001$; partial eta-squared = .91); *Condition*: RTs were slower in 'no' than 'yes' trials ($F_{1,59} = 98, p < .01$; partial eta-squared = .62), and *Display size*: RTs were slower with increasing number of distractors ($F_{2,118} = 157, p < .001$; partial eta-squared = .73). There was an interaction of *Display Size x Task* ($F_{2,118} = 176, p < .001$; partial eta-squared = .75) because number of distractors had a stronger influence in conjunction search and *Display Size x Task x Condition* ($F_{2,118} = 21, p < .001$; partial eta-squared = .26), because this effect was stronger with 'no' trials. Crucially, there was a marginal interaction of *Group x Task* ($F_{1,59} = 3.0, p = .052$; partial eta-squared = .013), because the PKU group was relatively more impaired in conjunction search, and an interaction of *Group x Display Size* ($F_{2,118} = 6.7, p < .01$; partial eta-squared = .10), because AwPKU showed a stronger effect of

display size. There was also a significant interaction of *Group x Condition* ($F_{1,59} = 8.8$, $p < .01$; partial eta-squared = .13), because AwPKU showed a stronger reduction of speed in target absent ('no') trials. There was also a three-way interaction: *Group x Display Size x Task* ($F_{2,118} = 3.2$, $p = .045$; partial eta-squared = .05), because AwPKU showed an effect of display size in feature search as well as in conjunction search, while controls did not. AwPKU showed a significant linear trend of *Display Size* in features search ($F_{1,30} = 8.6$, $p = .006$) as well as conjunction search ($F_{1,30} = 139$, $p < .001$). Instead, the controls showed a linear trend of *Display Size* only in conjunction search ($F_{1,29} = 197$, $p < .001$; feature search: $F_{1,29} = 1.2$, $p < .29$).

Fast and slow groups. In feature search, Bonferroni comparisons showed that the slow-PKU group performed worse than all the other groups ($ps < .001$) while the fast-PKU group were comparable to the fast-Controls ($p = 1.0$). There were also significant interactions of *Group x Condition* [$F_{3,28} = 6.6$, $p < .01$; partial eta-squared = .41] and *Group x Display size* [$F_{6,56} = 4.7$; $p < .001$; partial eta-squared = .33]. Only slow-PKUs took longer on the 'no' than 'yes' trials ($p = .001$) and were affected by display size, with RTs significantly slower with 8 and 12 items than 4 items ($p = .007$ and $p < 0.001$).

In conjunction search, Bonferroni comparisons showed that the slow-PKU ~~group~~ performed worse than all other groups ($ps < .001$) while fast-PKUs were comparable to fast-Controls ($p = .92$). There were also significant interactions of *Group x Condition* [$F_{3,28} = 15.1$, $p < .001$; partial eta-squared = .61], because slow-Controls and slow-PKUs (but not the fast groups), took longer with the 'no' trials ($ps < .001$); and *Group x Display size* [$F_{6,56} = 5.2$, $p < .001$; partial eta-squared = .37] because the slower groups showed a larger effect. Finally, there was a three-way interaction: *Group x Condition x Display size* [$F_{6,56} = 4.5$, $p < .001$; partial eta-squared = .32] because display size differences for the slower groups were more pronounced with 'no' trials. Finally, we tested if whether RTs increased more steeply with display size in slow-PKUs compared to slow-Controls by comparing regression slopes. For the "yes" condition there were no significant difference in the regression slopes [$t_{1,14} = -.5$, $p = .62$]. Instead, in the "no" condition the regression slope was steeper for slow-PKU [$t_{1,14} = -2.4$, $p = .03$].

Conclusions. In feature search, control participants (even the slow controls), and the fast PKU participants, were not affected by the number of distractors nor by if whether the target was present or absent. This indicates that the search was performed largely in parallel with a 'pop-out' effect for target present trials that speeded up RTs. Instead, the slow-PKU group carried out feature search similarly to conjunction search with slower RTs

on target-absent trials and an effect of the number of distractors. Effects of the number of distractors in feature search are unusual but they have been reported before (in young children see Ruskin & Kaye, 1990; Hommel et al., 2004; visual agnosia Humphreys & Riddoch, 1992; dementia with Lewis Bodies see Cormack, Gray, Ballard & Tovee, 2004; but also Landy et al., 2015 for a failure to replicate). ~~It is difficult to establish —w~~Why some AwPKU show this failure to ‘pop-out’ in feature search ~~is difficult to establish,~~ but ~~this~~ is consistent with reduced visuo-attentional span, which may not allow one to process more than a limited amount of information at once and, therefore, reduces any pop-out effect. This pattern, instead, is less consistent with EF impairments in planning/inhibitory control, which would have predicted good performance in feature search.

Across feature and conjunction search, AwPKU were particularly slow with target-absent trials and, here, they showed a particularly strong effect of ~~the~~ number of distractors. This is consistent with difficulties in visuo-spatial attention, but also with being more careful when a response is more uncertain. This is similar to what occurs in older adults (more time to search for an absent target and more time to search when there are more distractors; Folk & Lincourt, 1996; Hommel et al., 2004; Plude & Doussard-Roosevelt, 1989).

3.3.4 Patterns in Language Tasks

Picture Naming. Our picture naming task measures an effect of semantic interference that arises when pictures belonging to the same semantic category are named in succession one after the other. Previous results have shown that RTs progressively increase with ordinal position in a set of semantically related pictures, even when items in the set are intermixed with distractors and participants are not aware of any relationship between items (Howard et al., 2006; Oppenheim et al., 2007). This cumulative interference effect is believed to arise because naming previous exemplars of the same category increases activation of related items which compete with activation of the target name. Suppressing this activation has a cost and results in longer RTs. Figure 4 shows the average RTs of PKU and Control Groups as a function of item position. As previously, each group was subdivided into fast and slow subgroups.

Insert Figure 4 about here

-An ANOVA with *Group* (AwPKU, Controls) and *Item position* (1st, 2nd, 3rd, 4th, 5th) as factors showed a significant main effect of *Position* [$F_{4, 232} = 57.2$ $p < .001$; partial eta-squared = .50] and a marginal effect of *Group* [$F_{1, 58} = 3.6$ $p = .06$; partial eta-squared = .01]. The interaction *Group x Position* was not significant [$F_{4, 232} = 1.3$, $p = .28$; partial eta-squared = .02]. In other words, in AwPKU there is a tendency to be slower which does not increase with difficulty of the condition.

Comparisons of fast and slow groups also showed no interaction of *Group x Position* [$F_{12, 112} = 1.3$, $p = .25$; partial eta-squared = .12], indicating no difference among groups due to more difficult conditions. The post-hoc Bonferroni comparisons showed that the slow-PKUs performed worse than fast-PKUs ($p < .001$) and fast-Controls ($p < .001$), but similarly to the slow-Controls ($p = .59$). Similarly, fast-PKU were comparable to fast-Controls ($p = 1.0$). Overall, these analyses indicate minimal differences in speed between AwPKU and controls.

Reading: the effect of lexical variables. Results are shown in Figure 5. With the regularity list, an ANOVA with *Group* (AwPKU, Controls) and *Regularity* (regular, irregular) as factors showed a significant main effect of *Group* [$F_{1, 59} = 6.2$, $p = .02$; partial eta-squared = .10] and *Regularity* [$F_{1, 59} = 12.7$, $p < .001$; partial eta-squared = .17], but no interaction *Group x Regularity* [$F_{1, 59} = .22$, $p = .64$; partial eta-squared = .003]. Analyses by speed groups, showed that slow-PKUs performed worse than fast-PKUs ($p < .001$) and fast-Controls ($p < .001$), but similarly to slow-Controls ($p = .15$). Fast-PKU were comparable to fast-Controls ($p = 1.0$). There was no *Group x Regularity* interaction [$F_{3, 28} = .5$, $p = .68$; partial eta-squared = .05]

Similarly, with the frequency list, an ANOVA with *Group* (AwPKU, Controls) and *Frequency* (high, low) as factors showed a significant main effect of *Group* [$F_{1, 59} = 6.9$, $p = .01$; partial eta-squared = .10] and *Frequency* [$F_{1, 59} = 5.0$, $p = .03$; partial eta-squared = .08], but no interaction of *Group x Frequency* [$F_{1, 59} = .1$, $p = .75$; partial eta-squared = .002]. Analyses by speed groups, showed that the slow-PKUs performed worse than the fast-PKUs ($p < .001$) and fast-Controls ($p < .001$), but similarly to the slow-Controls ($p = .08$); fast-PKUs were comparable to fast-Controls ($p = 1.0$). There was no interaction of *Group x Frequency* [$F_{3, 28} = 1.0$, $p = .41$; partial eta-squared = .10].

 Insert Figure 5 about here

Reading: the effect of length. Results are shown in Figure 6. With words, an ANOVA with *Group* (AwPKU, Controls) and *Length* (very short, short, medium, long) showed a significant main effect of *Group* [$F_{1,59} = 8.0$, $p < .01$; partial eta-squared = .12] and *Length* [$F_{3,177} = 6.8$, $p < .001$; partial eta-squared = .10], but no interaction of *Group x Length* [$F_{3,177} = 0.6$, $p = .60$; partial eta-squared = .01]. Comparisons of fast and slow groups (Bonferroni test) showed that slow-PKU performed worse than fast-PKU ($p < .001$), fast-Controls ($p < .001$), and slow-Controls ($p = .049$). Fast-PKU were comparable to fast-Controls ($p = 1.0$). There was a marginal interaction of *Group x Length* [$F_{9,84} = 2.0$, $p = .051$; partial eta-squared = .18], indicating larger differences among groups with longer words.

With nonwords, an ANOVA with *Group* (AwPKU, Controls) and *Length* (very short, short, medium, long) as factors showed a significant main effect of *Group* [$F_{1,60} = 12.2$, $p < .001$; partial eta-squared = .17] and *Length* [$F_{3,180} = 46.1$, $p < .001$; partial eta-squared = .43] as well as a significant interaction of *Group x Length* [$F_{3,180} = 2.9$, $p = .04$; partial eta-squared = .04]. Post-hoc analysis (Bonferroni test) showed that AwPKU were slower than controls with medium ($p = .03$) and long ($p = .002$) nonwords, but not with very short ($p = .34$) and short ($p = .13$) nonwords.

Comparisons of fast and slow groups (Bonferroni test) showed that, overall, the slow-PKU group performed worse than all other groups ($ps < .001$) while fast-PKUs were comparable to fast-Controls ($p = 1.0$). The interaction *Group x Length* was significant [$F_{9,84} = 13.1$, $p < .001$; partial eta-squared = .58], indicating increasing differences between groups with longer nonwords. Specifically, the slow-PKUs performed worse than the slow-Controls with the medium ($p < 0.001$) and long ($p < .001$) nonwords, but not with very short ($p = 0.42$) and short ($p = .07$) nonwords. Fast-PKUs were comparable to fast-Controls in all length conditions ($ps = 1.0$).

 Insert Figure 6 about here

Conclusions. Our results show that AwPKU show a fixed delay in reading a word or naming a picture which is independent of the difficulty of lexical retrieval. Instead, differences with controls become larger as a function of letter length, especially in nonword reading. This is consistent with a deficit in visuo-spatial attention which is crucial for nonword reading (see Facchetti et al., 2006; Landerl & Wimmer, 2000; Romani, Tsouknida & Olson, 2014).

4. SUMMARY OF RESULTS

1. **Consistent with previous reports, the group of AwPKU shows deficits in tasks tapping executive functions and reduced speed across tasks.** Several findings from our experimental investigation allow us to better understand these deficits (see results compared with predictions in Table 1 above). We can conclude that:
2. **AwPKU do not suffer from a generalized speed deficit:**
 - a) The effect of poor metabolic control is different for different domains. Poor metabolic control in childhood particularly impacts the speed with which visuo-spatial attention is allocated; poor metabolic control in adulthood particularly impacts visuo-motor coordination; there is no detectable association between degree of metabolic control and speed in language tasks.
 - b) Patterns of speed reduction are different in different cognitive domains (as shown below);
3. **Patterns are consistent with a speed deficit in visuo-spatial attention, but not in lexical access:**
 - a) In visual search tasks, RT differences from controls increase with difficulty of condition (number of distractors in the display). This is consistent with an attentional spotlight that moves more slowly from one location to another and/or operates with reduced efficiency/capacity, so that a smaller area is covered at each step. Instead, in naming and in some reading conditions, differences in RT between AwPKU and controls remain constant with difficulty (number of preceding semantic distractors in naming; frequency and regularity in reading).
 - b) In reading, the conditions where differences from controls are larger are those where one can hypothesize a contribution of visuo-spatial attention: reading long vs. short words, where long words require more decomposition into smaller visual processing units, and reading nonwords vs. words, where nonwords require more sequential allocation of attention to individual letters.¹

¹ It is to be noted that AwPKU show no deficits in tasks tapping phonological awareness—such as spoonerisms and phoneme deletion tasks—excluding an alternative account for difficulties in nonword reading (see Palermo et al., 2017).

4. Some executive deficits are unlikely to be responsible for the reduced speed with which answers are returned across tasks:

- a) Difficulties with sustained attention cannot account for a reduction in speed of processing.
- In AwPKU, sustained attention did not correlate with speed in language tasks and, if anything, correlated with speed in visuo-spatial tasks *less* than in controls.
 - AwPKU were slower than controls across the whole distribution of RTs, even for relatively fast responses; this argues against a main contribution of lapses of attention, which should only be apparent in slow responses.
- b) Difficulties with inhibitory control are also unlikely.
- AwPKU did not show significant impairments in tasks and conditions tapping inhibitory control and inhibitory control did not correlate with processing speed in any domain.
 - Including distractors in a detection task did not produce significantly worse performance than controls.
 - In visual search, difficulties (in terms of z scores from controls) were as severe in 'feature' as in 'conjunction' search, where the inhibition of distractors is more difficult. These results indicate a difficulty in allocating attention, but not a specific difficulty in inhibiting distractors.

5. In contrast, slower responses across domains may be linked to a slower/more careful executive mechanism which decides when enough evidence is available to return an answer. A more conservative decision mechanism may wait for more evidence before returning an answer and/or hesitate/recheck the answer before returning it. This explains:

- a) A preference for accuracy over speed. There were high levels of accuracy but slow RTs across most tasks.
- b) Slow RTs in tasks which require a decision. RTs were slow when there were alternative answers (yes/no; right/left), but normal in a go-no-go detection task, which only requires a single response when a target is present.
- c) A fixed delay in language tasks. Response time will depend on personal ability and condition, but the deadline for returning an answer will be extended by a fixed amount.
- d) Particularly poor performance with 'no' trials in search tasks. In 'no' trials the answer is more uncertain.

5. DISCUSSION

Our study asked two main questions. 1) Is there a generalized deficit of speed of processing in AwPKU? 2) Are deficits in executive functions either the main cause of a reduction in speed of processing or a significant contributor? Our results provide evidence [to address](#) ~~for~~ both questions.

[Firstly, Answering the first question,](#) AwPKU do not show a generalized reduction in speed of processing. The hallmark of a speed of processing deficit (increased RT differences with difficulty of condition) was present in tasks tapping visuo-spatial attention, but not in tasks/conditions tapping lexical access. Moreover, speed reductions in different domains showed different associations with metabolic control at different ages. The lack of a generalized speed deficit makes it unlikely that any difficulty with higher order executive functions ~~present in this group~~ is a consequence of a reduced processing speed so that ~~in complex tasks~~ delays accumulate across operations to a breaking point [in complex tasks](#). More generally, these results support the hypothesis that the efficiency of EF (across impaired and healthy populations) is not a direct consequence of speed of processing.

[Evidence to address the](#) ~~The answer to the~~ second question is more complex, but, even here, some indications are clear. [It is established](#) ~~First, one may note~~ that EF are heterogeneous with poor inter-correlations among them (Jurado & Rosselli, 2007). Here we show that functions associated with sustained attention and inhibitory control do not necessarily contribute to speed reduction in other domains (i.e., lexical access and visual search). Instead, a more careful/less efficient decision component (arguably a type of EF) may reduce speed of answer across domains. We will now examine the theoretical and clinical implications of our findings.

Our results show that the disruption of neural metabolism present in PKU, and possibly in aging and other pathologies, affects speed of processing in some cognitive domains more than others. This suggests that **speed of processing is not a general resource which may be tapped by different cognitive modules, but is intrinsic to the processing efficiency of particular cognitive components**. According to this view, asking about the relation between a speed of processing and EF may be misleading. There may be no speed capacity which is supramodal and independent of executive functions. Instead, speed of processing may reflect the efficiency of specific functions: i.e., of visuo-spatial attention as well as of specific executive functions.

Our results raise the question of [which](#) ~~what~~ functions/components, if any, operate across domains. We have argued against a generalized reduction of speed of processing, but

we have also suggested that a reduction in the speed/efficiency of a decision component may affect the speed with which answers are returned across domains. One may debate, however, ~~if whether~~ we should ~~describe this as talk of~~ damage to a decision *component* or, more appropriately, ~~as~~ **a cognitive style or preference which applies across domains**. We find it difficult to ~~envisio~~envisage a decision component which evaluates evidence across all domains. Decision mechanisms should be ~~quite~~-specific to the ~~kind of~~ evidence that needs to be evaluated. It is easier, instead, to think of cognitive styles with a differential propensity to privilege either speed or accuracy. AwPKU, like older controls, may generally adopt a more careful decision style because they may be more aware of their potential weaknesses and more keen to ~~show~~display good performance. Making an error would subjectively be considered ~~feel~~ more serious than a slight delay in providing an answer.

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Our results have implications for how we think the cognitive system operates and potentially for conditions other than PKU—aging in particular—where brain health is similarly affected by a reduction of dopamine (e.g., in aging: Erixon-Lindroth et al., 2005; Kaasinen & Rinne 200; in PKU: McKean, 1972; Burlina et al., 2000; Pascucci et al., 2012) and by a reduction in white matter integrity (e.g., in aging: Gunning-Dixon et al., 2009; Madden, Bennett, & Song, 2009; Madden et al., 2012; in PKU: Anderson & Leuzzi, 2010). It is interesting that the pattern shown by AwPKU in tasks measuring speed of processing is similar to that reported in normal aging. In visual search tasks, similarly to AwPKU, older adults show more marked difficulty with ‘no’ than ‘yes’ trials and increased difficulties with number of distractors (Folk & Lincourt, 1996; Plude & Doussard-Roosevelt, 1989). This is in contrast with patterns reported in young children, where accuracy is not ~~favoured~~privileged over speed and there is no extra difficulty with ‘no’ trials (Ruskin & Kaye, 1990; Hommel, et al., 2004). In addition, selective difficulties with visuo-attentional tasks compared to language tasks have also been reported in older adults (see Hale & Myerson, 1996; Jenkins et al., 2000; Lawrence et al., 1998; see also Puopolo et al., 2013 for a similar pattern in traumatic brain injured patients). It is possible that older adults, as AwPKU, do not suffer from a generalized reduction in speed of processing, but from selective difficulties in the allocation of visual attention which combine with a more careful decisional style. Consistent with this interpretation it has been shown that older adults are not particularly slow in accumulating evidence, but, instead, set more conservative decision boundaries, thus responding more slow~~ly~~ than needed for an optimal speed-accuracy trade-off (see Starns & Ratcliff, 2009; 2012; and, also, Smith & Brewer, 1995; for the suggestion that older adults are more cautious at the point of decision see also, Hommel et al., 2004; Li, Lindenberger, &

Sikstrom, 2001; Welford, 1965). These results argue against a generalized decrease in processing speed in aging as in PKU (see Myerson, Hale, Wagstaff, Poon & Smith, 1990 for an expression of this view).

Our results provide further evidence for a degree of dissociation among cognitive functions in disorders with diffuse damage. It is possible that posterior areas of the brain supporting visual-attention are particularly affected. Consistent with this, some PKU studies have reported greater white matter pathology and more severe loss of grey matter volume in parieto-occipital areas than in temporal areas, which are more related to language processing (see Christ et al., 2016; Leuzzi et al., 2007; Scarabino et al., 2009). Similarly, although results are more mixed, most studies in aging research report more severe impairments in frontal and parietal areas and relative sparing of temporal areas (for review see Gunning-Dixon et al., 2009; Madden, Bennett, & Song, 2009; Madden et al., 2012). It is possible that cells in frontal and parietal areas are more vulnerable to the accumulation of metabolic damage. It is also possible that retrieval of strongly consolidated information, as in naming task, is more spared by diffuse brain damage (see also Bendlin et al., 2010 for correlations between white matter pathology and measures of speed of processing across age cohorts, but more modest correlations with memory and executive functions).

Clinically, our results help us to characterize the residual cognitive deficits present in early-treated AwPKU. We have suggested that there are deficits of visuo-spatial attention. These deficits may explain difficulties in tasks of visual search, but also difficulties with non-word reading, where there is a need to identify individual letters in position (linking identity and positional information; see Bosse & Valdois, 2009; Facoetti et al., 2006; Romani, Tsouknida, di Betta, & Olson, 2011) and where more resources are needed with increasing length. In contrast, word reading relies more on parallel processing of letters and on accessing stored orthographic and phonological stored representations. Visual attention is a complex skill which involves different components, including attention shifting and visual-span (number of positions which can be processed simultaneously). Identifying which component is affected in AwPKU would require further tests, outside the scope of the present investigation. However, we can note that a difficulty in shifting attention may relate more directly to a speed deficit, while a reduced visuo-attentional span may better explain the lack of a pop-out effect in Feature search (there may not be enough resources to process the whole display in parallel). Both types of deficits would account for other aspects of results equally well (hypothesizing slower steps in the first case, more steps in the second case).

Impairments were also evident in tasks involving visuo-motor coordination. Here, however, our exploration was limited since these tasks measured overall time to complete the task or number of items completed in a set time, but not RTs. We can only speculate that a combination of factors contributed to a slower speed in these tasks, such as reduced manual dexterity and ability in visual search.

It is important that AwPKU were not progressively slower with increasing difficulty of condition across domains. This limits the impact of this deficit on performing complex tasks and for daily living. Less positively, the observation of similar patterns in AwPKU and healthy older adults may indicate an acceleration of cognitive aging in PKU. This is consistent with recent reports of similar pathological markers (e.g., toxic fibrils) in PKU and Alzheimer Disease (Adler-Abramovich et al., 2012; Soloway, Soloway, & Warner, 2013). The present cohort of AwPKU is the first to reach adulthood with relatively minor cognitive impairments after the introduction of early dietary treatment in the 60s. Our results therefore highlight the need for further longitudinal investigations to assess ~~if whether~~ there is an acceleration of cognitive degradation with aging in this population.

Finally, Palermo et al. (2017) ~~have~~ highlighted the great variability in outcomes present in AwPKU with about a quarter showing evidence of impairment, but over ~~one third~~ ~~1/3~~ with completely normal performance across cognitive domains. Here we have strengthened this observation by showing that, in each task, the fastest PKU participants are as fast as the fastest controls. Therefore, a speed reduction is not a general characteristic of AwPKU, but it affects only specific individuals. Moreover, individuals differ in terms of the type of task in which they show a speed reduction. There was only partial overlap in the groups of people showing slowest and fastest performance across tasks, and, thus, correlation in speed of processing was significant, but only of medium strength. Future studies should explore the cause of this variability, which is only partially explained by differences in dietary compliancy and metabolic control.

Conclusions. Our study allowed a better understanding of the nature of ~~speed~~ processing ~~speed~~ deficits in AwPKU and their relationship with executive functions. Our results argue against an over-arching impairment of speed of processing affecting performance across domains and responsible for reduced intellectual capacity. Instead, they suggest an independent impairment in the allocation of visuo-spatial attention and a cognitive style which delays the deadline after which a response is returned (difficulties with manual dexterity could also contribute). These insights could potentially be applied to other conditions involving similar neurological impairments, and particularly aging. They also have

implications for our understanding of normal cognition. They stress: 1) ~~the absence of a general lack of an overarching speed of processing speed~~ capacity; 2) ~~the independence of The fact that EF deficits from are not a consequence of deficits affecting this such~~ capacity; and 3) ~~the The~~ potential contribution of cognitive styles to performance. Our results should be confirmed in future research by comparing cognitive profiles in different populations where brain metabolism is affected.

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Table 1. Predictions of patterns of speed deficits in AwPKU, according to different types of hypothesized deficits. Expected and observed results are reported. Predictions which are crucial for a given hypothesis are highlighted. Predicted effects refer to differences from controls.

	EXPECTED					OBSERVED
	General Speed Deficit	Reduced visual-attention	Executive Deficits in:			
			Sustained attention	Inhibitory control	Decision making	
PREDICTED EFFECTS						
Increased RT differences with difficulty of condition in <u>Visual Search</u>	+	+	+	+	-	+
Increased RT differences with difficulty of condition in <u>Naming</u>	+	-	+	+	-	-
Abnormally large effect of <u>Frequency in Reading</u>	+	-	+	+	-	-
Abnormally large effect of <u>Length in Reading</u>	+	+	+	+	-	+
Differences across the whole RT range (quartile analyses across speed tasks)	+	+	-	+	+	+
Slow RT mainly in high interference conditions (in picture naming and visual search)	-	-	-	+	-	-
Slow RT even in go-no-go tasks where decisions are easier (in simple <u>detection/detection</u> with distractors <u>detection</u> tasks)	+	+	+	-	-	-

Table 2. Demographic information, metabolic control and general cognitive performance for control and PKU participants. Blood Phe measured in $\mu\text{mol/L}$.

	Controls		PKU		Controls vs PKU
	Mean	SD	Mean	SD	
Age	27.6	<i>7.4</i>	27.5	<i>7.3</i>	$t_{(1,65)} = .08$; $p = .94$
Education years	15.2	<i>1.7</i>	14.4	<i>1.9</i>	$t_{(1,65)} = 1.6$; $p = .12$
Gender (M/F)	10//20		13//24		$\chi^2_{(1)} = .02$; $p = .88$
FIQ	113.8	<i>10.9</i>	103.9	<i>14.3</i>	$t_{(1,65)} = 3.1$; $p = .003$
<u>Childhood</u>					
(Mean N obs. =197; SD=165)					
Phe Average	--	--	452	<i>183</i>	
<u>Adolescence</u>					
(Mean N obs.=77; SD=70)					
Phe Average	--	--	714	<i>314</i>	
<u>Adulthood</u>					
(Mean N obs.=65; SD=74)					
Phe Average	--	--	787	<i>301</i>	
<u>Lifetime</u>					
(Mean N obs=340; SD=241)					
Phe Average	--	--	690	<i>255</i>	
<u>Current Phe</u>			720	<i>343</i>	

Note: Childhood: 0-10 Years-old; Adolescence: 11-16 Years-old; Adulthood: 17- present. N obs. = average N of measures for each participant in each time band. Phe average: Average of median of yearly values; Phe fluctuations are calculated by averaging standard deviations from median values (SD) for each year in the band.

Table 3. PKU performance in z scores for different cognitive domains. EF measures in terms of accuracy only. Correlations in bold are statistically significant ($p < .05$); Ns=not significant. Note that we do not correct for multiple comparisons since here we are interested in the patterns of results rather than in the significance of individual correlations.

	Z scores			CORRELATIONS WITH AVERAGE PHE				
	Mean	SD	Difference from controls P	Childhood	Adolescence	Adulthood	Current	Life Span
VISUAL-ATTENTION SPEED								
Simple Detection	0.3	0.9	Ns	0.27	0.17	0.10	0.10	0.17
Detection with Distractors	0.4	1	Ns	0.42	0.18	0.15	-0.04	0.21
Choice RT	0.8	1.3	<.01	0.43	0.23	0.21	0.05	0.25
Feature Search	1.5	2.3	<.01	0.55	0.32	0.36	0.12	0.41
Conjunction Search	1.3	1.9	0.001	0.46	0.26	0.36	0.19	0.39
Aggregated Score	0.8	1.3	<.01	0.52	0.28	0.29	0.13	0.33
LANGUAGE SPEED								
Color Naming	1.1	1.4	<.001	0.18	-0.05	0.18	-0.10	0.14
Picture Naming	0.4	1	Ns	-0.11	-0.18	-0.21	-0.23	-0.17
Word Reading	0.7	1.3	<.05	0.09	-0.01	0.18	-0.02	0.13
Nonw. Reading	1.8	2.9	0.001	0.13	0.12	0.22	0.02	0.19
Aggregated Score	1.1	1.5	<.001	0.11	0.03	0.17	-0.05	0.13
VISUO-MOTOR COHORDINATION								
Peg board	1.1	2.1	0.01	0.33	0.28	0.28	0.40	0.33
Digit Symbol	1	1.1	<.001	0.35	0.27	0.47	0.47	0.48
Trail Making A	1.1	2.1	0.01	0.23	0.35	0.33	0.27	0.31
Aggregated Score	1.1	1.7	0.001	0.34	0.40	0.41	0.42	0.42
EXECUTIVE FUNCTIONS								
Complex EF	1.1	1.5	<.001	0.39	0.39	0.25	0.26	0.30
Sustained Att.	0.6	1.3	<.05	0.11	0.20	0.29	0.49	0.34
STM	0.6	0.9	<.01	0.07	0.03	0.04	-0.14	-0.01
Inhibitory Control	0	0.8	Ns	-0.02	-0.22	-0.23	-0.05	-0.16
Aggregated Score	0.6	0.7	<.001	0.26	0.30	0.26	0.40	0.32

Table 4. Pearson's correlations between aggregated Speed and EF measures in AwPKU and controls. **< 0.01; * < 0.05; Boxed cells group correlations within: 1. within speed measures (dark grey), 2. within executive functions (white) and 3. between speed measures and executive functions (light grey).

	Visuo-spatial attention speed	Language speed	Visuo-motor coordination speed	Complex EF	Sustained attention - RVP	STM	Inhibitory control	VIQ	PIQ
AwPKU									
Visuo-spatial attention speed	1.00								
Language speed	0.46**	1.00							
Visuo-motor coordination	0.44**	0.45**	1.00						
Complex EF	0.38*	0.22	0.66**	1.00					
Sustained attention - RVP	0.38*	0.35	0.50**	0.17	1.00				
STM	0.27	0.53**	0.57**	0.18	0.12	1.00			
Inhibitory control	0.19	-0.18	0.24	0.17	-0.06	0.24	1.00		
VIQ	-0.41*	-0.30	-0.68**	-0.47**	-0.38*	-0.35*	-0.26	1.00	
PIQ	-0.46**	-0.39*	-0.72**	-0.55**	-0.49**	-0.49**	-0.07	0.72**	1.00
CONTROLS									
Visuo-spatial attention speed	1.00								
Language speed	0.11	1.00							
Visuo-motor coordination	0.39*	0.07	1.00						
Complex EF	0.36	0.15	0.11	1.00					
Sustained attention - RVP	0.60**	-0.01	0.08	0.35	1.00				
STM	0.10	0.14	0.21	0.43*	0.18	1.00			
Inhibitory control	0.04	0.00	0.05	0.40*	0.10	0.71**	1.00		
VIQ	-0.28	-0.10	-0.04	-0.03	-0.32	-0.03	-0.14	1.00	
PIQ	-0.56**	-0.23	-0.37*	-0.29	-0.44*	-0.15	-0.24	0.56**	1.00

Note: Tasks were aggregated across domains by averaging z scores across tasks/measures as follows:

- 1 Visuo-spatial attention speed: RT in *Simple Detection, Detection with Distractors, Choice Reaction Time, Feature Search, Conjunction Search*
 2. Language speed: RT in *Colour naming, Picture naming, Words and Nonword reading.*
 3. Visuo-motor coordination: *Trail Making A, Grooved Pegboard Test, Digit symbol*
 4. Complex executive functions: *WCST, Tower of Hanoi, Semantic fluency, Trail Making B-A*
 5. Sustained attention: *Rapid Visual Information Processing (RVP)*
 6. Short-term memory (STM): *Digit Span, Nonword repetition, Corsi Span*
 7. Inhibitory controls: *Stroop Colour-Word Test- Interference, Picture Naming - Semantic Interference.*
- VIQ: Verbal Intelligence Quotient; PIQ: Performance Intelligence Quotient

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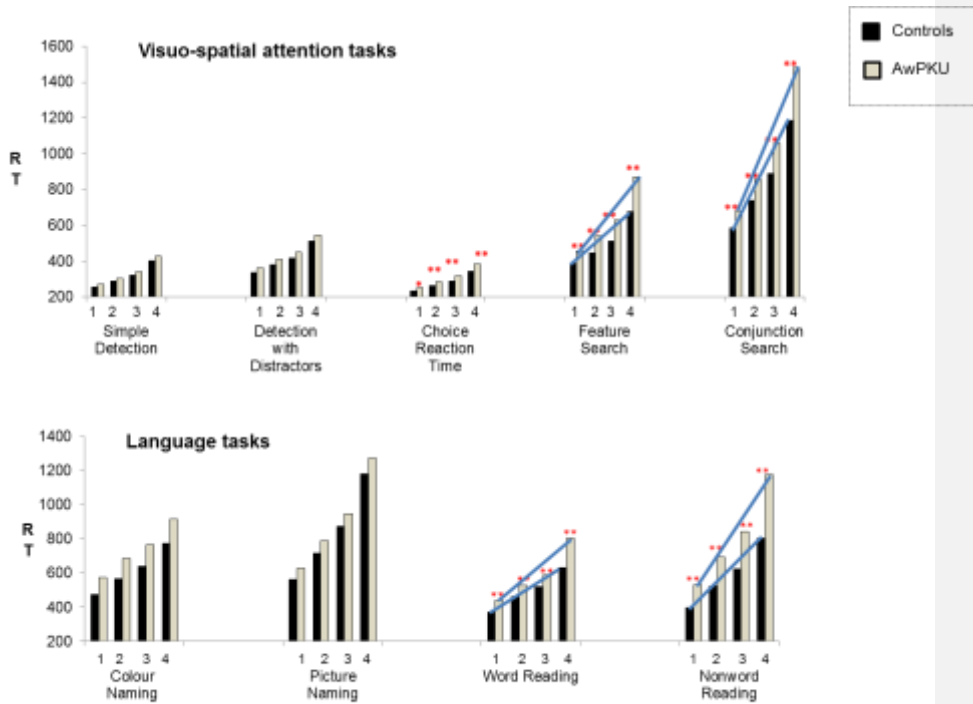
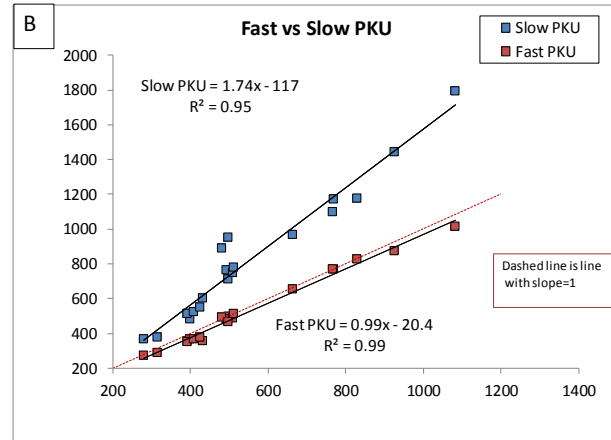
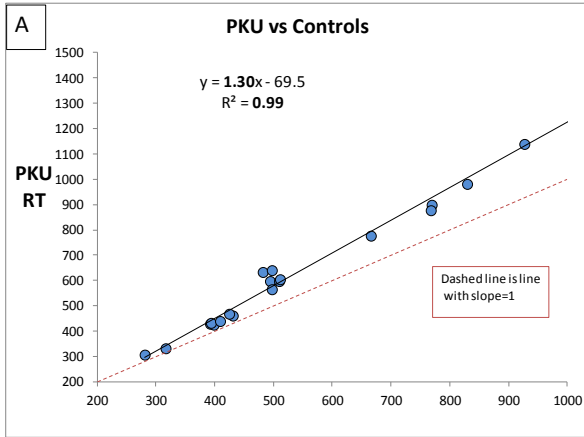


Figure 1: Distribution of reaction times (RT) in four speed quartiles for control and AwPKU participants and for different tasks. Numbers (1-4) on the x axis indicate quartiles from fastest to slowest. Significant differences (asterisks) are reported for the planned post-hoc comparisons for the tasks in which the interaction Group*Quartile was significant. * $p < .05$; ** $p < .01$.

VISUO-SPATIAL TASKS



LANGUAGE TASKS

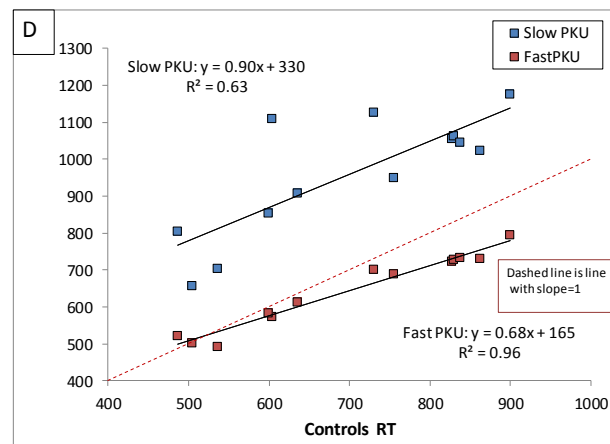
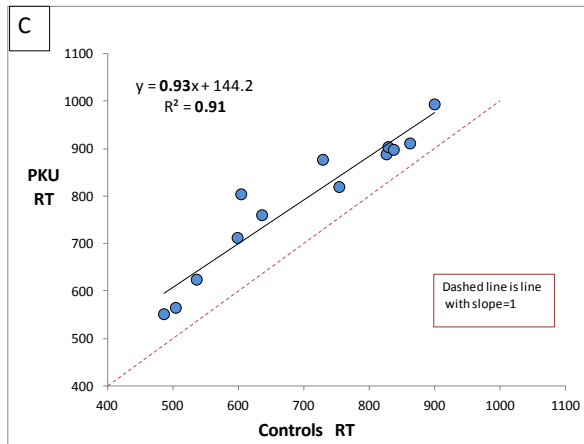


Figure 2. Brinley Plots. RTs of the PKU participants plotted against the Control RTs for different conditions. Each point in the graph refers to a different task condition. Language conditions include: Neutral and Control conditions of the Stroop, positions 1-6 for Picture Naming; Irregular and Regular words of high and low frequency and nonword reading for Reading. Visuo-spatial conditions include: simple detection, detection with distractors, choice response, and yes and no trials with 4, 6 and 8 distractors for feature search and conjunction search. Panels A and C plot RTs for the whole PKU group; panels B and D plot RTs for the fast and slow PKU groups separately. In the panels A and C the dotted line represents the equality line. If the RT for a particular condition is the same as the controls, the data point for that condition would fall along the dashed line. Fast and slow participants in visuo-spatial and language tasks were identified by averaging the z scores of each participant for each type of task, and then considering the participants in the fastest and slowest quartile.

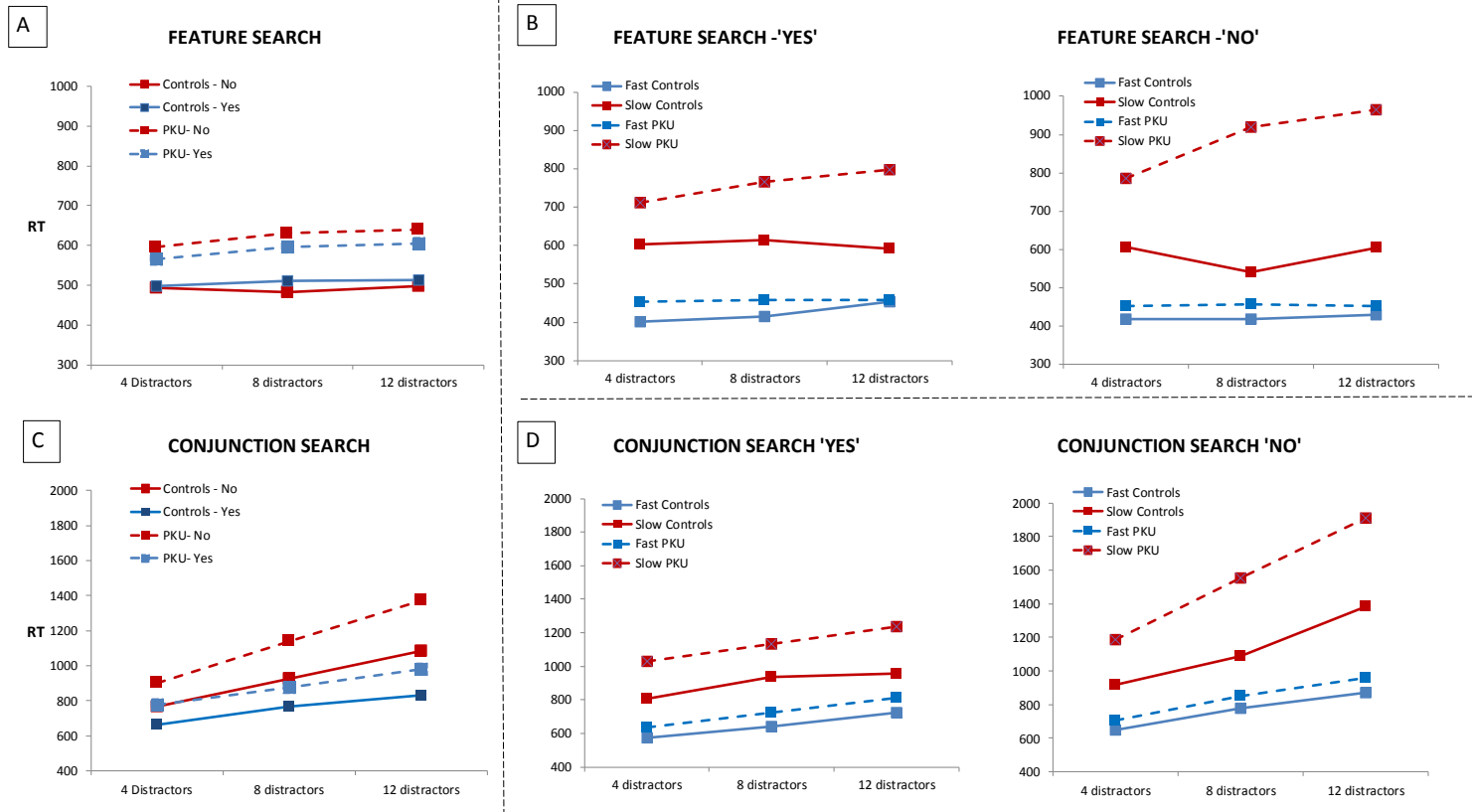


Figure 3. Visual search performance in AwPKU (dotted lines) and Controls (solid lines) by display size (4, 8, 12 items) and condition (yes/no trials). Fast and slow groups are the fastest and slowest quartile in feature and conjunction search. Panels A and C show differences between the control and PKU groups, overall. Panels B and D show differences between fast and slow participants within each group in Feature Search (panel B) and Conjunction search (panel D).

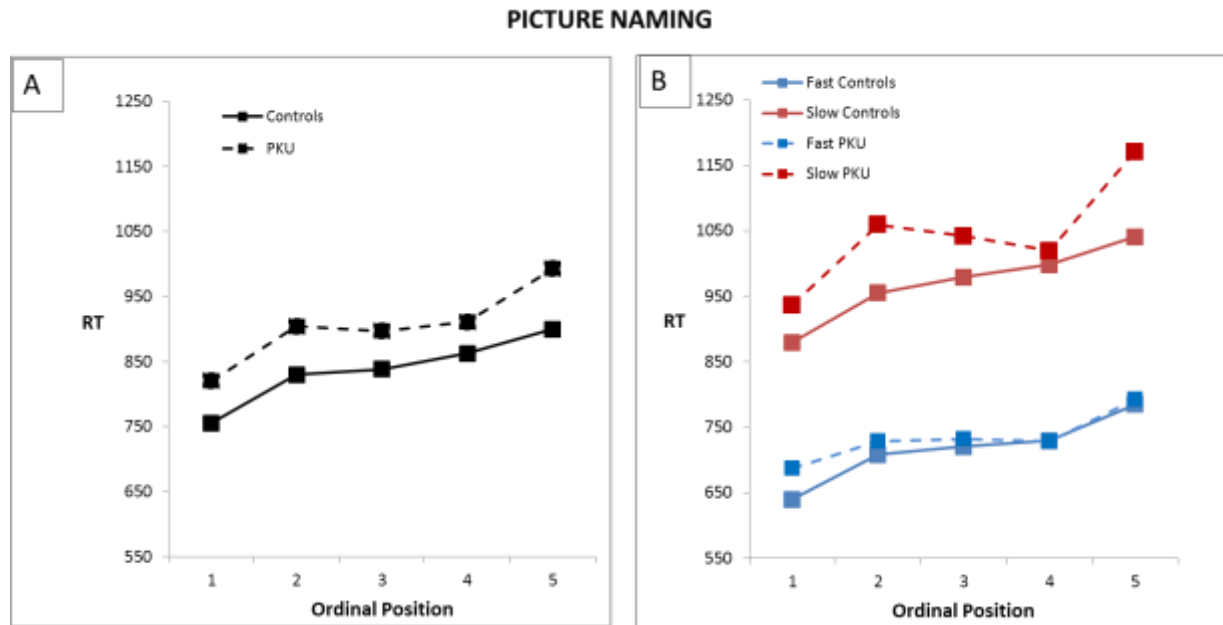


Figure 4 –Interference effects in picture naming. RTs increase with ordinal position in a set of semantically related pictures for AwPKU (dotted lines) and Controls (solid lines). Panel A shows overall differences between the control and PKU groups. Panel B shows differences between fast and slow participants within each group. Fast and slow groups were established on the basis of overall speed in this task (fastest and slowest quartile).

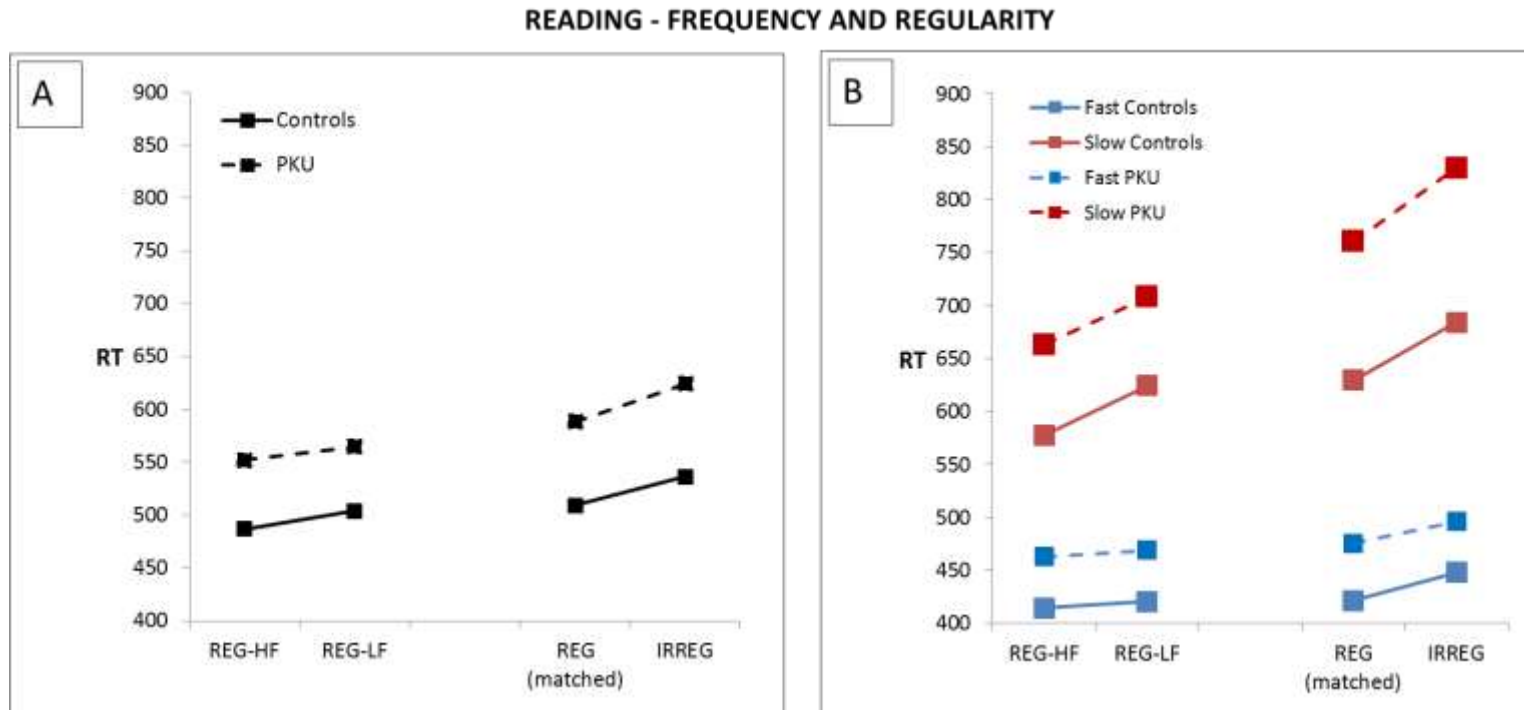
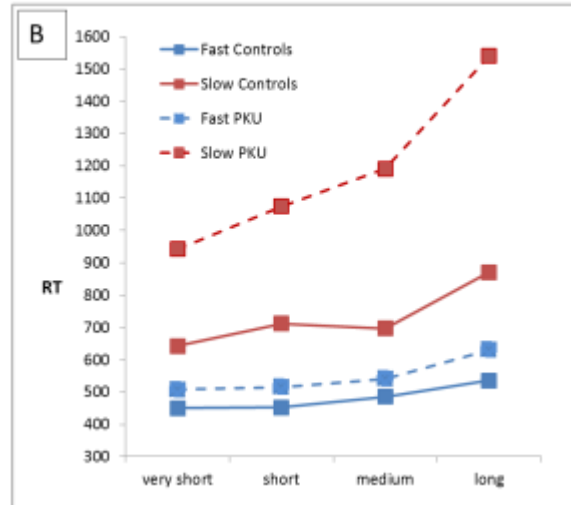
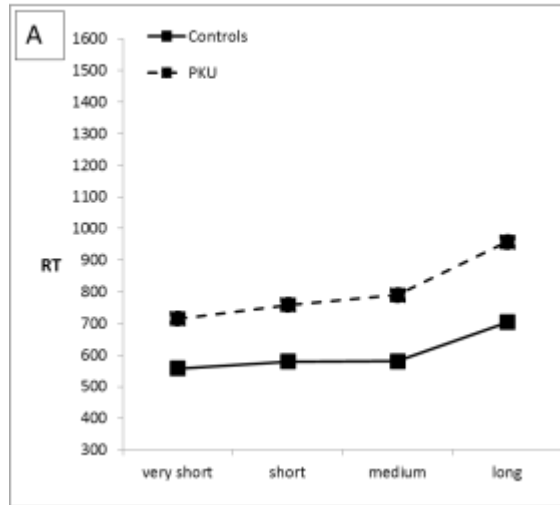


Figure 5: Word reading by frequency and regularity in AwPKU (dotted lines) and Controls (solid lines). Panel A shows overall differences between the control and PKU groups. Panel B shows differences between fast and slow participants within each group. Slow and fast groups were established on the basis of speed in word reading. REG-HF (Regular High Frequency Words); REG-LF (Regular Low Frequency Words); REG (Regular Words); IRREG (Irregular Words).

NONWORD READING - LENGTH



WORD READING - LENGTH

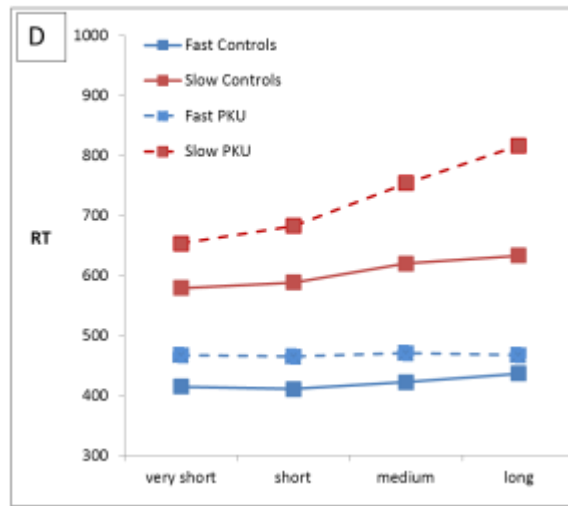
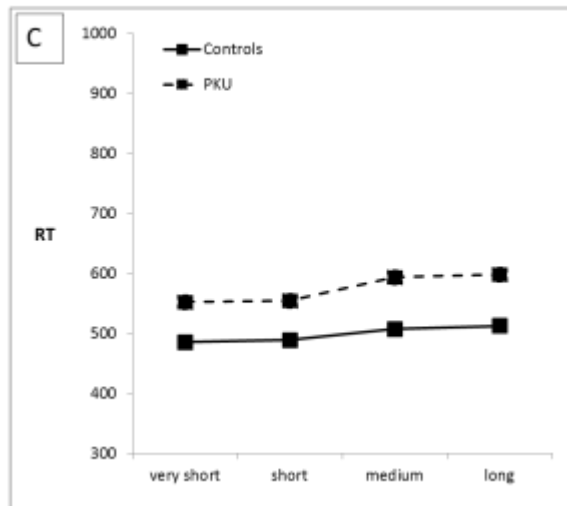


Figure 6: Word and non-word reading by length for AwPKU (dotted lines) and controls (solid lines); Panels A and C show overall differences between the control and PKU groups. Panels B and D show differences between fast and slow participants within each group. Fast and slow groups are subdivided in terms of overall speed in each of the two tasks.

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Appendix

Speed measures for control and PKU participants across tasks. N controls = 30; N AwPKU=37

Speed Measures	CONTROLS		PKU PARTICIPANTS			Controls vs. PKU t test and p
	Mean	SD	Mean	SD	N	
VISUO-SPATIAL ATTENTION						
Simple Detection (RT – ms.)	316	56.9	332	52.9	37	$t_{(1,65)} = -1.1$; $p = .266$
Detection with distractors						
2 Targets	393	81.8	428	86.7	31	$t_{(1,59)} = -1.7$; $p = .104$
1 Target	399	76.9	424	55.6	31	$t_{(1,59)} = -1.5$; $p = .145$
1 Distractors - 1Target	431	107.0	462	140.6	31	$t_{(1,59)} = -.9$; $p = .350$
Total	405	83.6	429	70.3	31	$t_{(1,59)} = -1.3$; $p = .19$
Detection with distractors - Opposite						
2 Targets	394	69.5	431	78.4	31	$t_{(1,59)} = -2.0$; $p = .053$
1 Target	409	64.1	441	75.2	31	$t_{(1,59)} = -1.7$; $p = .086$
1 Distractors - 1Target	425	67.5	468	84.8	31	$t_{(1,59)} = -2.2$; $p = .034$
Total	409	64.6	445	76.3	31	$t_{(1,59)} = -1.9$; $p = .050$
Choice Reaction Time	281	31.3	307	41.9	37	$t_{(1,65)} = -2.8$; $p = .007$
Feature Search						
4 items Yes	498	87.0	566	116.3	31	$t_{(1,59)} = -2.6$; $p = .012$
4 items No	494	97.4	596	155.0	31	$t_{(1,59)} = -3.1$; $p = .003$
8 items Yes	510	86.8	596	179.4	31	$t_{(1,59)} = -2.4$; $p = .021$
8 items No	483	60.1	632	214.6	31	$t_{(1,59)} = -3.7$; $p = .001$
12 items Yes	512	74.3	605	167.8	31	$t_{(1,59)} = -2.8$; $p = .007$
12 items No	497	97.3	640	248.4	31	$t_{(1,59)} = -3.0$; $p = .005$
Total	498	71.7	606	167.6	31	$t_{(1,59)} = -3.3$; $p = .002$
Conjunction Search						
4 items Yes	665	110.6	778	189.3	31	$t_{(1,59)} = -2.8$; $p = .006$
4 items No	769	127.4	899	218.8	31	$t_{(1,59)} = -2.8$; $p = .006$
8 items Yes	767	144.6	877	195.2	31	$t_{(1,59)} = -2.4$; $p = .015$
8 items No	926	138.2	1138	305.4	31	$t_{(1,59)} = -3.5$; $p = .001$
12 items Yes	830	129.9	980	236.0	31	$t_{(1,59)} = -3.0$; $p = .003$
12 items No	1084	220.2	1371	412.9	31	$t_{(1,59)} = -3.4$; $p = .001$
Total	841	126.3	1008	239.7	31	$t_{(1,59)} = -3.4$; $p = .001$
LANGUAGE						
Colour naming						
Stroop / Neutral	599	91.8	711	135.1	30	$t_{(1,58)} = -3.7$; $p = .000$
Stroop /Congruent	635	108.3	759	151.7	30	$t_{(1,58)} = -3.6$; $p = .001$
Stroop/Incongruent	730	130.3	877	206.1	30	$t_{(1,58)} = -3.3$; $p = .002$
Total	655	105.8	782	160.7	30	$t_{(1,58)} = -3.6$; $p = .001$

Speed of Processing in PKU 59

Pictures Naming						
Fillers	827	<i>145.0</i>	888	<i>150.4</i>	30	$t_{(1,58)} = -1.6; p = .115$
1 st Position	755	<i>131.7</i>	820	<i>131.8</i>	30	$t_{(1,58)} = -1.9; p = .062$
2 nd Position	829	<i>155.9</i>	904	<i>152.9</i>	30	$t_{(1,58)} = -1.9; p = .067$
3 rd Position	838	<i>142.2</i>	897	<i>154.6</i>	30	$t_{(1,58)} = -1.5; p = .133$
4 th Position	862	<i>145.6</i>	911	<i>144.0</i>	30	$t_{(1,58)} = -1.3; p = .197$
5 th Position	900	<i>150.7</i>	993	<i>168.1</i>	30	$t_{(1,58)} = -1.9; p = .028$
Total	835	<i>138.1</i>	902	<i>139.1</i>	30	$t_{(1,58)} = -1.9; p = .07$
Word Reading						
Regular -High frequency	487	<i>70.7</i>	552	<i>88.2</i>	31	$t_{(1,59)} = -3.2; p = .002$
Regular - Low frequency	504	<i>105.5</i>	565	<i>116.1</i>	31	$t_{(1,59)} = -2.1; p = .037$
Irregular words	536	<i>125.8</i>	624	<i>174.8</i>	31	$t_{(1,59)} = -2.2; p = .029$
Regular matched	509	<i>91.4</i>	589	<i>134.1</i>	31	$t_{(1,59)} = -2.7; p = .009$
Very Short	485	<i>69.8</i>	552	<i>85.0</i>	31	$t_{(1,59)} = -3.3; p = .001$
Short	489	<i>87.9</i>	554	<i>97.0</i>	31	$t_{(1,59)} = -2.8; p = .008$
Medium	507	<i>98.5</i>	593	<i>154.1</i>	31	$t_{(1,59)} = -2.6; p = .01$
Long	512	<i>95.8</i>	598	<i>188.9</i>	31	$t_{(1,59)} = -2.2; p = .03$
Total	507	<i>93.3</i>	578	<i>120.0</i>	31	$t_{(1,59)} = 2.6; p = .012$
Nonword Reading						
Very Short	557	<i>91.8</i>	715	<i>230.4</i>	32	$t_{(1,60)} = -3.5; p = .0009$
Short	579	<i>116.9</i>	757	<i>271.7</i>	32	$t_{(1,60)} = -3.3; p = .002$
Medium	580	<i>92.4</i>	789	<i>336.4</i>	32	$t_{(1,60)} = -3.3; p = .002$
Long	703	<i>151.1</i>	958	<i>402.7</i>	32	$t_{(1,60)} = -3.3; p = .002$
Total	604	<i>103.6</i>	803	<i>296.0</i>	32	$t_{(1,60)} = -3.6; p = .001$